European Journal of Applied Physiology
https://doi.org/10.1007/s00421-025-05832-z

INVITED REVIEW

Resistance exercise and skeletal muscle: protein synthesis, degradation, and controversies

Fujue Ji[1,2,4] · Hae Sung Lee[3] · Jong-Hee Kim[1,2,4]

Received: 19 March 2025 / Accepted: 26 May 2025

Abstract

Maintaining and enhancing skeletal muscle mass and strength are essential for optimizing metabolic function and preventing chronic diseases. Resistance exercise plays a pivotal role in this process by modulating the balance between synthesis and degradation of skeletal muscle protein. While the efficacy of such exercise in stimulating these processes is well established, uncertainties persist regarding the fibre-type specificity and contraction mode-dependent regulation of key signalling pathways, including mTORC1, AMPK, and the ubiquitin–proteasome system. Furthermore, the interplay between metabolic stressors—such as biopsy timing, muscle damage, inflammation, and oxidative stress—and skeletal muscle adaptation remains insufficiently characterized, posing challenges to mechanistic research. To address these gaps, this review systematically synthesizes current evidence on fibre-specific and contraction mode-specific regulation of skeletal muscle protein turnover. We critically examine the influence of these factors on major signalling pathways and muscle adaptation, identifying key areas of uncertainty and methodological limitations in existing studies. Based on these insights, we propose a novel theoretical framework and predictive model to guide future investigations. By providing a comprehensive and mechanistically driven analysis, this review advances the understanding of resistance exercise-induced muscle adaptations and their physiological implications. Our findings offer valuable insights for optimizing exercise strategies and developing targeted interventions for muscle-related conditions, including sarcopenia, cachexia, and metabolic disorders.

Keywords Hypertrophy · Contraction · Eccentric · Concentric · Fibre-type specific · Signalling pathway

Abbreviations

IGF-1	Insulin-like growth factor 1
IGF-1R	Insulin-like growth factor 1 receptor
MGF	Mechano-growth factor
FGFs	Fibroblast growth factors
TNF-α	Tumour necrosis factor-α
GH	Growth hormone
SOL	Soleus muscle
EDL	Extensor digitorum longus muscle
IRS-1	Insulin receptor substrate 1
EPI	Epitrochlear anconeus muscle
PI3K	Phosphoinositide 3-kinases
PIP2	(4, 5)-Bisphosphate
PIP3	Phosphatidylinositol (3, 4, 5)-trisphosphate
AKT	Protein kinase B
AMPK	AMP-activated protein kinase
PLA	Plantaris muscle
GAS	Gastrocnemius muscle
TA	Tibialis anterior muscle
VL	Vastus lateralis muscle
mTOR	Mammalian target of rapamycin
S6K1	Ribosomal protein S6 kinase
eIF4E	Eukaryotic translation initiation factor 4E
4E-BP1	Eukaryotic translation initiation factor 4E-binding protein
QD	Quadriceps muscle

Communicated by Michalis G Nikolaidis.

✉ Jong-Hee Kim
carachel07@hanyang.ac.kr

[1] Department of Physical Education, College of Performing Arts and Sport, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul, Republic of Korea

[2] BK21 FOUR Human-Tech Convergence Program, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea

[3] Department of Physical Education, College of Education, Wonkwang University, 460 Iksandae-ro, Iksan, Jeonbuk, Republic of Korea

[4] Aging and Aged Laboratory, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea

Published online: 13 June 2025

ATP	Adenosine triphosphate
FTI	Force–time integral
ERK1/2	Extracellular signal-regulated kinase 1/2
ECM	Extracellular matrix
PLD	Phospholipase D
PA	Phosphatidic acid
DGK ζ	Diacylglycerol kinase
DAG	Diacylglycerol
PTEN	Phosphatase and tensin homolog
FOXOs	Forkhead box proteins family
FOXO1	Forkhead box protein O1
FOXO3A	Forkhead box O3
MAFbx	Muscle atrophy F-box gene
MyoD	Myoblast determination protein 1
FHL	Flexor hallucis longus muscle
MuRF1	Muscle ring-finger protein-1
IKK	IκB kinase kinase
NF-κB	Nuclear factor kappa-light-chain enhancer of activated B cells
LPS	Lipopolysaccharide
ROS	Reactive oxygen species
PDTC	Pyrrolidine dithiocarbamate

Introduction

The skeletal muscle is essential not only for movement and posture, but also for overall health (Ji et al. 2025; Merz and Thurmond 2011). Impairments in skeletal muscle mass and strength are associated with an increased risk of various diseases, including type II diabetes, obesity, sarcopenia, cardiovascular disease, disability, and even cancer (Mcleod et al. 2019). Conversely, preserving and enhancing skeletal muscle function can help prevent or delay the onset of these conditions (Wolfe 2006). Consequently, strategies to maintain and improve skeletal muscle mass and strength have become a key focus in health promotion and disease prevention (Joanisse et al. 2020; Liu et al. 2025).

Resistance exercise is widely recognized as one of the most effective interventions for maintaining and increasing skeletal muscle mass and strength (McLeod et al. 2024). Its ability to stimulate protein synthesis has been well established, and it is a powerful tool for promoting skeletal muscle hypertrophy and functional improvement (Areta et al. 2013; Damas et al. 2015; McGlory et al. 2017; Wackerhage et al. 2019). In addition to activating protein synthesis pathways, resistance exercise simultaneously stimulates protein degradation pathways (Liu and Kim 2024; McGlory et al. 2017; McKendry et al. 2021; Zeng et al. 2020). While this may seem paradoxical, it reflects the dynamic and adaptive nature of skeletal muscle remodelling. This concurrent activation of synthesis and degradation is essential for continuous muscle adaptation, ensuring the maintenance of muscle mass, quality, and metabolic function. Understanding this balance is crucial for optimizing resistance exercise protocols and maximizing muscle health benefits.

Despite extensive research, gaps remain in our understanding of the molecular mechanisms underlying skeletal muscle protein turnover following resistance exercise. Key areas of uncertainty include fibre-type specificity, contraction mode-dependent regulation, and the interactions between metabolic stressors and muscle adaptation. Moreover, a comprehensive review synthesizing current evidence on these aspects is lacking.

This review aims to critically examine the changes in skeletal muscle protein synthesis and degradation in response to resistance exercise, with a particular focus on muscle fibre specificity, contraction mode-dependent regulation, metabolism, and adaptation. By identifying current limitations and knowledge gaps, we propose informed hypotheses and novel perspectives on underexplored areas. Ultimately, this review seeks to enhance our understanding of the molecular mechanisms governing skeletal muscle remodelling in response to resistance exercise, providing valuable insights for optimizing training strategies and developing therapeutic approaches for muscle-related diseases.

The effects of resistance exercise on protein synthesis pathways

IGF-1/IRS/1-PI3K/Akt/mTOR/S6K1 and 4E-BP1 pathway

Insulin-like growth factor 1 (IGF-1)

IGF-1 is a key upstream regulator of protein synthesis, playing a crucial role in cell proliferation, differentiation, and energy metabolism, while also inhibiting apoptosis (Yoshida and Delafontaine 2020). Studies on IGF-1 knockout mice have demonstrated delayed muscle development, whereas IGF-1 overexpression leads to increased body weight and muscle hypertrophy (Liu et al. 1993; Musarò et al. 2001; Yang et al. 1997). Additionally, IGF-1 has been shown to reverse dexamethasone-induced skeletal muscle atrophy in mice, further underscoring its critical role in muscle hypertrophy (Stitt et al. 2004).

A wealth of independent studies (Feng et al. 2022; Matheny et al. 2009; Suetta et al. 2010) have confirmed that resistance training facilitates skeletal muscle hypertrophy by activating IGF-1 signalling and counteracting disease-related muscle atrophy. However, some studies have failed to observe a significant increase in IGF-1 expression, following resistance exercise, suggesting that various factors can modulate this response (Roberts et al. 2010; Suetta et al. 2010; Sullivan et al. 2020). For instance, obesity has been shown

to attenuate IGF-1 stimulation due to increased expression of miR-206, an epigenetic regulator that post-transcriptionally inhibits IGF-1 (Sullivan et al. 2020). Additionally, the regulation of IGF-1 expression is highly complex, involving multiple signalling pathways with different temporal dynamics. Research indicates that specific IGF-1 splice variants, such as IGF-IEa and mechano-growth factor (MGF), exhibit distinct expression patterns at different time points post-exercise. As some variants are upregulated during the later stages of recovery, they may not show significant changes in the early post-exercise period (Hameed et al. 2003). Age and training status also influence IGF-1 expression following resistance exercise. Older individuals exhibit a delayed and attenuated IGF-1 response to mechanical loading compared to younger individuals, likely due to reduced sensitivity to anabolic stimuli (Roberts et al. 2010). This diminished response may be attributed to impaired MGF activation, which could explain the lack of significant IGF-1 upregulation in the ageing population (Roberts et al. 2010).

IGF-1 expression in skeletal muscle is influenced by contraction, with eccentric contractions eliciting significantly higher expression levels compared to other contraction types (Bamman et al. 2001; Heinemeier et al. 2007; Taghibeikzadehbadr et al. 2020). Eccentric contractions induce greater mechanical damage, triggering an increase in inflammatory mediators such as TNF-α, which can further activate the IGF-1 signalling pathway (Heemskerk et al. 1999). Additionally, these contractions elevate serum concentrations of acidic fibroblast growth factors (FGFs), which are released in response to mechanical injury and stimulate myocyte proliferation and hypertrophy in vitro (Clarke et al. 1998; Clarke and Feeback 1996; Florini 1987). These findings suggest that localized inflammation and mechanical damage following eccentric contractions enhance IGF-1 expression, accelerating skeletal muscle hypertrophy.

However, inflammation presents a double-edged sword: while moderate inflammation promotes muscle repair and growth, excessive or chronic inflammation may suppress IGF-1 expression. Pro-inflammatory cytokines, oxidative stress, and disruptions in the growth hormone (GH)/IGF-1 axis have been implicated in the downregulation of IGF-1 under conditions of excessive inflammation (Erlandsson et al. 2017; Guijarro et al. 2021; Novosyadlyy et al. 2009). Thus, further research is required to elucidate the balance between inflammatory responses and IGF-1-mediated muscle adaptation in different contraction modalities.

Moreover, the expression of IGF-1 in skeletal muscle appears to be specific, although direct evidence remains limited. An animal study demonstrated that, under resting conditions, type I muscle fibres exhibit higher levels of IGF-1 expression than type II fibres (Nagasao et al. 2022). Similarly, studies have shown that the rat soleus (SOL), which is predominantly composed of type I fibres, exhibits greater IGF-1 downstream protein activity and phosphorylation levels than the rat extensor digitorum longus (EDL), which is primarily composed of type II fibres (Song et al. 1999).

Although there have been no direct comparisons of fibre-specific IGF-1 expression post-resistance exercise, some evidence suggests that this type of exercise increases IGF-1 receptor (IGF-1R) expression in type I, but not type II fibres (Gallagher et al. 2013). Based on these findings, the present study hypothesized that IGF-1 expression will be more pronounced in type I fibres, following resistance exercise. However, this assumption requires further validation, as type II fibres experience greater mechanical loading and are more susceptible to damage during resistance exercise. Given that muscle damage and localized inflammation can significantly enhance IGF-1 expression (Clarke et al. 1998; Clarke and Feeback 1996; Florini 1987; Heemskerk et al. 1999), it is plausible that IGF-1 expression could also be elevated in type II fibres post-exercise.

In summary, while existing evidence suggests that IGF-1 expression is influenced by muscle fibre type, contraction mode, and physiological conditions such as ageing and obesity, direct experimental validation remains limited. Further research is needed to elucidate the precise fibre-specific IGF-1 responses to resistance exercise and their implications for muscle hypertrophy and adaptation.

Insulin receptor substrate 1 (IRS-1)

IRS-1 is a key signal transduction protein in the insulin receptor substrate family, undergoing tyrosine phosphorylation in response to IGF-1 stimulation and subsequently activating multiple intracellular signalling pathways. Although IRS-1 tyrosine phosphorylation is well established, the functional significance of its serine phosphorylation remains incompletely understood. The review by Gual et al. (2005) offers a comprehensive analysis of IRS-1 serine phosphorylation—particularly at residues such as IRS1^{Ser302} and IRS1^{Ser789}—which appear to mediate dual regulatory effects. Experimental studies highlight the critical role of IRS-1 in growth and development, as IRS-1 knockout mice can exhibit diabetes and severe growth retardation, weighing only 50% of their wild-type counterparts (Kido et al. 2000). Conversely, transgenic overexpression of IRS-1 in mouse skeletal muscle significantly increases PI3K activity and Akt phosphorylation, reinforcing its essential role in activating the PI3K/Akt pathway and promoting skeletal muscle hypertrophy (Morino et al. 2008).

Resistance exercise has been shown to enhance IRS-1 activity through various mechanisms, including increased p-IRS-1^{Tyr612} and/or decreased p-IRS-1^{Ser612} expression (de Matos et al. 2014; Jorge et al. 2011; Muñoz et al. 2021). These findings suggest that resistance exercise modulates IRS-1 function by altering its phosphorylation status.

However, some studies report no significant changes in IRS-1 activity post-resistance exercise, despite increased downstream signalling (Christ et al. 2002; Møller et al. 2013; West et al. 2019). One possible explanation for these discrepancies is the timing of muscle biopsies. IRS-1 signalling undergoes rapid and transient changes following stimulation, and missing the optimal detection window may lead to an underestimation of total IRS-1 or p-IRS-1 expression despite enhanced downstream activity (Khamzina et al. 2005). Validating this hypothesis requires precise experimental protocols with biopsy intervals less than 5 min, presenting a considerable technical challenge. Additionally, resistance exercise may activate mTOR through IGF-1/IRS-1-independent pathways (Hornberger 2011; Philp et al. 2011), potentially explaining increased downstream signalling activity in the absence of detectable IRS-1 changes. These alternative regulatory mechanisms will be discussed in detail in a later section.

A potential mechanism for the reduction in IRS-1 activity following resistance exercise involves negative feedback regulation. Activation of mTOR via S6K1 has been shown to induce IRS-1 serine phosphorylation at multiple sites, including Ser-270, Ser-307, Ser-636, and Ser-1101, leading to decreased IRS-1 activity and subsequent degradation (Zhang et al. 2008). This regulatory mechanism has also been observed under conditions characterized by elevated S6K1 activity, such as high nutrient availability, chronic insulin stimulation, and hepatitis C virus infection, where IRS-1 function is similarly impaired (Bose et al. 2012; Tremblay et al. 2007; Veilleux et al. 2010). The negative feedback loop between mTOR and IRS-1 likely serves as a homeostatic mechanism to prevent excessive signalling activation and maintain intracellular balance.

The impact of contraction mode on IRS-1 expression remains largely unexplored. Indirect evidence suggests that eccentric contractions may inhibit IRS-1 activity due to increased muscle damage and elevated inflammatory responses (Del Aguila et al. 2000). The suppression of IRS-1 activity by inflammatory mediators has been well demonstrated in both in vivo and in vitro studies (Hotamisligil et al. 1996; Kanety et al. 1995; Kirwan and del Aguila 2003). Moreover, when insulin is combined with eccentric contractions, IRS-1 tyrosine phosphorylation and associated PI3K activity increase, but to a lesser extent than insulin alone (Del Aguila et al. 2000), indirectly supporting the inhibitory effect of eccentric contractions on IRS-1 activity. Although direct comparisons of IRS-1 expression and activity between eccentric and concentric contractions are lacking, it is hypothesized that eccentric contractions, due to their greater induction of muscle damage and inflammatory factor activation, are more likely to suppress IRS-1 activity compared to concentric contractions. Future studies should directly compare these contraction modes under controlled experimental conditions to elucidate their specific effects on IRS-1 regulation in skeletal muscle.

Interestingly, although eccentric contractions have been reported to suppress IRS-1 activity more than concentric contractions—likely due to heightened muscle damage and inflammatory cytokine activation—this does not contradict the well-established fact that eccentric contractions induce greater skeletal muscle hypertrophy. Several mechanisms may explain this apparent paradox. First, the inhibition of IRS-1 is typically transient and localized, with signalling recovering during the post-exercise regeneration phase (Del Aguila et al. 2000). Second, eccentric contractions strongly activate alternative anabolic pathways that bypass IRS-1, such as the PLD/DGKζ/PA-mTOR axis and MAPK/ERK1/2 signalling, both of which are responsive to mechanical stress and membrane disruption. Third, eccentric contractions generate greater mechanical load and myofibrillar tension, leading to more substantial satellite cell activation, extracellular matrix remodelling, and protein turnover (LaStayo et al. 2003). These adaptations can outweigh the transient reduction in IRS-1 signalling. Lastly, the net effect on protein synthesis remains positive, as multiple hypertrophy-related pathways converge in a time-dependent and fibre-specific manner. Together, these findings suggest that IRS-1 suppression during eccentric contractions does not preclude, and may even be part of, a complex remodelling process that ultimately enhances muscle growth.

The skeletal muscle fibre-specific expression of IRS-1 following resistance exercise remains largely unexplored. While direct evidence is lacking, existing findings suggest potential fibre-type differences in IRS-1 activity. Song et al. (1999) reported that, under resting conditions, IRS-1 expression and signalling vary among muscle fibre types, with oxidative fibres (type I) exhibiting higher IRS-1 activity compared to glycolytic fibres (type II). This suggests that IRS-1 may be more active in type I fibres following resistance exercise. Furthermore, in vitro insulin stimulation studies have shown greater IRS-1 activity in SOL, a muscle predominantly composed of type I fibres, compared to epitrochlear anconeus (EPI) and EDL, which contain a larger proportion of type II fibres (Song et al. 1999). However, in vitro insulin stimulation may not fully reflect IRS-1 activity in skeletal muscle following resistance exercise. Therefore, these findings should be interpreted with caution. Future studies should directly investigate the effects of resistance exercise on IRS-1 expression and activity across muscle fibre types to clarify potential fibre-specific adaptation.

This discrepancy prompts further discussion regarding the relationship between fibre type-specific signalling and observed hypertrophic outcomes. Although type I fibres may show relatively higher basal levels of IGF-1 and IRS-1 expression, this does not contradict the fact that type II fibres generally undergo greater hypertrophy in response to

resistance exercise. This apparent paradox can be explained by several key factors. First, type II fibres possess inherently greater hypertrophic potential, characterized by a larger cross-sectional area, lower myonuclear density, and heightened sensitivity to mechanical load stimuli (Suetta et al. 2010). Second, hypertrophic adaptations depend more on the dynamic responsiveness to exercise rather than on basal expression levels. Type II fibres tend to exhibit greater amplitude in signalling activation post-exercise, including more rapid and robust activation of the Akt/mTOR/S6K1 pathway and higher peaks of protein synthesis. Third, resistance exercise preferentially recruits type II fibres under high-intensity loading, subjecting them to greater mechanical tension and metabolic stress—direct inducers of muscle remodelling. Fourth, the activity of IGF-1 is not solely dependent on expression quantity but also on the presence of splice variants such as MGF, which is more markedly upregulated in type II fibres following mechanical stimulation and more directly linked to localized hypertrophy (Hameed et al. 2003). Lastly, skeletal muscle hypertrophy is governed by the integrated contribution of multiple signalling pathways—not just IGF-1 or IRS-1—and these pathways appear to converge more potently in type II fibres during and after resistance training. Together, these factors explain why type II fibres, despite sometimes lower basal expression of certain anabolic factors, exhibit superior hypertrophic responses to resistance stimuli.

IRS-1 plays a central role in mediating skeletal muscle adaptation to resistance exercise through its involvement in the IGF-1/PI3K/Akt pathway. While resistance exercise can modulate IRS-1 phosphorylation and activity, its response appears to be highly dynamic and influenced by factors such as contraction mode, exercise timing, and negative feedback regulation via mTOR/S6K1. Additionally, indirect evidence suggests potential differences in IRS-1 activity across muscle fibre types, though direct experimental confirmation is needed. Future research should focus on the precise temporal dynamics of IRS-1 signalling, the effects of contraction mode, and the fibre-specific regulation of IRS-1 in response to resistance exercise.

Phosphoinositide 3-kinases (PI3K)

PI3K is a downstream signalling protein of IRS-1 and a family of enzymes involved in critical cellular processes such as growth, proliferation, and differentiation (Wymann and Pirola 1998). Upon IRS-1 activation, the regulatory p85 subunit binds to IRS-1, leading to activation of the catalytic p110 subunit, which initiates PI3K signalling. Structural abnormalities in PI3K, such as subunit deletions or dysfunction, result in embryonic lethality in mice, highlighting the indispensable role of intact PI3K in development (Yu and Cui 2016). Furthermore, PI3K activation has been shown to counteract dexamethasone-induced skeletal muscle atrophy (Stitt et al. 2004), indirectly suggesting its potential role in promoting skeletal muscle hypertrophy.

Several studies have documented that resistance exercise enhances PI3K activity (Li et al. 2022; Yin et al. 2020). However, PI3K activity in the PLA muscle fluctuates significantly in response to overloaded weight-bearing, decreasing at the 3rd hour, peaking at the 12th hour, and returning to baseline by the 24th hour (Carlson et al. 2001). These findings suggest that PI3K activation is stimulus dependent, with excessive or prolonged stimulation potentially leading to decreased activity due to energy stress and/or inflammatory responses as part of a negative feedback mechanism for muscle protection. Thus, future studies investigating PI3K expression should carefully control exercise intensity to optimize its activation.

Although most studies report an increase in PI3K activity following resistance exercise, some findings suggest otherwise. For instance, one study reported no significant increase in PIK3 activity or expression in skeletal muscle post-resistance exercise (Hamilton et al. 2010), though such observations are uncommon. This discrepancy may arise from the possibility that PI3K is not the sole key regulator of skeletal muscle hypertrophy; in certain conditions, alternative pathways such as MAPK, may compensate for PI3K signalling. The role of MAPK-related signalling in resistance exercise adaptation will be discussed in a later section.

The effect of contraction mode on PI3K expression remains largely unexplored. We hypothesize that eccentric contractions may further enhance PI3K expression in skeletal muscle. Eccentric contractions significantly stimulate the JNK signalling pathway, which is associated with inflammatory responses triggered by myofibre damage and repair (Boppart et al. 1999; Martineau and Gardiner 2001). JNK activation has been linked to increased PI3K activity, either directly or indirectly (Boppart et al. 1999; Park et al. 2006; Utsugi et al. 2009). Additionally, eccentric contractions have been shown to significantly upregulate the expression of S6K1, a downstream effector of the PI3K pathway (Eliasson et al. 2006; Rahbek et al. 2014). One possible explanation for these findings is an increase in upstream signalling through PI3K.

Comparative transcriptomic analysis of eccentric and concentric contractions further supports this hypothesis. Eccentric contractions have been found to significantly upregulate genes related to protein synthesis and muscle growth, including members of the IGF-1 and PGC-1α families (Taghibeikzadehbadr et al. 2020). Given that these signalling proteins serve as major upstream regulators of PI3K, their upregulation may contribute to increased PI3K expression following eccentric contractions. Although these findings provide indirect support for our hypothesis, direct

experimental evidence is required to establish the role of muscle contraction mode specificity in PI3K regulation.

The muscle fibre type-specific regulation of PI3K following resistance exercise remains unclear. Hamilton et al. (2010) investigated PI3K expression in different muscle types (PLA, SOL, and EDL) following electrically stimulated resistance exercise and found no significant changes. However, as PI3K expression may exhibit a delayed response post-exercise (Carlson et al. 2001; Yin et al. 2020), the immediate post-stimulation analysis used in that study may not accurately reflect its true dynamics.

Further evidence suggests that PI3K signalling may exhibit fibre-type specificity. Whole transcriptome RNA sequencing revealed that PI3K-related genes showed stronger responses in type II muscle fibres following resistance exercise (Dickinson et al. 2018). However, this finding was not validated at the protein expression level, leaving the extent of PI3K fibre-specific regulation uncertain. Future studies should integrate both gene expression analysis and protein quantification to elucidate the role of muscle fibre type in PI3K regulation post-resistance exercise.

PI3K is a crucial downstream effector of IRS-1, playing a key role in skeletal muscle adaptation to resistance exercise. While resistance exercise generally enhances PI3K activity, its response appears to be influenced by factors such as exercise intensity, contraction mode, and potential compensatory pathways like MAPK signalling. Current evidence suggests that eccentric contractions may further augment PI3K activation, potentially due to increased upstream signalling via JNK and IGF-1-related pathways, though direct validation is required. Additionally, while transcriptomic data indicate a preferential activation of PI3K-related genes in type II muscle fibres post-resistance exercise, further research is needed to confirm these findings at the protein level. Future studies should focus on the temporal regulation of PI3K activity, the effects of contraction mode, and potential fibre-type specificity to fully understand its role in skeletal muscle hypertrophy.

Protein kinase B (AKT/PKB)

AKT comprises a family of three serine/threonine-specific protein kinases that regulate various cellular processes. Upon PI3K activation, AKT translocates to the membrane, where it binds to PDK, leading to its partial activation. AKT knockout mice exhibit impaired skeletal muscle growth and reduced lifespan (Chen et al. 2001; Cho et al. 2001), while AKT overexpression promotes hypertrophy and inhibits dexamethasone-induced atrophy (Cleasby et al. 2007; Sandri et al. 2004). These findings highlight the essential role of AKT in promoting skeletal muscle hypertrophy and preventing muscle atrophy.

Resistance exercise has been widely documented to enhance AKT activity in skeletal muscle, as demonstrated in both human and animal studies (Camera et al. 2010; Kido et al. 2016; Li et al. 2022; Yin et al. 2020). However, some studies have reported no significant changes in AKT activity post-resistance exercise (Spiering et al. 2008; Vissing et al. 2013) despite increased downstream mTOR activity. This suggests that mTOR activation may occur independently of the IRS-1/PI3K/AKT pathways, a topic further explored in a later section. Additionally, a reduction in AKT activity following resistance exercise has been reported (Deldicque et al. 2008). This decline may be associated with AMPK activation, as studies have shown that AICAR, an AMPK activator, significantly reduces p-AKT^{Ser473} expression in skeletal muscle (Bolster et al. 2002; Koopman et al. 2006). Although AICAR and resistance exercise activate AMPK through distinct mechanisms, both significantly increase AMPK activity, suggesting that unchanged or decreased AKT expression post-exercise may be linked to elevated AMPK activity.

Other factors, including the metabolic state of exercise subjects, may also influence AKT activity. Research suggests that resistance exercise performed in a fasted or obese state leads to a significant reduction in AKT phosphorylation at Thr308 and Ser473 due to reduced nutrient availability and oxidative stress (Deldicque et al. 2008; Ji et al. 2024). Additionally, the timing of muscle biopsies may impact observed AKT expression changes, a topic further discussed in relation to skeletal muscle fibre type.

There is no substantial evidence indicating that contraction mode influences AKT expression (Ato et al. 2016; Eliasson et al. 2006; Rahbek et al. 2014). However, eccentric contractions have been shown to induce higher mTOR and S6K1 activation compared to concentric contraction (Eliasson et al. 2006; Rahbek et al. 2014). This supports the hypothesis that skeletal muscle hypertrophy mediated through mTOR and S6K1 involves pathways beyond the IRS-1/PI3K/AKT axis.

The role of inflammatory factors in AKT expression cannot be overlooked. Eccentric contraction-induced skeletal muscle damage elevates TNF-α levels, yet its effect on AKT expression remains unclear. While TNF-α downregulates IRS-1 (upstream of AKT), it does not appear to suppress AKT expression in eccentric contraction (Kirwan and del Aguila 2003; Newham et al. 1983). We hypothesize that, despite TNF-α-mediated IRS-1 inhibition, inflammatory signals directly activate AKT, compensating for reduced IRS-1 expression. Supporting this, in vitro studies demonstrate that TNF-α can enhance AKT expression, promoting cell survival and protecting against excessive programmed cell death (Burow et al. 2000; Hiraoka et al. 2001).

Skeletal muscle fibre type significantly influences AKT expression. In vitro electrical stimulation revealed a marked

increase in p-AKT^{Ser473} expression in multiple muscle types (EDL, SOL, PLA, GAS-red, and GAS-white), with the greatest increase in fast-twitch fibre-rich EDL and the lowest in slow-twitch fibre-rich SOL (Sakamoto et al. 2002). Similar findings were reported for rat TA and SOL (Nader and Esser 2001), where SOL exhibited a lack of AKT response to resistance exercise despite insulin stimulation. This suggests that resistance exercise-induced AKT expression is fibre-type dependent, with fast-twitch fibres showing greater responsiveness.

The timing of biopsies is another critical factor in AKT activity. In rats, AKT phosphorylation peaks at the 5th minute post-resistance exercise and returns to baseline within 15 min (Sakamoto et al. 2002). Another study reported a significant increase in p-AKT^{Ser473} only between 5 and 10 min post-resistance exercise, with no significant changes detected by the 20th minute (Bolster et al. 2003). In contrast, in humans, AKT phosphorylation at both p-Akt ^{Thr308} and p-Akt ^{Ser473} in the VL remains elevated for up to 30 min post-resistance exercise (Camera et al. 2010). Whether these discrepancies arise from differences in resistance exercise modalities (high-frequency electrical stimulation vs. leg extension machine) or species (rodent vs. human) remains unclear. Future studies should comprehensively evaluate the temporal aspects of AKT activity and expression to improve our understanding of its role in skeletal muscle adaptation.

Mammalian target of rapamycin (mTOR)

mTOR, a member of the phosphatidylinositol 3-kinase-related kinases family, is a critical regulator of cell growth and protein synthesis (Mitra et al. 2015). The key downstream effectors of mTOR in protein synthesis include the eukaryotic translation initiation factor 4E (eIF4E)-binding protein (4E-BP) and ribosomal protein S6 kinase (S6K1). Specific knockdown of mTOR and RAPTOR proteins in mouse skeletal muscle reduces phosphorylation of downstream targets S6K1 and 4EBP1, leading to severe myopathy and premature death between 22 and 38 weeks of age (Risson et al. 2009). These findings underscore the essential role of mTOR in skeletal muscle hypertrophy and growth.

Baar and Esser (1999) first demonstrated that mTOR activation promotes protein synthesis following resistance exercise, a finding widely confirmed in subsequent studies (Camera et al. 2010; Li et al. 2022; Yin et al. 2020). However, not all studies have reported increased mTOR expression or activity post-resistance exercise. For example, no significant changes in p-mTOR^{Ser2488} levels were observed in the quadriceps (QD) of older adults following resistance exercise (Francaux et al. 2016), potentially due to increased REDD1 expression with ageing and decreased insulin response (Choi et al. 2016; Katiyar et al. 2009). Similar results were observed in young male volunteers, where no significant change in p-mTOR expression was detected immediately and 1 h after resistance exercise (Kakigi et al. 2011). However, Mazo et al. (2021) found increased p-mTOR^{Ser2488} expression in skeletal muscle 4-h post-exercise. These discrepancies suggest that the timing of sample collection is a critical factor affecting mTOR expression. Specifically, mTOR phosphorylation begins to increase 30-min to 1-h post-exercise, peaks within 1–3 h, and gradually declines between 3 and 6 h, returning to baseline within 24 h (Dickinson and Rasmussen 2013; Dreyer et al. 2006).

Animal studies further support the importance of tissue collection timing and exercise frequency in mTOR expression. Takegaki et al. (2017) reported no significant changes in mTOR or p-mTOR^{Ser2488} expression over 72-h periods (three resistance exercise sessions spaced 72 h apart), but observed significant increases in p-mTOR^{Ser2488} expression in the 24-h and 8-h groups. These findings suggest that exercise frequency and rest intervals influence mTOR activation. Moreover, mTOR activation is modulated by metabolic status. In healthy mice, p-mTOR^{Ser2488} expression increases for 15 min, whereas that in obese mice peaks at 5 min and returns to baseline within 15 min (Khamzina et al. 2005). The inhibition of mTOR expression in obesity may be linked to decreased IGF-1 levels due to increased miR-206 expression. Thus, factors such as age, sampling time point, exercise frequency, rest intervals, and obesity significantly influence mTOR expression and activity following resistance exercise. Accounting for these variables can enhance experimental reproducibility and improve understanding of skeletal muscle protein synthesis mechanisms.

There is ongoing debate regarding contraction mode-specific mTOR activation. Some human and animal studies report increased mTOR expression following both maximal eccentric and concentric contractions, with no significant difference between the two modes (Eliasson et al. 2006; Sadri et al. 2021; Taghibeikzadehbadr et al. 2020). Similarly, Ato et al. (2016) found no significant differences in p-mTOR^{Ser2488} expression immediately or 3-h post-resistance exercise across concentric, eccentric, and isometric contractions. However, eccentric contractions elicit higher S6K1 phosphorylation levels than concentric and isometric contractions, suggesting greater mTOR activation (Eliasson et al. 2006; Rahbek et al. 2014). This may be due to prolonged mTOR^{Ser2488} phosphorylation following eccentric contractions, with elevated levels observed until 5-h post-exercise, whereas concentric contraction-induced phosphorylation returns to baseline by 3-h post-exercise (Rahbek et al. 2014). These findings suggest that, while mTOR activation does not differ between contraction modes, eccentric contractions sustain peak activation for a longer duration. Additionally, eccentric contractions may further enhance S6K1 expression via a non-AKT/mTOR pathway, such as the MAPK pathway, which warrants further investigation.

Skeletal muscle fibre type also influences mTOR expression following resistance exercise. Parkington et al. (2003) reported significant mTOR expression in PLA immediately post-exercise and in both TA and PLA at 6-h post-resistance exercise, but not in SOL. These findings suggest that mTOR expression and its delayed response are fibre-type specific. Compared to the SOL, the TA and PLA contain a larger proportion of type IIa fibres, which may explain the increased mTOR expression following resistance exercise. Further evidence suggests that phosphorylated mTOR at Ser2488 localizes predominantly within the intracellular regions and sarcolemma of type IIa fibres (Parkington et al. 2003). Supporting this, Edman et al. (2019) demonstrated a six-fold increase in mTOR phosphorylation in type II fibres following resistance exercise, compared to a twofold increase in mTOR phosphorylation in type I fibres under adequate nutrition. These data confirm that mTOR expression post-exercise is fibre-type specific, with preferential activation in type IIa fibres. While these findings explain the fibre-specific expression of mTOR, the delayed response in certain muscles remains unclear. We speculate that differences in muscle fibre composition between PLA and TA, particularly the higher proportion of type IIa fibres in PLA, may explain the earlier mTOR expression observed in PLA compared to the delayed response in TA.

Ribosomal protein S6 kinase beta-1 (S6K1)

S6K1 is a downstream target of mTOR that is activated by directly phosphorylating multiple sites, promoting skeletal muscle protein synthesis and muscle hypertrophy (Ochi et al. 2010). S6K1 knockout mice exhibit significantly lower skeletal muscle mass compared to wild-type mice, higher mortality rate, and slower development (Chen et al. 2001; Pende et al. 2004). Conversely, mice overexpressing the S6K1 gene display significant skeletal muscle hypertrophy (Ohanna et al. 2005), indicating that S6K1 plays a crucial role in skeletal muscle growth.

Both human and animal studies have widely demonstrated that resistance exercise significantly increases S6K1 expression (Atherton et al. 2005; Camera et al. 2010; Koopman et al. 2006; Li et al. 2022; Terzis et al. 2008). However, some studies have not observed a significant increase in S6K1 expression post-resistance exercise. One possible explanation for this discrepancy is the activation of AMPK. Although it remains unclear whether AMPK directly regulates S6K1, it can reduce p-mTOR^{Ser2446} expression, impairing insulin- and growth factor-induced S6K1 activation (Cheng et al. 2004; Thomson et al. 2008). Kazior et al. (2016) reported that 7 weeks of resistance exercise decreased S6K1 expression in human VL. Excluding AMPK's inhibitory effect, another plausible explanation is the negative feedback mechanism during skeletal muscle protein synthesis. While the precise mechanisms remain unclear, S6K1 upregulation amplifies its inhibitory feedback on IRS-1, impairing PI3K and AKT activation (Adams 1998; Harrington et al. 2004; Um et al. 2004). This feedback mechanism may serve to maintain metabolic homeostasis. However, the significance of reduced S6K1 levels remains speculative, necessitating further research. Additionally, sampling time point is critical for detecting changes in S6K1 expression. Significant increases in p-S6K1^{Thr389} were observed in EDL and TA only at 3-h post-resistance exercise (Baar and Esser 1999). In rats, significant increases were noted only at 6-h post-resistance exercise (Hernandez et al. 2000), suggesting a delayed positive effect of resistance exercise on S6K1 expression in skeletal muscle.

S6K1 expression is also contraction mode specific, with eccentric contraction inducing higher S6K1 phosphorylation levels than other modes. Post-maximal eccentric contraction, p-S6K1$^{Thr421/Ser424}$ increased fourfold and p-S6K1^{Thr389} expression doubled compared to pre-exercise levels, while maximal concentric contraction did not induce significant changes (Eliasson et al. 2006). Furthermore, eccentric contractions sustain high p-S6K1^{Thr389} levels for over 5 h, whereas concentric contractions maintain them for only 3 h (Rahbek et al. 2014). Ato et al. (2016) similarly reported significantly higher p-S6K1^{Thr389} expression after eccentric contraction at 3-h post-exercise. These findings suggest that eccentric contraction not only induces greater S6K1 upregulation but also sustains its expression longer than other contraction modalities.

Skeletal muscle fibre type significantly affects S6K1 expression post-resistance exercise. Parkington et al. (2003) reported significant increases in p-S6K1^{Thr389} in EDL immediately post-exercise and in TA at 6 h, whereas no significant increase was observed in SOL. Another study found significant increases in S6K1 expression in rat PLA, EDL, and TA at 3-h post-resistance exercise, persisting beyond 36 h, but not in SOL (Baar and Esser 1999). This may be attributed to the fibre type-specific localization of S6K1 expression following resistance exercise. Immunohistochemistry analysis revealed that p-S6K1^{Thr389} is almost exclusively expressed in type II fibres, with minimal expression in type I fibres (Koopman et al. 2006). A human study further confirmed that expression of p-S6K1^{Thr389}, p-S6K1$^{Thr421/Ser424}$, and p-S6K1$^{Ser424/Thr421}$ was significantly elevated only in type II fibres (Tannerstedt et al. 2009). These findings collectively indicate that p-S6K1 expression post-resistance exercise is fibre type specific and contributes primarily to type II fibre hypertrophy. However, differences in S6K1 expression among the three type II fibre subtypes (IIa, IIb, and IIx) after resistance exercise are not yet clear and require further investigation. As a key upstream signal for S6K1, mTOR signalling is primarily localized in type IIa fibres. It remains uncertain whether mTOR signalling continues to activate

S6K1 predominantly within type IIa fibres, or whether S6K1 activation "shifts" to other fibre types over time. Further research into the subcellular and fibre-type localization of S6K1 will enhance our understanding of the mechanisms underlying resistance exercise-induced skeletal muscle protein synthesis and provide scientific data to support exercise prescription development.

Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1)

Another key downstream effector of mTOR is 4E-BP1. mTOR phosphorylates multiple sites on 4E-BP1, leading to its dissociation from eIF4E and relieving the inhibition on protein translation initiation (Dreyer et al. 2006). Overexpression of the 4E-BP1 gene results in significant reductions in body weight, lean mass, and skeletal muscle cross-sectional area (Tsai et al. 2015). Conversely, 4E-BP1 knockout mice exhibit reduced adipose tissue accumulation and are protected against ageing-related diseases and sarcopenia (Tsukiyama-Kohara et al. 2001). These findings underscore the importance of 4E-BP1 inhibition in promoting skeletal muscle hypertrophy and overall health.

The effects of resistance exercise on 4E-BP1 expression remain controversial. In rats, resistance exercise induced a peak in p-4E-BP1 expression 10 min post-exercise, significantly exceeding pre-exercise levels (Bolster et al. 2003). Similarly, resistance exercise significantly increased p-4E-BP1$^{Thr37/Thr48}$ expression, which returned to baseline within 3 h (Atherton et al. 2005), supporting the hypothesis that resistance exercise enhances skeletal muscle protein synthesis. However, other studies have reported immediate decrease in p-4E-BP1^{Thr31} and p-4E-BP1$^{Thr37/Thr48}$ following resistance exercise, with levels returning to baseline within 30 min (Koopman et al. 2006). Likewise, Deldicque et al. (2008) observed significant reductions in p-4E-BP1$^{Thr37/46}$ immediately post- resistance exercise, with recovery occurring within 24 h. The underlying reasons for these discrepancies remain unclear.

One possible explanation for the reduction in p-4E-BP1 expression post-resistance exercise is the activation of AMPK. In a vitro study has shown that AICAR-induced AMPK activation significantly decreases p-4E-BP1^{Thr37} expression in skeletal muscle (Bolster et al. 2002). Although the physiological effects of AICAR and resistance exercise differ, both findings support AMPK's inhibitory effect on p-4E-BP1 expression. A negative correlation between AMPK and p-4E-BP1 has been observed, with Dreyer et al. (2006) reporting a 75% increase in AMPK following resistance exercise, accompanied by a 36% decrease in p-4E-BP1$^{Thr37/46}$ expression. Additionally, Bolster et al. (2002) demonstrated that an AICAR injection in mice led to decreased skeletal muscle p-4E-BP1 expression. However, whether AMPK inhibits p-4E-BP1 expression indirectly by suppressing upstream signals, such as AKT, or directly modulates remains to be clarified. Furthermore, mTOR, like AMPK, functions as an energy sensor, with reduced ATP levels leading to decreased mTOR expression and activity (Dennis et al. 2001). Thus, resistance exercise influences 4E-BP1 activity through multiple energy stress pathways. Future studies should investigate this mechanism under conditions of sufficient energy and nutrient reserves to yield more definitive insights.

Beyond investigating the physiological mechanisms, the development of more precise methods for assessing 4E-BP1 activity is essential. 4E-BP1 activity can potentially be assessed through its non-phosphorylated expression. Total 4E-BP1 is composed of three isoforms: α4E-BP1, β4E-BP1, and γ4E-BP1. The expression of γ4E-BP1 serves as a marker of 4E-BP1 activity, with increased γ4E-BP1 levels indicating a larger proportion of phosphorylated 4E-BP1 and subsequent enhancement of intracellular protein synthesis (Chen et al. 2017; Jansova et al. 2017; Takegaki et al. 2017). Notably, a study reported a significant increase in the γ4E-BP1/total 4E-BP1 ratio following resistance exercise, despite no significant changes in p-4E-BP1$^{Thr37/Thr48}$ levels (Takegaki et al. 2017). Therefore, future research should consider both phosphorylation status and γ4E-BP1 expression to provide a more comprehensive evaluation of 4E-BP1 activity post-resistance exercise.

The influence of contraction mode on 4E-BP1 expression remains inconclusive. Ato et al. (2016) found no significant differences in p-4E-BP1$^{Thr37/Thr46}$ expression immediately or 3-h post-exercise across concentric, eccentric, and isometric contractions when matched for the force–time integral (FTI). Similarly, Rahbek et al. (2014) reported no significant differences in p-4E-BP1 levels following acute concentric and eccentric contractions. However, after 12 weeks of resistance exercise, a greater reduction in 4E-BP1 expression was observed after concentric compared to eccentric contractions (Rahbek et al. 2014). One possible explanation is that prolonged eccentric contractions may induce inflammatory responses that exceed the muscle's self-regulatory threshold, inhibiting resistance exercise-mediated 4E-BP1 regulation. Supporting this hypothesis, an animal study demonstrated that TNF-α injection in rats significantly increased 4E-BP1 expression in GAS and decreased p-4E-BP1 expression (Lang et al. 2002). However, the physiological mechanisms underlying exogenous injections and prolonged eccentric contraction differ, necessitating cautious interpretation. Furthermore, some studies question the regulatory role of inflammatory factors like TNF-α on 4E-BP1 expression, suggesting they primarily affect other translation initiation and elongation factors rather than directly targeting 4E-BP1 phosphorylation sites (Lang and Frost 2007; Lang et al. 2002; Velásquez et al. 2016). Clarifying the role of

inflammatory factors in 4E-BP1 regulation will provide deeper insights into the influence of contraction modes on skeletal muscle protein synthesis.

Unlike mTOR and S6K1, the fibre-type specificity of 4E-BP1 expression and phosphorylation in skeletal muscle remains largely unknown. However, evidence suggests that 4E-BP1 level and its phosphorylation may be concentrated in type II fibres. Koopman et al. (2006) reported that 4E-BP1 expression is more pronounced in type II fibres compared to type I fibres during post-resistance exercise recovery, indicating a fibre type-specific regulatory mechanism. Additionally, anabolic agent-induced muscle hypertrophy models, such as clenbuterol treatment, have demonstrated increased 4E-BP1 phosphorylation, which is primarily associated with enhanced anabolic signalling in type II fibres (Sumi et al. 2014). Furthermore, 4E-BP1 activity has been implicated in the metabolic regulation of fast-twitch fibres, suggesting a role in adaptive responses to metabolic challenges (Tsai et al. 2015). Finally, exercise and nutrient stimuli robustly enhance 4E-BP1 phosphorylation in type II fibres, further underscoring its significant role in these fibres (Witard et al. 2009). Collectively, these findings support the hypothesis that 4E-BP1 expression and its phosphorylation are predominantly localized in type II fibres, reflecting their specialized metabolic and functional roles. However, direct evidence is lacking, necessitating further experimental studies to confirm these hypotheses (Tsai et al. 2015; Witard et al. 2009).

Deficiencies and limitations

Future research on the IGF-1/IRS-1/PI3Ks/Akt/mTOR/S6K1 and 4E-BP1 pathway should prioritize the following areas (Fig. 1).

1. Comprehensive analysis of the distinct responses of IGF-1, IRS-1, PI3K, and 4E-BP1 in different muscle fibre types (type I vs. type II) following exercise is needed. Studies should systematically examine these responses under standardized exercise conditions to establish clear distinctions.

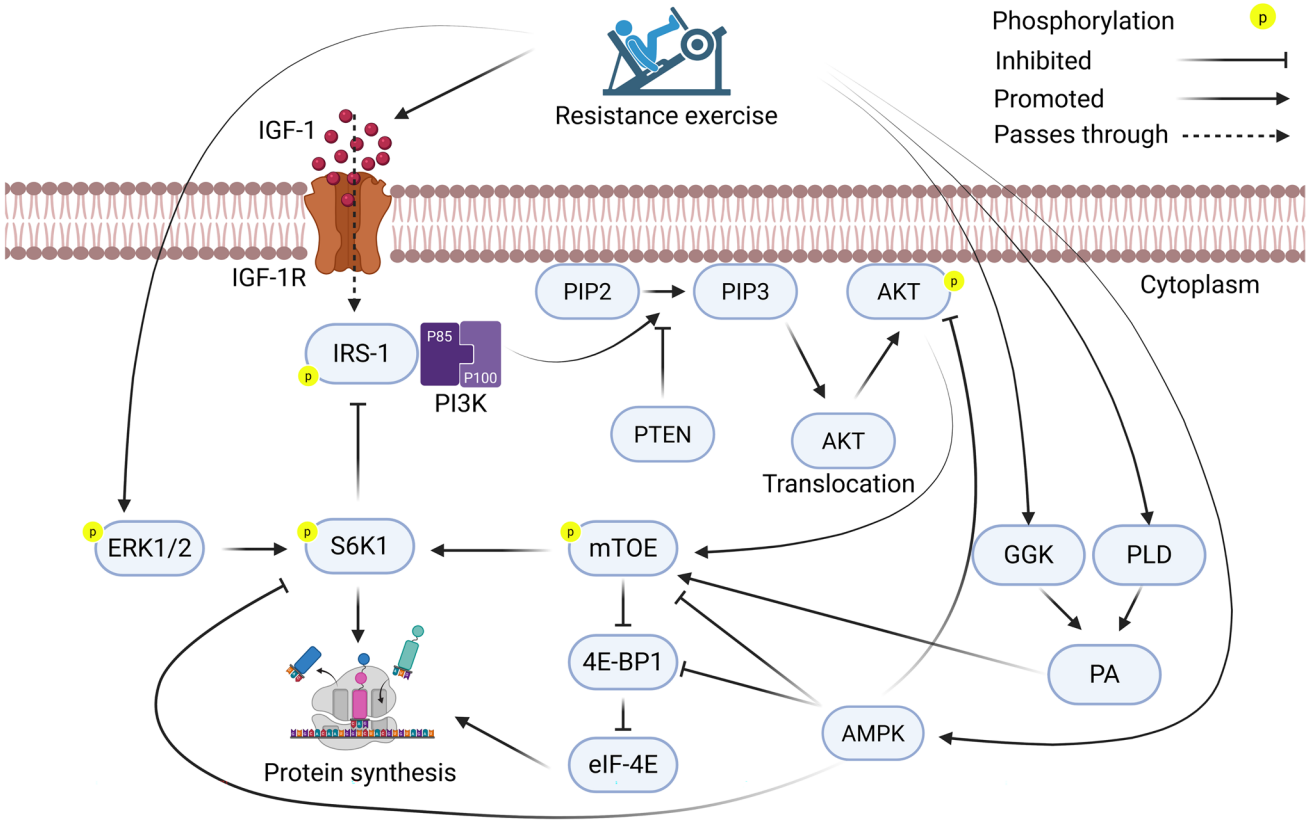

Fig. 1 Overview of resistance exercise-promoted protein synthesis pathway events in skeletal muscle. Abbreviations: 4E-binding protein 1 (4EBP1), eukaryotic initiation factor 4E (eIF4E), phosphatidic acid (PA), diacylglycerol kinase (DGK ζ), insulin receptor substrate1 (IRS-1), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-1 receptor (IGF-1R), p70 S6 kinase 1 (S6K1), (4, 5)-bisphosphate (PIP2), phosphatidylinositol (3, 4, 5)-trisphosphate (PIP3), phosphoinositide 3-kinase (PI3K), phospholipase D (PLD), protein kinase B (Akt), extracellular signal-regulated kinase 1/2 (ERK1/2), phosphatase and tensin homolog (PTEN), AMP-activated protein kinase (AMPK), and mammalian target of rapamycin (mTOR)

2. The effects of contraction mode (eccentric vs. concentric) on molecular signalling, particularly IGF-1, IRS-1, PI3K, mTOR, and 4E-BP1, must be further explored. Investigations are needed to elucidate their specific roles in muscle adaptation.
3. A deeper understanding of the temporal dynamics of key signalling molecules, such as IRS-1 and AKT, following resistance exercise is required. Future studies should aim to map the precise time course of activation and deactivation to clarify their role in muscle growth.
4. The interactions of metabolic stress induced by factors such as energy expenditure and AMPK activation with muscle growth pathways involving AKT, S6K1, Mtoe, and 4E-BP1 warrant further investigation. Understanding how metabolic stress modulates these pathways will provide critical insights into muscle adaptation mechanisms.

MAPK/S6K1 pathway

Extracellular signal-regulated kinase 1/2 (ERK1/2)

ERK1 and ERK2 share 85% sequence identity and play a critical role in skeletal muscle protein synthesis by promoting slow muscle fibre formation (Boulton and Cobb 1991; Boyer et al. 2019; Murgia et al. 2000). The essential function of ERK2 is evident from studies in transgenic mouse embryos, where ERK2 knockout resulted in embryonic lethality at day 6.5 (Yao et al. 2003). In contrast, ERK1-deficient mice survived, likely due to compensatory ERK2 activity, though immune cell development was significantly impaired (Pagès et al. 1999). These findings underscore the importance of ERK1/2 in growth and development.

ERK1/2 expression and activity significantly increase in skeletal muscle following resistance exercise (Deldicque et al. 2008; Dreyer et al. 2006; Takegaki et al. 2019a, b; Taylor et al. 2012). Similarly, p-ERK1/2$^{Thr180/Tyr182}$ levels were markedly elevated following high-frequency electrical stimulation of isolated rat EDL, simulating resistance exercise (Atherton et al. 2005). Another study found significant changes in p-ERK1/2$^{Thr180/Tyr182}$ expression in SOL and PLA muscles following mechanical overload induced by surgical removal of the GAS in mice (Carlson et al. 2001). Although the exact mechanism by which p-ERK1/2 activates S6K1 remains unclear, in vivo and in vitro studies suggest that ERK1/2 positively regulates S6K1 expression (Deldicque et al. 2008). Notably, resistance exercise significantly increases S6K1 expression without altering upstream AKT and mTOR levels, suggesting that ERK1/2 activation may contribute to S6K1 signalling independent of the AKT/mTOR pathway (Barnabé et al. 2023; Boppart et al. 1999).

However, some studies have reported conflicting findings, indicating that resistance exercise may not enhance ERK1/2 expression and may even suppress it (Brown et al. 2017; Coffey et al. 2005; Takegaki et al. 2017; Williamson et al. 2003). For example, in obese Zucker rats, resistance exercise did not alter p-ERK1/2$^{Thr202/Tyr204}$ levels in the GAS (Brown et al. 2017). Similarly, no significant changes were observed in p-ERK1/2$^{Thr202/Tyr204}$ levels in the VL of human subjects following resistance exercise (Coffey et al. 2005). Furthermore, a study reported that p-ERK1/2$^{Thr202/Tyr204}$ expression was significantly reduced in rat GAS following 10 repetitions of resistance exercise (Takegaki et al. 2017), and a similar reduction was observed in elderly human after resistance exercise (Williamson et al. 2003). These findings suggest that resistance exercise may lead to aberrant ERK1/2 expression under certain conditions.

A potential explanation for this inconsistency is extracellular matrix (ECM) damage in skeletal muscle following exercise. The ECM, which transduces mechanical stress signals, is susceptible to alterations caused by obesity, ageing, and exercise-induced damage (Kragstrup et al. 2011; Takagi et al. 2016). The α7β1 integrin, a key ECM protein in skeletal muscle, is upregulated in response to ECM damage (Kääriäinen et al. 2002; Song et al. 1992). Overexpression of α7β1 integrin has been shown to reduce p-ERK1/2$^{Thr202/Tyr204}$ expression (Boppart et al. 2006). Therefore, resistance exercise-induced ECM damage may elevate α7β1 integrin expression, leading to reduced ERK1/2 phosphorylation. Additionally, ERK1/2 has been implicated in slow muscle fibre formation while inhibiting fast fibre differentiation (Higginson et al. 2002; Murgia et al. 2000). Since resistance exercise primarily promotes fast muscle fibre protein synthesis, the observed decrease in ERK1/2 expression post-resistance exercise may facilitate this process. Supporting this hypothesis, in vitro experiments demonstrated that ERK1/2 inhibition reduced myosin heavy chain I mRNA expression while increasing myosin heavy chain IIx and IIb mRNA levels (Higginson et al. 2002).

ERK1/2 expression also varies depending on the mode of skeletal muscle contraction. Eccentric contraction has been shown to induce greater ERK1/2 expression compared to concentric contraction (Boppart et al. 1999). In rat PLA, p-REK1/2 levels were significantly higher following eccentric contraction than after isometric and concentric contractions (Martineau and Gardiner 2001). Similarly, in human VL, eccentric contraction during a 30- minute resistance exercise session significantly increased p-ERK1/2$^{Thr202/Tyr204}$ expression, whereas concentric contraction did not (Franchi et al. 2014). These findings indicate that eccentric contraction is a more potent stimulus for ERK1/2 activation. S6K1 regulation by ERK1/2 through a non-AKT/mTOR pathway explains why S6K1 phosphorylation is higher after eccentric contraction despite similar mTOR activation levels between the two contraction modes.

The greater ERK1/2 activation observed following eccentric contraction may be related to skeletal muscle microdamage. Eccentric contraction induces greater muscle damage, leading to increased cytokine and inflammatory factor concentrations, both of which are known to promote ERK1/2 phosphorylation (Close et al. 2005; Raingeaud et al. 1995). Additionally, the higher absolute tensions generated during eccentric contraction may also be a reason for this. Absolute tensions generated by eccentric contractions may contribute to greater ERK1/2 activation (Hather et al. 1991; Lieber 1992). However, these interpretations require caution. While ECM damage and α7β1 integrin overexpression have been associated with reduced ERK1/2 expression, muscle damage-induced cytokines and inflammatory factors can enhance ERK1/2 phosphorylation (Liao et al. 2010; Szelenyi and Urso 2012). These contradictory findings highlight the need for further research on the interactions among α7β1 integrin, cytokines, and inflammatory factors in response to resistance exercise-induced muscle damage.

ERK1/2 expression also exhibits fibre-type specificity following resistance exercise. In resting skeletal muscle, p-ERK expression appears to be positively correlated with fast-twitch fibre content (Oishi et al. 2019). Studies in mice and rats have reported significantly higher p-ERK1/2 levels in fast fibre-dominant muscles following resistance exercise (Shi et al. 2008). However, within the same muscle, no significant differences in p-ERK1/2 expression were observed between different fibre types post-resistance exercise (Eliasson et al. 2006). Based on available data, we hypothesize that the fibre type-dependent activation of ERK1/2 likely reflects differences in responsiveness at the level of muscle groups, rather than an intrinsic specificity of individual muscle fibres. Accordingly, it is plausible that ERK1/2 signalling in skeletal muscle is predominantly regulated by mechanical loading patterns and the architectural and functional properties of specific muscle groups, rather than by fibre type alone.

Deficiencies and limitations

Future research on the MAPK/S6K1 pathway should focus on the following key areas (Fig. 1).

1. The interplay between cytokines and inflammatory factors induced by eccentric contractions and α7β1 integrin upregulation following skeletal muscle damage requires further investigation to clarify their integrated effects on ERK1/2 signalling.
2. The conflicting findings on ERK1/2 activation at both the whole-muscle and muscle fibre levels underscore the need for molecular-level investigations to elucidate how specific muscle fibre types differentially respond to specific exercise modalities.

PLD or DGK ζ/PA/mTOR

Resistance exercise is widely accepted to regulate mTOR expression through the IGF-1/AKT pathway, enhancing skeletal muscle protein synthesis. However, Coppola et al. (1994) demonstrated that transgenic mice expressing a dominantly inactivated IGF-1R in skeletal muscle failed to activate downstream AKT signalling following IGF-1 stimulation, but exhibited a preserved hypertrophic response induced by skeletal muscle contraction. This finding was the first indication that skeletal muscle hypertrophy can occur independent of IGF-1/ATK activation. Subsequent research further established that passive stretching of skeletal muscle activates mTOR signalling without altering IGF-1/AKT activity (Hornberger and Chien 2006). O'Neil et al. (2009) reported that IGF-1/AKT activation following resistance exercise is transient, lasting less than 30 min, whereas mTOR activation persists for longer than 12 h. While IGF-1/AKT signalling may contribute to contraction-induced hypertrophy, its transient nature suggests the existence of alternative pathways mediating mTOR activation. These findings challenge the exclusivity of the IGF-1/AKT pathway in mTOR-mediated skeletal muscle hypertrophy.

Supporting this perspective, You et al. (2012) demonstrated that mTOR activation can occur independent of IGF-1/AKT signalling by using the ERK1/2 inhibitor U0126 on passively stretched mouse EDL muscle. While U0126 effectively blocked stretch-induced ERK1/2 phosphorylation, it only partially reduced S6K1 phosphorylation, suggesting the presence of an alternative pathway that activates S6K1 and enhances skeletal muscle protein synthesis in response to mechanical stimuli. Further studies by O'Neil et al. (2009) and You et al. (2014) proposed the existence of the PLD or DGK ζ/PA/mTOR pathway, which mediates mTOR activation in response to resistance contraction. There in vitro studies on mouse EDL muscle highlighted this pathway as an independent regulator of mTOR, distinct from the conventional PI3K/AKT signalling pathway.

Phospholipase D (PLD)

Phospholipase D (PLD) is integral to numerous physiological processes, including protein synthesis (Damnjanovic and Iwasaki 2013). It also catalyses the hydrolysis of phosphatidylcholine into phosphatidic acid and choline (Jenkins and Frohman 2005). Research has shown that PLD expression is closely linked to skeletal muscle growth and development. In vitro studies revealed that inhibiting PLD with FIPI (a PLD inhibitor) in L6 myotubes led to significant atrophy, while PLD overexpression induced hypertrophy in the GAS of mice and reversed atrophy caused by dexamethasone and inflammatory factors (Jaafar et al. 2013). These findings

highlight the essential role of PLD in promoting and maintaining skeletal muscle hypertrophy.

PLD is located in the Z-bands of skeletal muscle, which are critical for force transmission (Fridén and Lieber 2001). During repeated skeletal muscle resistance contractions, PLD dissociates from α-actinin, reducing its inhibition and enhancing PLD activation (Hornberger et al. 2006). This suggests that repeated contractions increase PLD activity. Hornberger and Chien (2006) found that AKT expression remained unchanged, but S6K1 was activated in a rapamycin-sensitive manner after intermittent stretching of isolated mouse muscle. This implies that intermittent stretching activates downstream mTOR signalling through an AKT-independent mechanism.

However, conflicting findings exist. Another study on isolated muscle stretching reported no significant changes in PLD activity despite a notable increase in mTOR activity (You et al. 2014). This suggests that PLD is not the sole regulator of mTOR activation following mechanical stretching. Furthermore, these findings are based on ex vivo mouse skeletal muscle studies, providing indirect insights rather than direct evidence of the role of PLD in mTOR regulation following in vivo resistance exercise. It is not known whether PLD-mediated mTOR activation in human skeletal muscle aligns with that found in animal studies. Additionally, the expression of PLD in different muscle fibre types and its response to distinct contraction modes remain unclear. Elucidating the role of PLD in mTOR regulation could enhance our understanding of resistance exercise-induced muscle protein synthesis.

Diacylglycerol kinase (DGK ζ)

Hornberger et al. (2006) were the first to demonstrate that ex vivo skeletal muscle stretching increases PLD expression. They further showed that inhibiting PLD with 1-butanol blocked the PLD/PA/mTOR pathway, supporting PLD's role in mTOR regulation through PA. However, several challenges have arisen regarding this conclusion. First, many biological effects of 1-butanol are not solely attributable to PLD inhibition (Gardiner et al. 2003). Second, blocking PLD expression does not prevent mTOR activation induced by ex vivo stretching (You et al. 2014). Third, the timeline of PLD expression increase does not correlate with PA accumulation (You et al. 2014). These discrepancies suggest an alternative pathway for PA synthesis, potentially involving diacylglycerol (DAG) phosphorylation by DGK ζ.

Evidence indicates that DGK ζ activity increases with prolonged ex vivo stretching (O'Neil et al. 2009), leading to elevated DAG concentration (Vaughan et al. 2014; Zick et al. 2014). This provides substrates for subsequent PA synthesis. DGK ζ-knockout mice exhibit reduced skeletal muscle mass and impaired hypertrophic responses compared to wild-type mice, particularly in type II fibre–rich muscles such as the PLA, while DGK ζ overexpression increases the cross-sectional area in mouse TA and mitigates rapamycin-induced atrophy (You et al. 2014, 2018). High-frequency electrical stimulation to simulate resistance exercise resulted in two-fold increases in DAG and PA levels in rat skeletal muscle (Cleland et al. 1989). These findings suggest that DGK ζ plays a crucial role in skeletal muscle hypertrophy.

Compared to PLD, the role of DGK ζ in regulating skeletal muscle hypertrophy through resistance exercise has been validated using in vivo animal experiments. In rat PLA muscle, DGK ζ expression significantly increased following resistance exercise (You et al. 2018). Moreover, resistance exercise-induced upregulation of DGK ζ was observed to mitigate the inhibitory effects of FOXO transcription factors and the ubiquitin system on skeletal muscle protein synthesis (You et al. 2018). These findings support the physiological role of DGK ζ in promoting skeletal muscle hypertrophy in response to resistance exercise. Furthermore, we hypothesize that DGK ζ expression following resistance exercise exhibits muscle fibre specificity. Specifically, DGK ζ expression may may predominantly regulated in type IIb fibres. This hypothesis is supported by findings in DGK ζ-knockout rats, where type IIb fibres continued to atrophy after resistance exercise, whereas the cross-sectional areas of type IIa and type IIx fibres significantly increased (You et al. 2018).

Nevertheless, current research on the regulation of DGK ζ expression in response to resistance exercise remains limited. First, while existing studies highlight the involvement of FOXO transcription factors and the ubiquitin system in DGK ζ regulation, they fail to explore other potential upstream signalling pathways that may interact with DGK ζ and influence its expression following resistance exercise. Second, most research focuses on the acute changes in DGK ζ expression immediately after resistance exercise, lacking data on its dynamic regulation with long-term resistance training. Third, skeletal muscle contractions during resistance exercise can be classified into concentric, eccentric, and isometric types, which may differentially regulate DGK ζ expression. Finally, most studies rely on rodent models, which, despite their utility in elucidating fundamental muscle biology mechanisms, exhibit physiological differences from humans. Future research should focus on the multiple regulatory mechanisms of DGK ζ expression in response to resistance exercise and explore how different types of exercise and long-term adaptive changes affect this pathway. Additionally, it is crucial to perform human studies to better understand the physiological mechanisms regulating skeletal muscle protein synthesis in response to resistance exercise.

Phosphatidic acid (PA)

Phosphatidic acid (PA) functions as a lipid second messenger crucial for cellular signalling. Its inhibition disrupts mTOR-Rictor association, impairing protein synthesis (Mehri et al. 2023). Although debates persist regarding the regulatory mechanisms of PA on mTOR (Frias et al. 2023), its role in mTOR activation is well supported (Avila-Flores et al. 2005; Hornberger et al. 2006; Tang et al. 2006). Exogenous PA or overexpression of PA-producing enzymes increase mTOR expression, whereas limiting PA production suppresses it (Chen et al. (2005).

Both PLD and DGK ζ, upstream regulators of PA, can be activated by ex vivo skeletal muscle stretching and resistance exercise (O'Neil et al. 2009; Rasmussen 2009; You et al. 2018, 2014). Thus, PA expression appears to be closely linked to resistance exercise. Passive skeletal muscle stretching increases PA levels, maintaining elevated levels for at least 90 min (Hornberger et al. 2006; You et al. 2014). Similarly, electrical stimulation-simulated resistance exercise in rats significantly increased PA levels in skeletal muscle (Cleland et al. 1989). Additionally, electrical stimulation of the rat EDL to simulate eccentric contraction significantly elevated PA concentrations, which were maintained for at least 60 min (O'Neil et al. 2009). The changes in PA concentration following contractions appear to be muscle fibre specific, with potentially higher levels in fast-twitch fibres. This is supported by findings that PA level increased immediately in the rat TA and was sustained for a prolonged period, whereas no changes were observed in the rat SOL muscle (O'Neil et al. 2009). However, this is the only such study available so far, and more evidence is needed to support these findings.

Despite these insights, the precise physiological mechanisms by which resistance exercise regulates the PLD- or DGK ζ-mediated PA/mTOR pathway remain unclear. Significant alterations in signalling of those pathways have been observed predominantly in response to eccentric contractions induced by ex vivo stretching or in vivo electrical stimulation. While such stimulation can simulate certain aspects of resistance exercise, these findings should be interpreted cautiously. The regulatory mechanisms of the PLD or DGK ζ/PA/mTOR pathway in skeletal muscle following resistance exercise require further investigation.

Deficiencies and limitations

Current research priorities for the PLD or DGK ζ/PA/mTOR include the following (Fig. 1).

1. Validating whether PLD or DGK ζ/PA regulation following actual resistance exercise aligns with in vitro and electrical stimulation findings.
2. Identifying upstream regulators of PLD and DGK ζ in controlling PA synthesis.
3. Investigating muscle fibre-specific and contraction mode-specific variations in PLD or DGK ζ/PA pathway activation following resistance exercise.

The effects of resistance exercise on protein degradation pathways

AKT/FOXOs/MAFbx and MuRF-1

Forkhead box proteins family (FOXOs)

FOXOs are transcription factors that play crucial roles in metabolic regulation, longevity, and tumour suppression (Mammucari et al. 2007; Sandri et al. 2004). The upregulation of MuRF1 and MAFbx genes is typically associated with increased nuclear translocation and decreased phosphorylation of FOXOs (Lee 2004; Stitt et al. 2004). AKT phosphorylates FOXO proteins, preventing their translocation to the nucleus and subsequent DNA binding (Brunet et al. 1999; Kops et al. 1999). Overexpression of FOXO genes in mice leads to reduced skeletal muscle mass, decreased cross-sectional area, and increased myofibre atrophy (Kamei et al. 2005; Southgate et al. 2007). Conversely, FOXO gene knockdown reverses skeletal muscle atrophy and significantly reduces MAFbx expression (Liu et al. 2007; Sandri et al. 2004). These findings underscore the essential role of FOXOs in skeletal muscle atrophy.

Resistance exercise has been widely shown to inhibit skeletal muscle atrophy by reducing the nuclear translocation of FOXOs (Léger et al. 2006; Takegaki et al. 2019a, b; Williamson et al. 2010; Yu et al. 2022). However, some studies have reported contradictory findings (Fry et al. 2013; Sullivan et al. 2020). One study found no significant changes in FOXO1 levels at 15-min and 3-h post-resistance exercise in either sedentary obese or lean individuals (Sullivan et al. 2020). Additionally, p-FOXO3A^{Ser253} expression remained below baseline for 24 h after resistance exercise (Fry et al. 2013). These discrepancies may be due to the regulation of FOXOs by other signalling pathways following resistance exercise. For instance, while AKT levels increase post-exercise, they may be counteracted by AMPK, modulating FOXO activity (Greer et al. 2007; Sanchez et al. 2012). Furthermore, resistance exercise-induced skeletal muscle hypertrophy follows a "damage–repair–hypertrophy" process. Notably, FOXO1 and FOXO3A expression levels significantly increased in the GAS after high-frequency eccentric contraction-induced muscle damage in rats (Lee et al. 2015), suggesting that FOXO upregulation may facilitate the clearance of damaged cells and proteins, creating an environment conducive to muscle growth.

Another perspective suggests that increased FOXO expression may be associated with post-exercise muscle inflammation (Ito et al. 2009; Kim et al. 2019; Lundell et al. 2019). However, inflammation is unlikely to be the primary driver of FOXO expression as its duration typically exceeds that of FOXO upregulation (Nedergaard et al. 2007). Ageing may also be a contributing factor. In aged rats, FOXO3A expression increased following nine weeks of resistance exercise (Luo et al. 2013), and the p-FOXO3A-^{Ser253}/FOXO3A ratio in the GAS was significantly reduced post-resistance exercise (Zeng et al. 2020). Decreased p-FOXO levels can lead to muscle mass loss and impaired functional capacity. One hallmark of ageing is the excessive accumulation of " garbage " and/or damaged proteins in skeletal muscle (Demontis and Perrimon 2010). Therefore, we hypothesize that resistance exercise-induced FOXO upregulation may facilitate the clearance of these cellular debris, potentially slowing the decline of skeletal muscle function.

The effect of contraction mode on FOXO expression is also noteworthy. Following chronic resistance exercise, no significant differences were observed in FOXO1 mRNA, FOXO3A mRNA, FOXO3A, FOXO1, p-FOXO1^{Ser256}, and p-FOXO3A^{Ser253} levels between eccentric and concentric contractions (Stefanetti et al. 2014a, b). However, at 5-h post-acute resistance exercise, concentric contractions induced greater reduction in p-FOXO1^{Ser256} and p-FOXO3A^{Ser253} expression than did eccentric contractions, while p-FOXO1^{Ser256} expression was higher (Stefanetti et al. 2014a, b). This suggests that the interaction between exercise duration (chronic and acute) and contraction mode influences FOXO expression and activity. Additionally, some studies have shown that concentric contractions result in greater FOXO1 expression than eccentric contractions (Nedergaard et al. 2007; Sabouri et al. 2022). Among FOXO family members, FOXO1 is more sensitive to changes in cellular energy levels (Nedergaard et al. 2007). LaStayo et al. (2000) demonstrated that, under the same absolute workload, concentric contractions required higher energy expenditure than eccentric contractions. Supporting this, endurance exercise significantly upregulates FOXO1 expression (Jorgensen et al. 2005; Li et al. 2014; Sanchez 2015). This suggests that differences in FOXO responses to contraction mode may be due to variability in adaptation to energetic stress. Further studies are needed to validate this hypothesis for understanding skeletal muscle protein adaptations to resistance exercise.

Not all FOXO family members exhibit muscle fibre specificity. Specifically, FOXO3A does not show muscle fibre-type specificity, whereas FOXO1 does. Following both low- (Macedo et al. 2014) and high-intensity (Krug et al. 2016) chronic resistance exercise (8 weeks), no significant changes in FOXO3A expression were observed in the FHL (flexor hallucis longus), TA, and SOL. In contrast, FOXO1 expression significantly decreased in SOL but remained unchanged in GAS (Ribeiro et al. 2019). These findings suggest that type I muscle fibres selectively regulate FOXO1 expression in response to resistance exercise. Kamei et al. (2005) demonstrated that FOXO1 overexpression in mice downregulated type I fibre-associated genes but did not affect type II fibre-associated genes, further supporting the link between FOXO1 and type I muscle fibres. This mechanism may help protect type I fibres from damage caused by prolonged mechanical loading (Sandri et al. 2006).

We propose that FOXO3A does not exhibit fibre-type specificity after resistance exercise because its role in protein degradation and metabolic stress regulation is consistent across all muscle fibre types. Resistance exercise induces metabolic stress such as energy depletion, myofibre damage, and nutrient deficiency, which activate FOXO3A to meet the increased demand for protein degradation. In this process, FOXO3A activation is widespread and not fibre-type dependent. All muscle fibres rely on FOXO3A to regulate energy balance and maintain cellular homeostasis (Raue et al. 2007; Schachter et al. 2012). The consistent behaviour of FOXO3A across fibre types reflects its crucial role in muscle function (Zheng et al. 2010).

Muscle atrophy F-box gene (MAFbx/atrogin-1) MAFbx was first identified through transcriptional analysis in a rodent model of skeletal muscle atrophy (Bodine et al. 2001). In skeletal muscle, MAFbx expression is tightly regulated at the transcription of upstream FOXO factors (Ni et al. 2006; Sandri et al. 2004). Overexpression of MAFbx leads to the polyubiquitination of MyoD, inhibiting MyoD-induced myotube differentiation and formation (Lagirand-Cantaloube et al. 2009). Conversely, MAFbx knockdown prevents endogenous MyoD protein degradation and effectively mitigates skeletal muscle atrophy in vivo (Lagirand-Cantaloube et al. 2009). These findings confirm that MAFbx plays a pivotal role in skeletal muscle hypertrophy and atrophy.

Resistance exercise is a primary intervention to prevent skeletal muscle atrophy and promote hypertrophy, and its inhibitory effect on MAFbx expression has been widely demonstrated (Feng et al. 2022; Kazior et al. 2016; Li et al. 2022). However, some studies challenge this notion (Borgenvik et al. 2012; Stefanetti et al. 2014a, b). For instance, no significant change in MAFbx expression was observed in human VL 3-h post-acute resistance exercise (Borgenvik et al. 2012). Similarly, Stefanetti et al. (2014a, b) reported no alteration in MAFbx mRNA expression in human skeletal muscle even 22 h after acute resistance exercise. A plausible explanation is that short-term assessments may not accurately reflect changes in MAFbx protein and mRNA expression levels. Supporting this, Mascher et al. (2008) found that MAFbx mRNA expression significantly decreased only 48 h after the first resistance exercise session. Also, MAFbx

expression is regulated by FOXOs (Ni et al. 2006; Sandri et al. 2004). During or shortly after exercise, AMPK and other energy-sensing signals may inhibit the AKT/mTOR pathway and activate FOXOs, upregulating MAFbx expression (Greer et al. 2007; Sanchez et al. 2012). However, as the energy availability is restored and AKT/mTOR signalling is reactivated, MAFbx expression gradually declines, allowing protein synthesis pathways to dominate. This dynamic regulation reflects the adaptive balance of skeletal muscle post-resistance exercise: an initial increase in protein degradation facilitates repair, followed by enhanced protein synthesis to promote skeletal muscle hypertrophy. Moreover, changes in MAFbx expression may not fully reflect alterations in protein degradation rates post-resistance exercise. Increased MAFbx expression following resistance exercise is more likely a marker of skeletal muscle's adaptive response rather than an indicator of heightened degradation (Nedergaard et al. 2007). While eccentric contractions increase skeletal muscle damage, the concurrent downregulation of MAFbx appears counterintuitive. However, this may not be paradoxical. As discussed previously, MAFbx expression is likely dynamic: it may promote early degradation of damaged proteins post-eccentric contraction, but sustained activation could impede muscle regeneration. Therefore, a transient upregulation followed by timely suppression may represent an optimal repair mechanism. To test this hypothesis, future studies should implement precisely timed tissue sampling strategies.

MAFbx expression is also contraction mode specific. Significant reduction in MAFbx mRNA expression has been observed in human skeletal muscle following eccentric contractions compared to concentric contractions (Sabouri et al. 2022). Chronic resistance exercise with eccentric contractions has been shown to significantly reduce MAFbx mRNA expression, maintaining lower levels of certain isoforms for up to 1 week (Nedergaard et al. 2007). This suggests that MAFbx expression is sensitive to contraction mode, with greater decreases following eccentric contractions. One possible explanation is that eccentric contractions impose lower physiological stress and metabolic cost compared to concentric contractions (Hody et al. 2019; Peñailillo et al. 2013; Perrey et al. 2001). Lower motor unit recruitment during eccentric contractions results in reduced oxygen and energy consumption, potentially diminishing the need for MAFbx-mediated protein degradation (Hody et al. 2019). An alternative explanation attributes the significant decrease in MAFbx expression after eccentric contractions to the higher mechanical load and muscle damage they induce, which trigger a stronger repair response. During eccentric contractions, the extent of skeletal muscle damage is greater, leading myofibres to downregulate atrophy-related proteins such as MAFbx to support regeneration and repair (Kostek et al. 2007). While studies consistently show that eccentric contractions lead to reduced MAFbx expression, the underlying mechanisms remain debated. Some emphasize lower metabolic demand, while others highlight the role of damage-induced repair responses, underscoring the complexity of skeletal muscle adaptation.

MAFbx expression also exhibits muscle fibre-type specificity. At rest, MAFbx mRNA expression is significantly higher in type I fibres than in type II fibres (Yang et al. 2006b). Following resistance exercise, MAFbx mRNA expression decreases in type I fibres but remains unchanged in type II fibres (Yang et al. 2006b). An animal study further demonstrated that MAFbx mRNA expression significantly decreased in the SOL but remained unchanged in the GAS after resistance exercise (Ribeiro et al. 2019). This suggests that MAFbx expression differences stem from distinct metabolic characteristics and adaptive responses of type I and type II fibres to resistance exercise. After resistance exercise, type I fibres may downregulate MAFbx expression to reduce protein degradation and enhance protein synthesis, preserving metabolic stability, maintaining muscle structure and function, and reducing the risk of atrophy (Raue et al. 2007). In contrast, type II fibres may maintain higher MAFbx expression to facilitate timely removal of damaged proteins and support rapid remodelling and hypertrophy. Given that type II fibres experience greater mechanical stress, their dynamic balance between protein degradation and synthesis is more active, preventing a significant decrease in MAFbx expression (Yang et al. 2006b).

Resistance exercise intensity also influences MAFbx expression in different muscle fibre types. Two independent studies utilized the same resistance exercise protocol (5 days/week, 8 weeks) but at different intensities. The low-intensity group trained at 60% of the maximum voluntary tolerance (14–20 stair climbs per session) (Macedo et al. 2014), while the high-intensity group trained at 80% (9–10 stair climbs per training session) (Krug et al. 2016). The results revealed that MAFbx expression decreased only in the FHL after chronic low-intensity resistance exercise (Macedo et al. 2014). The FHL, TA, and SOL in rats are mainly composed of type IIa and IIx fibres (Lee et al. 2004), type IIb fibres (Zhong et al. 2007), and type I types (Pellegrino et al. 2004), respectively. This suggests that MAFbx expression in type IIa and IIx fibres is more sensitive to resistance exercise intensity.

Muscle ring-finger protein-1 (MuRF1) MuRF1 is an E3 ubiquitin ligase identified through transcriptional analysis in rodent models of muscular atrophy induced by fasting and immobilization (Bodine et al. 2001). While MuRF1 and MAFbx share several common features, they differ in regulatory mechanisms and substrate targets (Cai et al. 2004). MuRF1 preferentially interacts with structural proteins, such as myosin, mediating their degradation under condi-

tions like dexamethasone treatment, denervation, and fasting (Centner et al. 2001; Cohen et al. 2009; Foletta et al. 2011). These findings suggest that MAFbx primarily targets molecules affecting protein synthesis, whereas MuRF1 regulates protein degradation and contributes to skeletal muscle metabolism and structural remodelling (Foletta et al. 2011). Notably, MuRF1 gene-knockout rats exhibit preserved skeletal muscle mass and resistance to atrophy (Bodine and Baehr 2014). In contrast, MuRF1 overexpression increases skeletal muscle protein ubiquitination and neuromuscular junction instability (Baehr et al. 2021). These findings suggest that MuRF1 plays a key role in skeletal muscle protein degradation, and its inhibition may promote muscle mass and function.

Resistance exercise is generally believed to promote skeletal muscle hypertrophy by suppressing MuRF1 expression (Borgenvik et al. 2012; Feng et al. 2022; Li et al. 2022). However, these conclusions face challenges. Kazior et al. (2016) found no significant changes in MuRF1 expression in human quadriceps (QD) following chronic resistance exercise. Similarly, Stefanetti et al. (2015) reported no significant alterations in MuRF1 protein and mRNA expression levels 22-h post-acute resistance exercise, with no changes in its protein substrate targets. Another study found no significant change in MuRF1 expression post-acute resistance exercise regardless of age (Stefanetti et al. 2014a, b). We hypothesize that variations in MuRF1 expression following resistance exercise are closely related to an individual's training history. In untrained individuals, MuRF1 and MuRF1 mRNA expression increased post-resistance exercise (Borgenvik et al. 2012; Glynn et al. 2010). In contrast, trained individuals show no significant changes in MuRF1 expression (Churchley et al. 2007). This suggests that increased MuRF1 expression may be a stress response specific to those unaccustomed to resistance training, as their baseline physiological state influences the acute genetic response of skeletal muscle (Coffey et al. 2006; Mascher et al. 2008). A study on untrained individuals demonstrated a significant rise in MuRF1 expression at 2-h post-resistance exercise, returning to baseline before the second exercise (48 h later), and increasing again afterward (Mascher et al. 2008). This implies that post-exercise MuRF1 expression fluctuations reflect an adaptive response to physiological stress. Additionally, the simultaneous increase in MAFbx and MuRF1 expression may establish a new basal level necessary for maintaining protein degradation in the hypertrophied muscle environment.

In contrast, individuals with long-term weight training experience or athletes do not exhibit significant changes in MuRF1 expression following resistance exercise. This is likely due to skeletal muscles having adapted to repeated training stimuli, effectively balancing protein synthesis and degradation and reducing the activation of protein degradation-related genes like MuRF1. Long-term resistance exercise minimizes excessive acute stress responses, particularly those associated with protein degradation, maintaining skeletal muscle homeostasis and fostering adaptive growth (Mascher et al. 2008). Moreover, trained muscle may develop more efficient recovery mechanisms, mitigating acute catabolic response triggered by resistance exercise (Coffey et al. 2006).

Current findings on MuRF1 expression concerning contraction modes remain inconclusive. Sabouri et al. (2022) reported that concentric and eccentric contractions did not alter MuRF1 expression in human VL post-resistance exercise. Similarly, Ato et al. (2017) found no changes in MuRF1 expression, regardless of contraction mode, under the same force–time integral (FTI) conditions. Conversely, other studies observed downregulated MuRF1 mRNA expression following eccentric contractions and upregulation following concentric contractions (Nedergaard et al. 2007; Stefanetti et al. 2014a, b). This discrepancy may be related to skeletal muscle energy stress. Compared to eccentric contractions, concentric have higher energy demands, which could reduce upstream AKT-mediated FOXO inhibition to increase MuRF1 expression. However, due to the limited number of studies, definitive conclusions cannot be drawn, necessitating further research on the regulatory mechanisms of MuRF1 expression in response to resistance exercise.

Post-resistance exercise, MuRF1 expression exhibits muscle fibre-type specificity. At rest, MuRF1 mRNA expression is significantly higher in type I fibres than in type II fibres (Yang et al. 2006b). Following resistance exercise, MuRF1 mRNA levels increase in both type I and type II fibres at 4-h post-exercise, with no significant differences between them. By 24 h, MuRF1 mRNA levels return to baseline in both fibre types (Yang et al. 2006b). These findings suggest that differences in MuRF1 mRNA expression in different fibres at rest are reversed post-resistance exercise, and the interaction of time and fibre types significantly affects MuRF1 expression. Chronic resistance exercise induces specific changes in MuRF1 mRNA levels in skeletal muscle, with significant reductions in the SOL, but not in the GAS (Ribeiro et al. 2019). This may be due to the higher resting state MuRF1 mRNA content in the SOL (Yang et al. 2006b), composed mainly of type I fibres. Alternatively, MuRF1 mRNA expression that decreased in type I fibres might be more sensitive to resistance exercise.

The absence of detectable changes in MuRF1 mRNA levels in GAS following resistance exercise should not be overlooked, as this may be related to biopsy timing. Specifically, MuRF1 mRNA levels significantly increase within 1-h post-resistance exercise before gradually declining (Louis et al. 2007; Mascher et al. 2008). Consequently, the failure to observe MuRF1 mRNA expression changes in GAS may result from missing the optimal sampling window.

Additionally, some studies reported no changes in MuRF1 expression in rat FHL (type IIa and IIx), TA (type IIb), and SOL (type I) following chronic high- or low-intensity resistance exercise (Krug et al. 2016; Macedo et al. 2014). These inconsistencies likely stem from the interplay between timing and fibre types. Unfortunately, many studies fail to specify the exact euthanasia time following the final intervention, further complicating data interpretation.

Deficiencies and limitations Current research on FOXOs, MAFbx, and MuRF-1 highlights several key gaps and limitations (Fig. 2).

1. The regulation and specific role of FOXOs under different resistance exercise conditions remain unclear. Their activity appears to vary depending on exercise protocols and intensities.
2. The distinct responses of different muscle fibre types to resistance exercise in relation to FOXO activity and the expression of MAFbx and MuRF-1 require more detailed analysis. Understanding these differences could contribute to the development of more tailored exercise protocols.
3. Interactions of FOXO signalling with other pathways, such as AMPK, and its integration with the AKT/FOXO axis during and after resistance exercise need further elucidation.
4. The relationship between sampling time point and signal intensity must be clarified to accurately assess changes in the expression of FOXO, MAFbx, and MuRF-1 following resistance exercise.

IKK/NF-κB/MuRF-1

IκB kinase kinase (IKK) IKK is a crucial component in the upstream regulation of NF-κB signalling. Its critical role in skeletal muscle development is closely related to the interactions between epithelium and mesenchyme. Failure of epithelial differentiation disrupts these interactions, affecting normal skeletal morphogenesis (Sil et al. 2004). IKK-knockout mice exhibit severe limb deformities and die within 1 h of birth (Hu et al. 1999). These data underscore

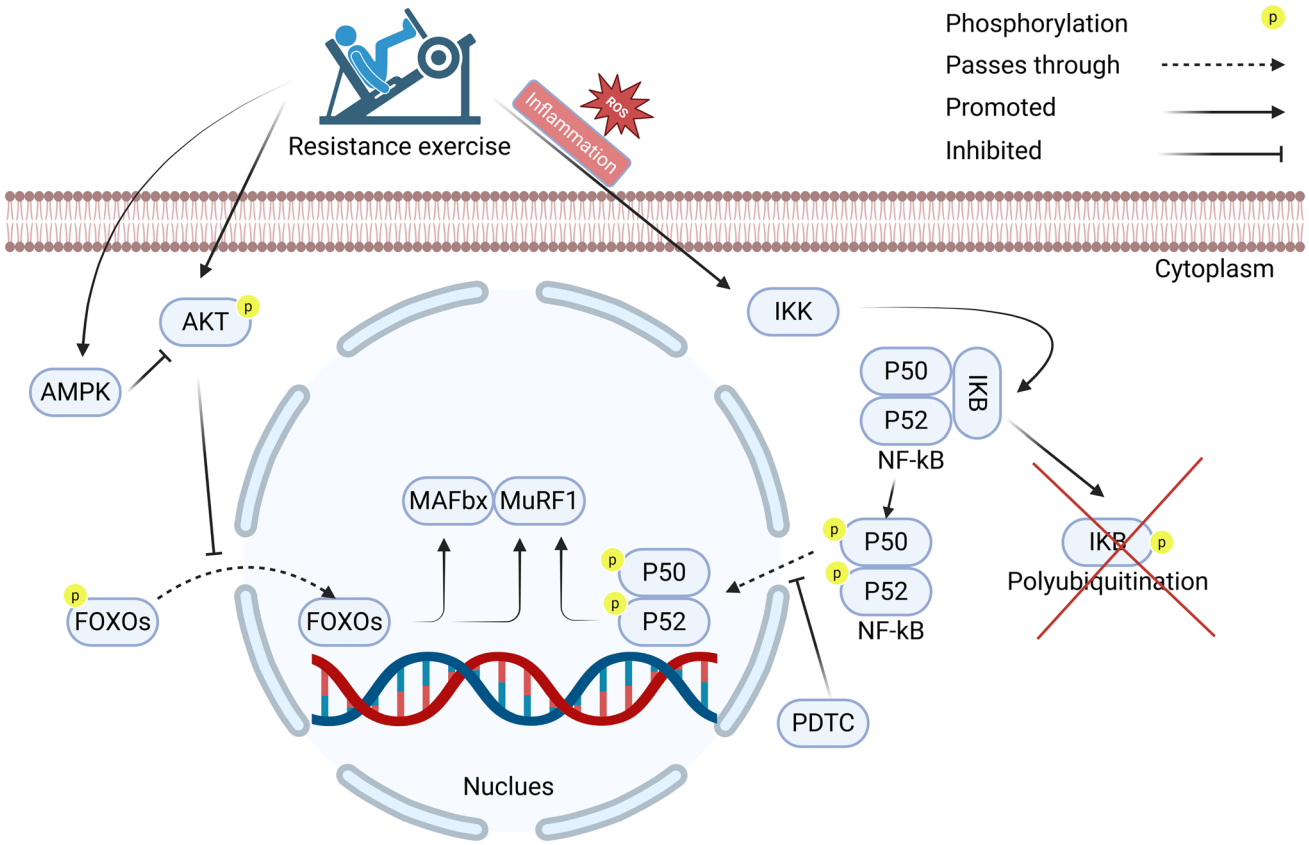

Fig. 2 An overview of the effects of resistance exercise in the skeletal muscle protein degradation pathway. Phosphate groups (P) in yellow indicate activating events. Abbreviations: forkhead box proteins family (FOXOs), muscle atrophy F-box gene (MAFbx/ atrogin-1), muscle ring-finger protein-1 (MuRF1), IkappaB kinase (IKK), inhibitor of κB (IκB), nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB), pyrrolidine dithiocarbamate (PDTC), and AMP-activated protein kinase (AMPK)

the importance of IKK in normal growth and skeletal muscle development.

Resistance exercise is known to promote skeletal muscle hypertrophy by increasing the rate of protein synthesis. We hypothesize that, after resistance exercise, IKK and IκB activation decreases to inhibit NF-κB activity and translocation, slowing the rate of skeletal muscle protein degradation. However, there is no direct evidence to suggest decrease in IKK and IκB activation in skeletal muscle post-resistance exercise. However, a study reported that chronic resistance exercise decreased the expression of p-IKK^{Ser172} in the liver of obese mice (Antunes et al. 2022). These research data indirectly support our hypothesis, but experimental limitations hinder confirmation in skeletal muscle.

Conversely, most experimental data indicate that IKK and IκB expression increase in skeletal muscle following resistance exercise. Studies have reported elevated p-IκB expression 5-h post-resistance exercise (Townsend et al. 2016), consistent with animal research demonstrating increased p-IκB and p-IKK complex levels in rat skeletal muscle after resistance exercise (Ho et al. 2005). These increases are likely linked to the inflammatory response induced by resistance exercise, with TNF-α being a primary target of IKK signalling (Chen et al. 2006; Møller et al. 2013). A study found a strong correlation between TNF-α and p-IKK expression post-resistance exercise (Coffey et al. 2007). However, while inflammatory cytokines such as IL1β, IL6, IL8, and TNFα mRNA levels significantly increase post-resistance exercise, p-IKK expression does not always show a corresponding change (Møller et al. 2013). These data suggest that inflammatory factors promote the expression of p-IKK and p-IκB, but are not the sole determinants. We hypothesize that this may be related to the different patterns by which inflammatory factors activate the IKK signalling. Specifically, TNF-α-induced IKK activity is quickly regulated by negative feedback, whereas LPS (lipopolysaccharide)-mediated activation is sustained through a positive feedback mechanism (Werner et al. 2005). These differential regulatory mechanisms may influence activation of the IKK signalling pathway through varying temporal dynamics and feedback mechanisms. Additionally, IKK is involved in processes such as metabolic regulation and autophagy, indicating that its function is not limited to IKK activation in the inflammatory response (Schröfelbauer et al. 2012). Therefore, the specific role and downstream targets of IKK may vary across physiological processes. Future in-depth studies on this issue will help deepen our understanding of the mechanisms of protein degradation under inflammatory conditions in skeletal muscle after resistance exercise.

Another potential cause of increased IKK and IκB expression following resistance exercise is oxidative stress. Reactive oxygen species (ROS), generated as byproducts of anaerobic energy pathways during high-energy demand exercises, play a critical role in growth, differentiation, proliferation, and apoptosis (Finkel and Holbrook 2000; Meyer et al. 1994). Resistance exercise, which primarily relies on anaerobic pathways, accelerates ATP consumption and subsequently increases ROS production (Bindoli et al. 1988). ROS can act as signalling molecules to activate multiple cellular stress pathways, including NF-κB. Through the action of ROS, the IKK kinase complex is activated, leading to the phosphorylation of IκB proteins, which promotes NF-κB translocation into the nucleus and activation of downstream gene expression (Ji et al. 2004). Notably, oxidative stress-induced increase in IκB activity may also exert beneficial effects on skeletal muscle. Research suggests that oxidative stress is closely linked to IKK/NF-κB pathway activation, which contributes to skeletal muscle adaptation and repair following resistance exercise (Ji et al. 2004).

Nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) IKK phosphorylates IκB, leading to its degradation and the subsequent release and activation of NF-κB (Sun 2011). In its inactive state, NF-κB is sequestered in the cytoplasm; upon activation, it translocates to the nucleus, where it regulates the expression of target genes containing NF-κB DNA-binding sites. NF-κB plays a pivotal role in skeletal muscle degradation pathways.

Animal studies suggest that persistent oxidative stress enhances NF-κB binding to DNA in the nuclei of unloaded SOL and hindlimb-suspended skeletal muscles (Durham et al. 2004; Hunter et al. 2002). This suggests a close connection between oxidative stress-induced NF-κB nuclear translocation and skeletal muscle mass atrophy. Moreover, NF-κB plays an important role in the stimulation of skeletal muscle atrophy by inflammatory factors (e.g. TNF-α). Given that resistance exercise reduces oxidative stress (Çakir-Atabek et al. 2010; Parise et al. 2005; Thirupathi et al. 2021) and inflammation (Ogawa et al. 2010; Sardeli et al. 2018) in skeletal muscle, it is reasonable to hypothesize that it also inhibits NF-κB activity and nuclear translocation. However, limited research findings support our hypothesis. Durham et al. (2004) observed reduced NF-κB activity in VL immediately after resistance exercise in humans, which returned to baseline within 1 h of rest. This suggests that NF-κB activity initially declines post-exercise but recovers quickly. Conversely, Townsend et al. (2016) reported significantly increased p-NF-κB ^{Ser536} expression at 5- and 48-h post-resistance exercise compared to the control group. These conflicting findings highlights the need to investigate the temporal dynamics of NF-κB activity in skeletal muscle after resistance exercise. We propose that NF-κB activity initially decreases following resistance exercise, potentially as a protective mechanism to reduce acute stress and prevent excessive muscle damage. As the demand for repair increases, NF-κB activity may gradually recover and become

reactivated to promote the expression of repair-associated genes. This dynamic regulation likely plays a crucial role in balancing muscle repair and the inflammatory response. Given the limited research on NF-κB regulation in skeletal muscle following resistance exercise, further studies are necessary to elucidate the time-dependent changes in its activity.

Contrary to the hypothesis that NF-κB activity decreases post-exercise, several studies have reported increased NF-κB activation and nuclear translocation following resistance exercise (Hyldahl et al. 2011; Townsend et al. 2016). As detailed above, oxidative stress is the primary cause of the increased activity of IKK and IkB, which enhances NF-κB activity and nuclear translocation. Notably, a study using pyrrolidine dithiocarbamate (PDTC), an antioxidant inhibitor of NF-κB, found that NF-κB binding to the nucleus was partially blocked by PDTC and completely prevented resistance exercise-induced increases in p-IkB (Ji et al. 2004). Furthermore, numerous studies in cells and other tissues, not just skeletal muscle, have confirmed the ability of antioxidants to reduce or repair the increase in NF-κB activity and nuclear translocation triggered by oxidative stress (Alhusaini et al. 2019; Campo et al. 2008; Saliou et al. 1999; Schenk et al. 1994). These findings suggest that resistance exercise-induced increase in NF-κB activity and nuclear translocation is at least partially mediated by oxidative stress and can be mitigated by antioxidants. However, the binding of NF-κB to the nucleus only is partially blocked by PDTC, indicating the involvement of additional regulatory factors. It has also been suggested that the inflammation in skeletal muscle fibres induced by resistance exercise may also contribute to the increase in NF-κB activity (Hunter et al. 2002). It has been found that the damage caused by skeletal muscle biopsies is strong enough to stimulate and change signalling pathways, including NF-κB (ConstantinTeodosiu et al. 1996). Hyldahl et al. (2011) reported that NF-κB expression in skeletal muscle was changed by up to 20% as a result of biopsy sampling. These factors may limit our ability to accurately reflect changes in NF-κB expression after resistance exercise. Development of a less invasive biopsy technique is essential for obtaining more reliable data.

Currently, there is no direct evidence to suggest that NF-κB expression exhibits skeletal muscle fibre specificity following resistance exercise. Limited evidence suggests that NF-κB activity is higher in the SOL compared to the GAS and EDL muscles in resting mice (Durham et al. 2004). This may be related to the supply of type I muscle fibres mainly with oxidative energy. As described earlier, oxidative stress may increase NF-κB activity in skeletal muscle. However, we hypothesize that NF-κB activity in skeletal muscle fibres may be reversed following resistance exercise, with a larger increase in NF-κB activity in fast-twitch fibres than in slow-twitch fibres. After resistance exercise, the higher expression of NF-κB in fast-twitch fibres may be due to their greater sensitivity to mechanical stress and damage, requiring a stronger repair response (Yang et al. 2006a). Additionally, fast-twitch fibres rely on glycolysis and experience higher levels of oxidative stress, which lead to stronger NF-κB activation (Osório Alves et al. 2020). This mechanism helps fast-twitch fibres respond quickly to post-resistance exercise metabolic stress and structural recovery. This hypothesis requires future validation through both in vivo and in vitro experiments, which will help us gain a deeper understanding of the skeletal muscle degradation mechanisms following resistance exercise.

Deficiencies and limitations Current research priorities regarding IKK/NF-κB/MuRF-11 include the following (Fig. 2).

1. There is need for direct evidence regarding the effects of resistance exercise on activation of IKK and IκB, which are key regulators of NF-κB.
2. Discrepancies in the timing and duration of NF-κB activation post-exercise suggest potential issues with current sampling methods and the transient nature of this activation and must be resolved.
3. The influence of prior exercise history and physiological stress on NF-κB responses requires additional study.
4. The role of oxidative stress in modulating NF-κB activity during high-intensity anaerobic exercise requires further investigation to determine its impact on muscle adaptation and recovery.
5. Research is needed to determine if resistance exercise-induced NF-κB expression differs between oxidative and glycolytic muscle fibres, which could provide insights for optimizing training and rehabilitation strategies.
6. The contributions of inflammatory responses and muscle injury to NF-κB activity post-exercise need to be defined to develop targeted strategies for mitigating inflammation while enhancing muscle adaptation.

Conclusion and future perspectives

Resistance exercise has been widely studied for its beneficial effects on the synthesis and degradation of skeletal muscle protein, highlighting the intricate regulatory mechanisms underlying these processes. The specificity of skeletal muscle fibre types and contraction modes add further complexity to muscle adaptation, necessitating a more detailed understanding of these interactions.

Future research should prioritize the temporal dynamics of key signalling pathways following resistance exercise to optimize training protocols for maximizing skeletal muscle growth. A deeper investigation into fibre type-specific

responses and the distinct effects of different contraction modes on protein synthesis and degradation pathways is essential. Additionally, the PLD or DGK ζ/PA/mTOR pathway remains an underexplored area that requires further investigation to clarify its regulatory role and interactions with other signalling networks in vivo. To improve accuracy and reproducibility of experimental findings, understanding of the integration of metabolic and inflammatory signals with skeletal muscle protein turnover and standardizing sample collection timing and methodologies are crucial. Finally, variability in pre- and post-exercise nutritional status across studies may also contribute to inconsistencies in signalling responses and should be considered in future research. Addressing these challenges will deepen our understanding of the molecular mechanisms by which resistance exercise regulates protein synthesis and degradation. Ultimately, these insights will contribute to the development of targeted strategies for preventing and managing skeletal muscle-related disorders associated with ageing, disease, and physical inactivity.

Acknowledgements We appreciate the help of Mr. Yichen Zhang (Hebei Medical University, China) for providing us with numerous references. We are grateful to Mr. Hyeonseung Rheem (Hanyang University, Korea) for his contribution to the visualization of manuscript.

Author contributions Fujue Ji: conceptualization, data conceptualization, curation, formal analysis, and writing—original draft. Haesung Lee: data conceptualization, curation, formal analysis. Jong-Hee Kim: conceptualization, supervision, and writing—review and editing.

Funding No funding was received.

Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. All data supporting the findings of this study will be made available by the authors, without undue reservation.

Declarations

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the author (s).

References

Adams GR (1998) Role of insulin-like growth factor-I in the regulation of skeletal muscle adaptation to increased loading. Exerc Sport Sci Rev 26:31–60

Alhusaini A, Fadda LM, Ali HM, Hasan IH, Ali RA, Zakaria EA (2019) Mitigation of acetamiprid—induced renotoxicity by natural antioxidants via the regulation of ICAM, NF-kB and TLR 4 pathways. Pharmacol Rep 71:1088–1094

Antunes GC, de Lima RD, Vieira RFL, Macêdo APA, Muñoz VR, Zambalde EP, Romeiro CF, Simabuco FM, Prada PO, da Silva ASR, Ropelle ER, Cintra DE, Pauli JR (2022) Resistance exercise attenuates IKKε phosphorylation and hepatic fat accumulation of obese mice. Clin Exp Pharmacol Physiol 49(10):1072–1081. https://doi.org/10.1111/1440-1681.13687

Areta JL, Burke LM, Ross ML, Camera DM, West DWD, Broad EM, Jeacocke NA, Moore DR, Stellingwerff T, Phillips SM, Hawley JA, Coffey VG (2013) Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. J Physiol-Lond 591(9):2319–2331. https://doi.org/10.1113/jphysiol.2012.244897

Atherton PJ, Babraj JA, Smith K, Singh J, Rennie MJ, Wackerhage H (2005) Selective activation of AMPK-PGC-1α or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. FASEB J 19(2):786. https://doi.org/10.1096/fj.04-2179fje

Ato S, Makanae Y, Kido K, Fujita S (2016) Contraction mode itself does not determine the level of mTORC1 activity in rat skeletal muscle. Physiol Rep 4(19):e12976. https://doi.org/10.14814/phy2.12976

Ato S, Makanae Y, Kido K, Sase K, Yoshii N, Fujita S (2017) The effect of different acute muscle contraction regimens on the expression of muscle proteolytic signaling proteins and genes. Physiol Rep 5(15):e13364. https://doi.org/10.14814/phy2.13364

Avila-Flores A, Santos T, Rincón E, Mérida I (2005) Modulation of the mammalian target of rapamycin pathway by diacylglycerol kinase-produced phosphatidic acid. J Biol Chem 280(11):10091–10099. https://doi.org/10.1074/jbc.M412296200

Baar K, Esser K (1999) Phosphorylation of p70(S6k) correlates with increased skeletal muscle mass following resistance exercise. Am J Physiol 276(1):C120-127. https://doi.org/10.1152/ajpcell.1999.276.1.C120

Baehr LM, Hughes DC, Lynch SA, Van Haver D, Maia TM, Marshall AG, Radoshevich L, Impens F, Waddell DS, Bodine SC (2021) Identification of the MuRF1 skeletal muscle ubiquitylome through quantitative proteomics. Function 2(4):zqab029. https://doi.org/10.1093/function/zqab029

Bamman MM, Shipp JR, Jiang J, Gower BA, Hunter GR, Goodman A, McLafferty CL Jr, Urban RJ (2001) Mechanical load increases muscle IGF-I and androgen receptor mRNA concentrations in humans. Am J Physiol Endocrinol Metab 280(3):E383-390. https://doi.org/10.1152/ajpendo.2001.280.3.E383

Barnabé MA, Elliott J, Harris PA, Menzies-Gow NJ (2023) Insulin, but not adiponectin, is detectable in equine saliva using an automated, commercial assay. Equine Vet J. https://doi.org/10.1111/evj.14019

Bindoli A, Cavallini L, Rigobello MP, Coassin M, Dilisa F (1988) Modification of the xanthine-converting enzyme of perfused rat-heart during ischemia and oxidative stress. Free Radical Biol Med 4(3):163–167. https://doi.org/10.1016/0891-5849(88)90024-X

Bodine SC, Baehr LM (2014) Skeletal muscle atrophy and the E3 ubiquitin ligases MuRF1 and MAFbx/atrogin-1. Am J Physiol Endocrinol Metab 307(6):E469-484. https://doi.org/10.1152/ajpendo.00204.2014

Bodine SC, Latres E, Baumhueter S, Lai VKM, Nunez L, Clarke BA, Poueymirou WT, Panaro FJ, Na EQ, Dharmarajan K, Pan ZQ, Valenzuela DM, DeChiara TM, Stitt TN, Yancopoulos GD, Glass DJ (2001) Identification of ubiquitin ligases required for skeletal muscle atrophy. Science 294(5547):1704–1708. https://doi.org/10.1126/science.1065874

Bolster DR, Crozier SJ, Kimball SR, Jefferson LS (2002) AMP-activated protein kinase suppresses protein synthesis in rat skeletal muscle through down-regulated mammalian target of rapamycin (mTOR) signaling. J Biol Chem 277(27):23977–23980. https://doi.org/10.1074/jbc.C200171200

Bolster DR, Kubica N, Crozier SJ, Williamson DL, Farrell PA, Kimball SR, Jefferson LS (2003) Immediate response of mammalian target of rapamycin (mTOR)-mediated signalling following acute resistance exercise in rat skeletal muscle. J Physiol-Lond 553(1):213–220. https://doi.org/10.1113/jphysiol.2003.047019

Boppart MD, Aronson D, Gibson L, Roubenoff R, Abad LW, Bean J, Goodyear LJ, Fielding RA (1999) Eccentric exercise markedly increases c-Jun NH2-terminal kinase activity in human skeletal muscle. J Appl Physiol 87(5):1668–1673. https://doi.org/10.1152/jappl.1999.87.5.1668

Boppart MD, Burkin DJ, Kaufman SJ (2006) Alpha7beta1-integrin regulates mechanotransduction and prevents skeletal muscle injury. Am J Physiol Cell Physiol 290(6):C1660-1665. https://doi.org/10.1152/ajpcell.00317.2005

Borgenvik M, Apró W, Blomstrand E (2012) Intake of branched-chain amino acids influences the levels of MAFbx mRNA and MuRF-1 total protein in resting and exercising human muscle. Am J Physio-Endocrinol Metab 302(5):E510–E521. https://doi.org/10.1152/ajpendo.00353.2011

Bose SK, Shrivastava S, Meyer K, Ray RB, Ray R (2012) Hepatitis C virus activates the mTOR/S6K1 signaling pathway in inhibiting IRS-1 function for insulin resistance. J Virol 86(11):6315–6322

Boulton TG, Cobb MH (1991) Identification of multiple extracellular signal-regulated kinases (Erks) with antipeptide antibodies. Cell Regul 2(5):357–371. https://doi.org/10.1091/mbc.2.5.357

Boyer JG, Prasad V, Song T, Lee D, Fu X, Grimes KM, Sargent MA, Sadayappan S, Molkentin JD (2019) ERK1/2 signaling induces skeletal muscle slow fiber-type switching and reduces muscular dystrophy disease severity. JCI Insight 5(10):e127356. https://doi.org/10.1172/jci.insight.127356

Brown JL, Rosa-Caldwell ME, Lee DE, Brown LA, Perry RA, Shimkus KL, Blackwell TA, Fluckey JD, Carson JA, Dridi S, Washington TA, Greene NP (2017) PGC-1α4 gene expression is suppressed by the IL-6-MEK-ERK 1/2 MAPK signalling axis and altered by resistance exercise, obesity and muscle injury. Acta Physiol (Oxf) 220(2):275–288. https://doi.org/10.1111/apha.12826

Brunet A, Bonni A, Zigmond MJ, Lin MZ, Juo P, Hu LS, Anderson MJ, Arden KC, Blenis J, Greenberg ME (1999) Akt promotes cell survival by phosphorylating and inhibiting a forkhead transcription factor. Cell 96(6):857–868. https://doi.org/10.1016/S0092-8674(00)80595-4

Burow ME, Weldon CB, Melnik LI, Duong BN, Collins-Burow BM, Beckman BS, McLachlan JA (2000) PI3-K/AKT regulation of NF-κB signaling events in suppression of TNF-induced apoptosis. Biochem Biophys Res Commun 271(2):342–345

Cai DS, Frantz JD, Tawa NE, Melendez PA, Oh BC, Lidov HGW, Hasselgren PO, Frontera WR, Lee J, Glass DJ, Shoelson SE (2004) IKKβ/NF-κB activation causes severe muscle wasting in mice. Cell 119(2):285–298. https://doi.org/10.1016/j.cell.2004.09.027

Çakir-Atabek H, Demir S, PinarbaSili RD, Gündüz N (2010) Effects of different resistance training intensity on indices of oxidative stress. J Strength Cond Res 24(9):2491–2497

Camera DM, Edge J, Short MJ, Hawley JA, Coffey VG (2010) Early time course of Akt phosphorylation after endurance and resistance exercise. Med Sci Sports Exerc 42(10):1843–1852. https://doi.org/10.1249/MSS.0b013e3181d964e4

Campo GM, Avenoso A, Campo S, D'Ascola A, Traina P, Samà D, Calatroni A (2008) The antioxidant effect exerted by TGF-1β-stimulated hyaluronan production reduced NF-kB activation and apoptosis in human fibroblasts exposed to FeSo 4 plus ascorbate. Mol Cell Biochem 311:167–177

Carlson CJ, Fan ZQ, Gordon SE, Booth FW (2001) Time course of the MAPK and PI3-kinase response within 24 h of skeletal muscle overload. J Appl Physiol 91(5):2079–2087. https://doi.org/10.1152/jappl.2001.91.5.2079

Centner T, Yano J, Kimura E, McElhinny AS, Pelin K, Witt CC, Bang ML, Trombitas K, Granzier H, Gregorio CC, Sorimachi H, Labeit S (2001) Identification of muscle specific ring finger proteins as potential regulators of the titin kinase domain. J Mol Biol 306(4):717–726. https://doi.org/10.1006/jmbi.2001.4448

Chen WS, Xu PZ, Gottlob K, Chen ML, Sokol K, Shiyanova T, Roninson I, Weng W, Suzuki R, Tobe K, Kadowaki T, Hay N (2001) Growth retardation and increased apoptosis in mice with homozygous disruption of the gene. Genes Dev 15(17):2203–2208. https://doi.org/10.1101/gad.913901

Chen YH, Rodrik V, Foster DA (2005) Alternative phospholipase D/mTOR survival signal in human breast cancer cells. Oncogene 24(4):672–679. https://doi.org/10.1038/sj.onc.1208099

Chen ZJ, Bhoj V, Seth RB (2006) Ubiquitin, TAK1 and IKK: is there a connection? Cell Death Differ 13(5):687–692. https://doi.org/10.1038/sj.cdd.4401869

Chen Y, Wang J, Fan H, Xie J, Xu L, Zhou B (2017) Phosphorylated 4E-BP1 is associated with tumor progression and adverse prognosis in colorectal cancer. Neoplasma 64(5):787–794

Cheng SW, Fryer LG, Carling D, Shepherd PR (2004) Thr2446 is a novel mammalian target of rapamycin (mTOR) phosphorylation site regulated by nutrient status. J Biol Chem 279(16):15719–15722. https://doi.org/10.1074/jbc.C300534200

Cho H, Thorvaldsen JL, Chu QW, Feng F, Birnbaum MJ (2001) Akt1/PKBα is required for normal growth but dispensable for maintenance of glucose homeostasis in mice. J Biol Chem 276(42):38349–38352. https://doi.org/10.1074/jbc.C100462200

Choi HS, Ahn JH, Park JH, Won MH, Lee CH (2016) Age-dependent changes in the protein expression levels of Redd1 and mTOR in the gerbil hippocampus during normal aging. Mol Med Rep 13(3):2409–2414. https://doi.org/10.3892/mmr.2016.4835

Christ CY, Hunt D, Hancock J, Garcia-Macedo R, Mandarino LJ, Ivy JL (2002) Exercise training improves muscle insulin resistance but not insulin receptor signaling in obese Zucker rats. J Appl Physiol (1985) 92(2):736–744. https://doi.org/10.1152/japplphysiol.00784.2001

Churchley EG, Coffey VG, Pedersen DJ, Shield A, Carey KA, Cameron-Smith D, Hawley JA (2007) Influence of preexercise muscle glycogen content on transcriptional activity of metabolic and myogenic genes in well-trained humans. J Appl Physiol 102(4):1604–1611. https://doi.org/10.1152/japplphysiol.01260.2006

Clarke MSF, Feeback DL (1996) Mechanical load induces sarcoplasmic wounding and FGF release in differentiated human skeletal muscle cultures. FASEB J 10(4):502–509. https://doi.org/10.1096/fasebj.10.4.8647349

Clarke MS, Bamman MM, Feeback DL (1998) Bed rest decreases mechanically induced myofiber wounding and consequent wound-mediated FGF release. J Appl Physiol (1985) 85(2):593–600. https://doi.org/10.1152/jappl.1998.85.2.593

Cleasby ME, Reinten TA, Cooney GJ, James DE, Kraegen EW (2007) Functional studies of Akt isoform specificity in skeletal muscle: maintained insulin sensitivity despite reduced insulin receptor substrate-1 expression. Mol Endocrinol 21(1):215–228. https://doi.org/10.1210/me.2006-0154

Cleland PJ, Appleby GJ, Rattigan S, Clark MG (1989) Exercise-induced translocation of protein kinase C and production of diacylglycerol and phosphatidic acid in rat skeletal muscle in vivo. Relationship to changes in glucose transport. J Biol Chem 264(30):17704–17711

Close GL, Kayani A, Vasilaki A, McArdle A (2005) Skeletal muscle damage with exercise and aging. Sports Med 35:413–427

Coffey VG, Zhong ZH, Shield A, Canny BJ, Chibalin AV, Zierath JR, Hawley JA (2005) Early signaling responses to divergent exercise stimuli in skeletal muscle from well-trained humans. FASEB J 19(13):190–192. https://doi.org/10.1096/fj.05-4809fje

Coffey VG, Shield A, Canny BJ, Carey KA, Cameron-Smith D, Hawley JA (2006) Interaction of contractile activity and training@@history on mRNA abundance in skeletal muscle from trained athletes. Am J Physiol-Endocrinol Metab 290(5):E849–E855. https://doi.org/10.1152/ajpendo.00299.2005

Coffey VG, Reeder DW, Lancaster GI, Yeo WK, Febbraio MA, Yaspelkis BB, Hawley JA (2007) Effect of high-frequency resistance exercise on adaptive responses in skeletal muscle. Med Sci Sports Exerc 39(12):2135–2144. https://doi.org/10.1249/mss.0b013e31815729b6

Cohen S, Brault JJ, Gygi SP, Glass DJ, Valenzuela DM, Gartner C, Latres E, Goldberg AL (2009) During muscle atrophy, thick, but not thin, filament components are degraded by MuRF1-dependent ubiquitylation. J Cell Biol 185(6):1083–1095. https://doi.org/10.1083/jcb.200901052

ConstantinTeodosiu D, Casey A, Short AH, Hultman E, Greenhaff PL (1996) The effect of repeated muscle biopsy sampling on ATP and glycogen resynthesis following exercise in man. Eur J Appl Physiol 73(1–2):186–190. https://doi.org/10.1007/Bf00262830

Coppola D, Ferber A, Miura M, Sell C, Dambrosio C, Rubin R, Baserga R (1994) A functional insulin-like growth-factor-I receptor is required for the mitogenic and transforming activities of the epidermal growth-factor receptor. Mol Cell Biol 14(7):4588–4595. https://doi.org/10.1128/Mcb.14.7.4588

Damas F, Phillips S, Vechin FC, Ugrinowitsch C (2015) A review of resistance training-induced changes in skeletal muscle protein synthesis and their contribution to hypertrophy. Sports Med 45(6):801–807. https://doi.org/10.1007/s40279-015-0320-0

Damnjanovic J, Iwasaki Y (2013) Phospholipase D as a catalyst: application in phospholipid synthesis, molecular structure and protein engineering. J Biosci Bioeng 116(3):271–280. https://doi.org/10.1016/j.jbiosc.2013.03.008

de Matos MA, Ottone VD, Duarte TC, Sampaio PFD, Costa KB, Fonseca CA, Neves MPC, Schneider SM, Moseley P, Coimbra CC, Magalhaes FD, Rocha-Vieira E, Amorim FT (2014) Exercise reduces cellular stress related to skeletal muscle insulin resistance. Cell Stress Chaperones 19(2):263–270. https://doi.org/10.1007/s12192-013-0453-8

Del Aguila LF, Krishnan RK, Ulbrecht JS, Farrell PA, Correll PH, Lang CH, Zierath JR, Kirwan JP (2000) Muscle damage impairs insulin stimulation of IRS-1, PI 3-kinase, and Akt-kinase in human skeletal muscle. Am J Physiol-Endocrinol Metab 279(1):E206–E212. https://doi.org/10.1152/ajpendo.2000.279.1.E206

Deldicque L, Atherton P, Patel R, Theisen D, Nielens H, Rennie MJ, Francaux M (2008) Decrease in Akt/PKB signalling in human skeletal muscle by resistance exercise. Eur J Appl Physiol 104(1):57–65. https://doi.org/10.1007/s00421-008-0786-7

Demontis F, Perrimon N (2010) FOXO/4E-BP signaling in Drosophila muscles regulates organism-wide proteostasis during aging. Cell 143(5):813–825. https://doi.org/10.1016/j.cell.2010.10.007

Dennis PB, Jaeschke A, Saitoh M, Fowler B, Kozma SC, Thomas G (2001) Mammalian TOR: a homeostatic ATP sensor. Science 294(5544):1102–1105. https://doi.org/10.1126/science.1063518

Dickinson JM, Rasmussen BB (2013) Amino acid transporters in the regulation of human skeletal muscle protein metabolism. Curr Opin Clin Nutr Metab Care 16(6):638–644. https://doi.org/10.1097/MCO.0b013e3283653ec5

Dickinson JM, D'Lugos AC, Naymik MA, Siniard AL, Wolfe AJ, Curtis DR, Huentelman MJ, Carroll CC (2018) Transcriptome response of human skeletal muscle to divergent exercise stimuli. J Appl Physiol 124(6):1529–1540

Dreyer HC, Fujita S, Cadenas JG, Chinkes DL, Volpi E, Rasmussen BB (2006) Resistance exercise increases AMPK activity and reduces 4E-BP1 phosphorylation and protein synthesis in human skeletal muscle. J Physiol-Lond 576(2):613–624. https://doi.org/10.1113/jphysiol.2006.113175

Durham WJ, Li YP, Gerken E, Farid M, Arbogast S, Wolfe RR, Reid MB (2004) Fatiguing exercise reduces DNA binding activity of NF-κB in skeletal muscle nuclei. J Appl Physiol 97(5):1740–1745. https://doi.org/10.1152/japplphysiol.00088.2004

Edman S, Söderlund K, Moberg M, Apró W, Blomstrand E (2019) mTORC1 signaling in individual human muscle fibers following resistance exercise in combination with intake of essential amino acids. Front Nutr 6:96. https://doi.org/10.3389/fnut.2019.00096

Eliasson J, Elfegoun T, Nilsson J, Köhnke R, Ekblom B, Blomstrand E (2006) Maximal lengthening contractions increase p70 S6 kinase phosphorylation in human skeletal muscle in the absence of nutritional supply. Am J Physiol-Endocrinol Metab 291(6):E1197–E1205. https://doi.org/10.1152/ajpendo.00141.2006

Erlandsson MC, Silfverswärd ST, Nadali M, Turkkila M, Svensson MN, Jonsson M, Andersson KM, Bokarewa MI (2017) IGF-1R signalling contributes to IL-6 production and T cell dependent inflammation in rheumatoid arthritis. Biochim Biophys Acta (BBA) Mol Basis Dis 1863(9):2158–2170

Feng LL, Li BW, Xi Y, Cai MX, Tian ZJ (2022) Aerobic exercise and resistance exercise alleviate skeletal muscle atrophy through IGF-1/IGF-1R-PI3K/Akt pathway in mice with myocardial infarction. Am J Physiol Cell Physiol 322(2):C164–C176. https://doi.org/10.1152/ajpcell.00344.2021

Finkel T, Holbrook NJ (2000) Oxidants, oxidative stress and the biology of ageing. Nature 408(6809):239–247. https://doi.org/10.1038/35041687

Florini JR (1987) Hormonal-control of muscle growth. Muscle Nerve 10(7):577–598. https://doi.org/10.1002/mus.880100702

Foletta VC, White LJ, Larsen AE, Léger B, Russell AP (2011) The role and regulation of MAFbx/atrogin-1 and MuRF1 in skeletal muscle atrophy. Pflugers Archiv-Eur J Physiol 461(3):325–335. https://doi.org/10.1007/s00424-010-0919-9

Francaux M, Demeulder B, Naslain D, Fortin R, Lutz O, Caty G, Deldicque L (2016) Aging reduces the activation of the mTORC1 pathway after resistance exercise and protein intake in human skeletal muscle: potential role of REDD1 and impaired anabolic sensitivity. Nutrients 8(1):47. https://doi.org/10.3390/nu8010047

Franchi MV, Atherton PJ, Reeves ND, Flück M, Williams J, Mitchell WK, Selby A, Valls RMB, Narici MV (2014) Architectural, functional and molecular responses to concentric and eccentric loading in human skeletal muscle. Acta Physiol 210(3):642–654. https://doi.org/10.1111/apha.12225

Frias MA, Hatipoglu A, Foster DA (2023) Regulation of mTOR by phosphatidic acid. Trends Endocrinol Metab 34(3):170–180. https://doi.org/10.1016/j.tem.2023.01.004

Fridén J, Lieber RL (2001) Eccentric exercise-induced injuries to contractile and cytoskeletal muscle fibre components. Acta Physiol Scand 171(3):321–326. https://doi.org/10.1046/j.1365-201x.2001.00834.x

Fry CS, Drummond MJ, Glynn EL, Dickinson JM, Gundermann DM, Timmerman KL, Walker DK, Volpi E, Rasmussen BB (2013) Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults. J Gerontol Ser A Biol Sci Med Sci 68(5):599–607. https://doi.org/10.1093/gerona/gls209

Gallagher PM, Touchberry CD, Teson K, McCabe E, Tehel M, Wacker MJ (2013) Effects of an acute bout of resistance exercise on fiber-type specific to and expression. Appl Physiol Nutr Metab-Physiologie Appliquee Nutrition Et Metabolisme 38(5):581–586. https://doi.org/10.1139/apnm-2012-0301

Gardiner J, Collings DA, Harper JD, Marc J (2003) The effects of the phospholipase D-antagonist 1-butanol on seedling development and microtubule organisation in Arabidopsis. Plant Cell Physiol 44(7):687–696

Glynn EL, Fry CS, Drummond MJ, Dreyer HC, Dhanani S, Volpi E, Rasmussen BB (2010) Muscle protein breakdown has a minor role in the protein anabolic response to essential amino acid and carbohydrate intake following resistance exercise. FASEB J 24:740–745

Greer EL, Oskoui PR, Banko MR, Maniar JM, Gygi MP, Gygi SP, Brunet A (2007) The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. J Biol Chem 282(41):30107–30119. https://doi.org/10.1074/jbc.M705325200

Gual P, Le Marchand-Brustel Y, Tanti JF (2005) Positive and negative regulation of insulin signaling through IRS-1 phosphorylation. Biochimie 87(1):99–109. https://doi.org/10.1016/j.biochi.2004.10.019

Guijarro LG, Cano-Martínez D, Toledo-Lobo MV, Salinas PS, Chaparro M, Gómez-Lahoz AM, Zoullas S, Rodríguez-Torres R, Román ID, Monasor LS (2021) Relationship between IGF-1 and body weight in inflammatory bowel diseases: cellular and molecular mechanisms involved. Biomed Pharmacother 144:112239

Hameed M, Orrell R, Cobbold M, Goldspink G, Harridge S (2003) Expression of IGF-I splice variants in young and old human skeletal muscle after high resistance exercise. J Physiol 547(Pt 1):247–254. https://doi.org/10.1113/jphysiol.2002.032136

Hamilton DL, Philp A, MacKenzie MG, Baar K (2010) A limited role for PI(3, 4, 5) P3 regulation in controlling skeletal muscle mass in response to resistance exercise. PLoS ONE 5(7):e11624. https://doi.org/10.1371/journal.pone.0011624

Harrington LS, Findlay GM, Gray A, Tolkacheva T, Wigfield S, Rebholz H, Barnett J, Leslie NR, Cheng S, Shepherd PR, Gout I, Downes CP, Lamb RE (2004) The TSC1-2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. J Cell Biol 166(2):213–223. https://doi.org/10.1083/jcb.200403069

Hather BM, Tesch PA, Buchanan P, Dudley GA (1991) Influence of eccentric actions on skeletal-muscle adaptations to resistance training. Acta Physiol Scand 143(2):177–185. https://doi.org/10.1111/j.1748-1716.1991.tb09219.x

Heemskerk VH, Daemen MA, Buurman WA (1999) Insulin-like growth factor-1 (IGF-1) and growth hormone (GH) in immunity and inflammation. Cytokine Growth Factor Rev 10(1):5–14

Heinemeier KM, Olesen JL, Schjerling P, Haddad F, Langberg H, Baldwin KM, Kjaer M (2007) Short-term strength training and the expression of myostatin and IGF-I isoforms in rat muscle and tendon: differential effects of specific contraction types. J Appl Physiol 102(2):573–581

Hernandez JM, Fedele MJ, Farrell PA (2000) Time course evaluation of protein synthesis and glucose uptake after acute resistance exercise in rats. J Appl Physiol 88(3):1142–1149. https://doi.org/10.1152/jappl.2000.88.3.1142

Higginson J, Wackerhage H, Woods N, Schjerling P, Ratkevicius A, Grunnet N, Quistorff B (2002) Blockades of mitogen-activated protein kinase and calcineurin both change fibre-type markers in skeletal muscle culture. Pflugers Archiv-Eur J Physiol 445(3):437–443. https://doi.org/10.1007/s00424-002-0939-1

Hiraoka E, Kawashima S, Takahashi T, Rikitake Y, Kitamura T, Ogawa W, Yokoyama M (2001) TNF-α induces protein synthesis through PI3-kinase-Akt/PKB pathway in cardiac myocytes. Am J Physiol-Heart Circ Physiol 280(4):H1861–H1868

Ho RC, Hirshman MF, Li YF, Cai DS, Farmer JR, Aschenbach WG, Witczak CA, Shoelson SE, Goodyear LJ (2005) Regulation of IκB kinase and NF-κB in contracting adult rat skeletal muscle. Am J Physiol Cell Physiol 289(4):C794–C801. https://doi.org/10.1152/ajpcell.00632.2004

Hody S, Croisier JL, Bury T, Rogister B, Leprince P (2019) Eccentric muscle contractions: risks and benefits. Front Physiol 10:536. https://doi.org/10.3389/fphys.2019.00536

Hornberger TA (2011) Mechanotransduction and the regulation of mTORC1 signaling in skeletal muscle. Int J Biochem Cell Biol 43(9):1267–1276. https://doi.org/10.1016/j.biocel.2011.05.007

Hornberger TA, Chien S (2006) Mechanical stimuli and nutrients regulate rapamycin-sensitive signaling through distinct mechanisms in skeletal muscle. J Cell Biochem 97(6):1207–1216. https://doi.org/10.1002/jcb.20671

Hornberger TA, Chu WK, Mak YW, Hsiung JW, Huang SA, Chien S (2006) The role of phospholipase D and phosphatidic acid in the mechanical activation of mTOR signaling in skeletal muscle. Proc Natl Acad Sci USA 103(12):4741–4746. https://doi.org/10.1073/pnas.0600678103

Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM (1996) IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 271(5249):665–668. https://doi.org/10.1126/science.271.5249.665

Hu Y, Baud V, Delhase M, Zhang P, Deerinck T, Ellisman M, Johnson R, Karin M (1999) Abnormal morphogenesis but intact IKK activation in mice lacking the IKKalpha subunit of IkappaB kinase. Science 284(5412):316–320. https://doi.org/10.1126/science.284.5412.316

Hunter RB, Stevenson EJ, Koncarevic A, Mitchell-Felton H, Essig DA, Kandarian SC (2002) Activation of an alternative NF-κB pathway in skeletal muscle during disuse atrophy. FASEB J 16(6):529–538. https://doi.org/10.1096/fj.01-0866com

Hyldahl RD, Xin L, Hubal MJ, Moeckel-Cole S, Chipkin S, Clarkson PM (2011) Activation of nuclear factor-κB following muscle eccentric contractions in humans is localized primarily to skeletal muscle-residing pericytes. FASEB J 25(9):2956–2966. https://doi.org/10.1096/fj.10-177105

Ito Y, Daitoku H, Fukamizu A (2009) Foxo1 increases pro-inflammatory gene expression by inducing C/EBPβ in TNF-α-treated adipocytes. Biochem Biophys Res Commun 378(2):290–295

Jaafar R, De Larichaudy J, Chanon S, Euthine V, Durand C, Naro F, Bertolino P, Vidal H, Lefai E, Némoz G (2013) Phospholipase D regulates the size of skeletal muscle cells through the activation of mTOR signaling. Cell Commun Signal 11:55. https://doi.org/10.1186/1478-811x-11-55

Jansova D, Koncicka M, Tetkova A, Cerna R, Malik R, Del Llano E, Kubelka M, Susor A (2017) Regulation of 4E-BP1 activity in the mammalian oocyte. Cell Cycle 16(10):927–939

Jenkins GM, Frohman MA (2005) Phospholipase D: a lipid centric review. Cell Mol Life Sci 62(19–20):2305–2316. https://doi.org/10.1007/s00018-005-5195-z

Ji L, Gomezcabrera MC, Steinhafel N, Vina J (2004) Acute exercise activates nuclear factor (NF)-κB signaling pathway in rat skeletal muscle. FASEB J 18(13):1499–1506. https://doi.org/10.1096/fj.04-1846com

Ji F, Park JH, Rheem H, Kim J-H (2024) Overlapping and distinct physical and biological phenotypes related to pure frailty and frail obesity. Biosci Rep. https://doi.org/10.1042/BSR20240784

Ji F, Lee HS, Lee H, Kim J-H (2025) The impact of frailty syndrome on skeletal muscle histology: preventive effects of exercise. FEBS Open Bio. https://doi.org/10.1002/2211-5463.70049

Joanisse S, Lim C, McKendry J, McLeod JC, Stokes T, Phillips SM (2020) Recent advances in understanding resistance exercise training-induced skeletal muscle hypertrophy in humans. F1000Res 9:141. https://doi.org/10.12688/f1000research.21588.1

Jorge MLMP, de Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz ALD, Resende ES, Ropelle ER, Carvalheira JB, Espindola FS, Jorge PT, Geloneze B (2011) The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. Metab-Clin Exp 60(9):1244–1252. https://doi.org/10.1016/j.metabol.2011.01.006

Jorgensen SB, Wojtaszewski JFP, Viollet B, Andreelli F, Birk JB, Hellsten Y, Schjerling P, Vaulont S, Neufer PD, Richter EA, Pilegaard H (2005) Effects of α-AMPK knockout on exercise-induced gene

activation in mouse skeletal muscle. FASEB J 19(7):1146–1148. https://doi.org/10.1096/fj.04-3144fje

Kääriäinen M, Nissinen L, Kaufman S, Sonnenberg A, Järvinen M, Heino J, Kalimo H (2002) Expression of α7β1 integrin splicing variants during skeletal muscle regeneration. Am J Pathol 161(3):1023–1031. https://doi.org/10.1016/S0002-9440(10)64263-0

Kakigi R, Naito H, Ogura Y, Kobayashi H, Saga N, Ichinoseki-Sekine N, Yoshihara T, Katamoto S (2011) Heat stress enhances mTOR signaling after resistance exercise in human skeletal muscle. J Physiol Sci 61(2):131–140. https://doi.org/10.1007/s12576-010-0130-y

Kamei Y, Miura S, Ezaki O (2005) Skeletal muscle FOXO1 (FKHR)-transgenic mice have less skeletal muscle mass, down-regulated type I (slow twitch/red muscle) fiber genes, and impaired glycemic control. FASEB J 19(4):A467–A467

Kanety H, Feinstein R, Papa MZ, Hemi R, Karasik A (1995) Tumor-necrosis-factor-alpha induced phosphorylation of insulin-receptor substrate-1 (Irs-1)—possible mechanism for suppression of insulin-stimulated tyrosine phosphorylation of Irs-1. J Biol Chem 270(40):23780–23784. https://doi.org/10.1074/jbc.270.40.23780

Katiyar S, Liu E, Knutzen CA, Lang ES, Lombardo CR, Sankar S, Toth JI, Petroski MD, Ronai Z, Chiang GG (2009) REDD1, an inhibitor of mTOR signalling, is regulated by the CUL4A-DDB1 ubiquitin ligase. EMBO Rep 10(8):866–872. https://doi.org/10.1038/embor.2009.93

Kazior Z, Willis SJ, Moberg M, Apró W, Calbet JAL, Holmberg HC, Blomstrand E (2016) Endurance exercise enhances the effect of strength training on muscle fiber size and protein expression of Akt and mTOR. PLoS ONE 11(2):e0149082. https://doi.org/10.1371/journal.pone.0149082

Khamzina L, Veilleux A, Bergeron S, Marette A (2005) Increased activation of the mammalian target of rapamycin pathway in liver and skeletal muscle of obese rats: possible involvement in obesity-linked insulin resistance. Endocrinology 146(3):1473–1481. https://doi.org/10.1210/en.2004-0921

Kido Y, Burks DJ, Withers D, Bruning JC, Kahn CR, White MF, Accili D (2000) Tissue-specific insulin resistance in mice with mutations in the insulin receptor, IRS-1, and IRS-2. J Clin Investig 105(2):199–205. https://doi.org/10.1172/Jci7917

Kido K, Ato S, Yokokawa T, Makanae Y, Sato K, Fujita S (2016) Acute resistance exercise-induced IGF1 expression and subsequent GLUT4 translocation. Physiol Rep 4(16):e12907. https://doi.org/10.14814/phy2.12907

Kim DH, Lee B, Lee J, Kim ME, Lee JS, Chung JH, Yu BP, Dong HH, Chung HY (2019) FoxO6-mediated IL-1β induces hepatic insulin resistance and age-related inflammation via the TF/PAR2 pathway in aging and diabetic mice. Redox Biol 24:101184

Kirwan JP, del Aguila LF (2003) Insulin signalling, exercise and cellular integrity. Biochem Soc Trans 31:1281–1285

Koopman R, Zorenc AH, Gransier RJ, Cameron-Smith D, van Loon LJ (2006) Increase in S6K1 phosphorylation in human skeletal muscle following resistance exercise occurs mainly in type II muscle fibers. Am J Physiol-Endocrinol Metab 290(6):E1245–E1252. https://doi.org/10.1152/ajpendo.00530.2005

Kops GJPL, de Ruiter ND, De Vries-Smits AMM, Powell DR, Bos JL, Burgering BMT (1999) Direct control of the Forkhead transcription factor AFX by protein kinase B. Nature 398(6728):630–634. https://doi.org/10.1038/19328

Kostek MC, Chen Y-W, Cuthbertson DJ, Shi R, Fedele MJ, Esser KA, Rennie MJ (2007) Gene expression responses over 24 h to lengthening and shortening contractions in human muscle: major changes in CSRP3, MUSTN1, SIX1, and FBXO32. Physiol Genomics 31(1):42–52

Kragstrup TW, Kjaer M, Mackey AL (2011) Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. Scand J Med Sci Sports 21(6):749–757. https://doi.org/10.1111/j.1600-0838.2011.01377.x

Krug ALO, Macedo AG, Zago AS, Rush JWE, Santos CF, Amaral SL (2016) High-intensity resistance training attenuates dexamethasone-induced muscle atrophy. Muscle Nerve 53(5):779–788. https://doi.org/10.1002/mus.24906

Lagirand-Cantaloube J, Cornille K, Csibi A, Batonnet-Pichon S, Leibovitch MP, Leibovitch SA (2009) Inhibition of Atrogin-1/MAFbx mediated MyoD proteolysis prevents skeletal muscle atrophy. PLoS ONE 4(3):e4973. https://doi.org/10.1371/journal.pone.0004973

Lang CH, Frost RA (2007) Sepsis-induced suppression of skeletal muscle translation initiation mediated by tumor necrosis factor α. Metab-Clin Exp 56(1):49–57. https://doi.org/10.1016/j.metabol.2006.08.025

Lang CH, Frost RA, Nairn AC, MacLean DA, Vary TC (2002) TNF-α impairs heart and skeletal muscle protein synthesis by altering translation initiation. Am J Physiol-Endocrinol Metab 282(2):E336–E347. https://doi.org/10.1152/ajpendo.00366.2001

LaStayo PC, Pierotti DJ, Pifer J, Hoppeler H, Lindstedt SL (2000) Eccentric ergometry: increases in locomotor muscle size and strength at low training intensities. Am J Physiol-Regul Integr Comp Physiol 278(5):R1282–R1288. https://doi.org/10.1152/ajpregu.2000.278.5.R1282

LaStayo PC, Woolf JM, Lewek MD, Snyder-Mackler L, Reich T, Lindstedt SL (2003) Eccentric muscle contractions: their contribution to injury, prevention, rehabilitation, and sport. J Orthop Sports Phys Ther 33(10):557–571. https://doi.org/10.2519/jospt.2003.33.10.557

Lee SJ (2004) Regulation of muscle mass by myostatin. Annu Rev Cell Dev Biol 20:61–86. https://doi.org/10.1146/annurev.cellbio.20.012103.135836

Lee S, Barton ER, Sweeney HL, Farrar RP (2004) Viral expression of insulin-like growth factor-I enhances muscle hypertrophy in resistance-trained rats. J Appl Physiol 96(3):1097–1104. https://doi.org/10.1152/japplphysiol.00479.2003

Lee K, Ochi E, Song H, Nakazato K (2015) Activation of AMP-activated protein kinase induce expression of FoxO1, FoxO3a, and myostatin after exercise-induced muscle damage. Biochem Biophys Res Commun 466(3):289–294. https://doi.org/10.1016/j.bbrc.2015.08.126

Léger B, Cartoni R, Praz M, Lamon S, Dériaz O, Crettenand A, Gobelet C, Rohmer P, Konzelmann M, Luthi F, Russell AP (2006) Akt signalling through GSK-3β, mTOR and Foxo1 is involved in human skeletal muscle hypertrophy and atrophy. J Physiol-Lond 576(3):923–933. https://doi.org/10.1113/jphysiol.2006.116715

Li W, Jeong JH, Park HG, Lee YR, Li M, Lee SK (2014) Endurance exercise training inhibits neointimal formation via enhancement of FOXOs expression in balloon-induced atherosclerosis rat model. J Exerc Nutr Biochem 18(1):105–110. https://doi.org/10.5717/jenb.2014.18.1.105

Li BW, Feng LL, Wu XN, Cai MX, Yu JJ, Tian ZJ (2022) Effects of different modes of exercise on skeletal muscle mass and function and IGF-1 signaling during early aging in mice. J Exp Biol 225(21):jeb244650. https://doi.org/10.1242/jeb.244650

Liao P, Zhou J, Ji LL, Zhang Y (2010) Eccentric contraction induces inflammatory responses in rat skeletal muscle: role of tumor necrosis factor-alpha. Am J Physiol Regul Integr Comp Physiol 298(3):R599-607. https://doi.org/10.1152/ajpregu.00480.2009

Lieber RL (1992) Skeletal muscle structure and function: implications for rehabilitation and sports medicine. Williams & Wilkins

Liu J, Kim J-H (2024) The effects of nordic walking on the cardiovascular risk factors in older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr 2024:105663

Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A (1993) Mice carrying null mutations of the genes encoding insulin-like growth

factor-I (Igf-1) and type-1 Igf receptor (Igf1r). Cell 75(1):59–72. https://doi.org/10.1016/0092-8674(93)90679-K

Liu CM, Yang Z, Liu CW, Wang R, Tien P, Dale R, Sun LQ (2007) Effect of RNA oligonucleotide targeting Foxo-1 on muscle growth in normal and cancer cachexia mice. Cancer Gene Ther 14(12):945–952. https://doi.org/10.1038/sj.cgt.7701091

Liu J, Ji F, Lee H, Kim J-H (2025) Association between the appendicular skeletal muscle mass-to-visceral fat area ratio and bone mineral density and osteoporosis: a cross-sectional study. Exp Gerontol 2025:112772

Louis E, Raue U, Jemiolo B, Yang Y, Trappe S (2007) Time course of proteolytic, apoptotic, and cytokine gene expression after resistance exercise in humans. Wiley Online Library

Lundell LS, Massart J, Altıntaş A, Krook A, Zierath JR (2019) Regulation of glucose uptake and inflammation markers by FOXO1 and FOXO3 in skeletal muscle. Mol Metab 20:79–88

Luo L, Lu AM, Wang Y, Hong A, Chen YL, Hu J, Li XN, Qin ZH (2013) Chronic resistance training activates autophagy and reduces apoptosis of muscle cells by modulating IGF-1 and its receptors, Akt/mTOR and Akt/FOXO3a signaling in aged rats. Exp Gerontol 48(4):427–436. https://doi.org/10.1016/j.exger.2013.02.009

Macedo AG, Krug ALO, Herrera NA, Zago AS, Rush JWE, Amaral SL (2014) Low-intensity resistance training attenuates dexamethasone-induced atrophy in the flexor hallucis longus muscle. J Steroid Biochem Mol Biol 143:357–364. https://doi.org/10.1016/j.jsbmb.2014.05.010

Mammucari C, Milan G, Romanello V, Masiero E, Rudolf R, Del Piccolo P, Burden SJ, Di Lisi R, Sandri C, Zhao J, Goldberg AL, Schiaffino S, Sandri M (2007) FoxO3 controls autophagy in skeletal muscle in vivo. Cell Metab 6(6):458–471. https://doi.org/10.1016/j.cmet.2007.11.001

Martineau LC, Gardiner PF (2001) Insight into skeletal muscle mechanotransduction: MAPK activation is quantitatively related to tension. J Appl Physiol 91(2):693–702

Mascher H, Tannerstedt J, Brink-Elfegoun T, Ekblom B, Gustafsson T, Blomstrand E (2008) Repeated resistance exercise training induces different changes in mRNA expression of MAFbx and MuRF-1 in human skeletal muscle. Am J Physiol-Endocrinol Metab 294(1):E43–E51

Matheny RW, Merritt E, Zannikos SV, Farrar RP, Adamo ML (2009) Serum IGF-I-deficiency does not prevent compensatory skeletal muscle hypertrophy in resistance exercise. Exp Biol Med (Maywood) 234(2):164–170. https://doi.org/10.3181/0808-RM-251

Mazo CE, D'Lugos AC, Sweeney KR, Haus JM, Angadi SS, Carroll CC, Dickinson JM (2021) The effects of acute aerobic and resistance exercise on mTOR signaling and autophagy markers in untrained human skeletal muscle. Eur J Appl Physiol 121(10):2913–2924. https://doi.org/10.1007/s00421-021-04758-6

McGlory C, Devries MC, Phillips SM (2017) Skeletal muscle and resistance exercise training; the role of protein synthesis in recovery and remodeling. J Appl Physiol (1985) 122(3):541–548. https://doi.org/10.1152/japplphysiol.00613.2016

McKendry J, Stokes T, Mcleod JC, Phillips SM (2021) Resistance exercise, aging, disuse, and muscle protein metabolism. Compr Physiol 11(3):2249–2278. https://doi.org/10.1002/cphy.c200029

Mcleod JC, Stokes T, Phillips SM (2019) Resistance exercise training as a primary countermeasure to age-related chronic disease. Front Physiol 10:645. https://doi.org/10.3389/fphys.2019.00645

McLeod JC, Currier BS, Lowisz CV, Phillips SM (2024) The influence of resistance exercise training prescription variables on skeletal muscle mass, strength, and physical function in healthy adults: an umbrella review. J Sport Health Sci 13(1):47–60. https://doi.org/10.1016/j.jshs.2023.06.005

Mehri S, Chaaba R, Finsterer J, Khamlaoui W, Hammami S, Hammami M (2023) Relevance of oxidative stress biomarkers, hemoglobin A1c, troponin-I, and angiotensin-converting enzyme metabolism to blood pressure in acute myocardial infarction: a case–control study. Redox Rep 28(1):2209360. https://doi.org/10.1080/13510002.2023.2209360

Merz KE, Thurmond DC (2011) Role of skeletal muscle in insulin resistance and glucose uptake. Compr Physiol 10(3):785–809

Meyer M, Pahl HL, Baeuerle PA (1994) Regulation of the transcription factors NF-kappa B and AP-1 by redox changes. Chem Biol Interact 91(2–3):91–100. https://doi.org/10.1016/0009-2797(94)90029-9

Mitra A, Luna JI, Marusina AI, Merleev A, Kundu-Raychaudhuri S, Fiorentino D, Raychaudhuri SP, Maverakis E (2015) Dual mTOR inhibition is required to prevent TGF-β-mediated fibrosis: implications for scleroderma. J Investig Dermatol 135(11):2873–2876. https://doi.org/10.1038/jid.2015.252

Møller AB, Vendelbo MH, Rahbek SK, Clasen BF, Schjerling P, Vissing K, Jessen N (2013) Resistance exercise, but not endurance exercise, induces IKKβ phosphorylation in human skeletal muscle of training-accustomed individuals. Pflugers Arch 465(12):1785–1795. https://doi.org/10.1007/s00424-013-1318-9

Morino K, Neschen S, Bilz S, Sono S, Tsirigotis D, Reznick RM, Moore I, Nagai Y, Samuel V, Sebastian D, White M, Philbrick W, Shulman GI (2008) Muscle-specific IRS-1 Ser→Ala transgenic mice are protected from fat-induced insulin resistance in skeletal muscle. Diabetes 57(10):2644–2651. https://doi.org/10.2337/db06-0454

Muñoz VR, Gaspar RC, Severino MB, Macêdo APA, Simabuco FM, Ropelle ER, Cintra DE, da Silva ASR, Kim YB, Pauli JR (2021) Exercise counterbalances Rho/ROCK2 signaling impairment in the skeletal muscle and ameliorates insulin sensitivity in obese mice. Front Immunol 12:702025. https://doi.org/10.3389/fimmu.2021.702025

Murgia M, Serrano AL, Calabria E, Pallafacchina G, Lomo T, Schiaffino S (2000) Ras is involved in nerve-activity-dependent regulation of muscle genes. Nat Cell Biol 2(3):142–147. https://doi.org/10.1038/35004013

Musarò A, McCullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M, Barton ER, Sweeney HL, Rosenthal N (2001) Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. Nat Genet 27(2):195–200. https://doi.org/10.1038/84839

Nader GA, Esser KA (2001) Intracellular signaling specificity in skeletal muscle in response to different modes of exercise. J Appl Physiol 90(5):1936–1942. https://doi.org/10.1152/jappl.2001.90.5.1936

Nagasao J, Fukasawa H, Yoshioka K, Fujimura N, Kobayashi M, Tsunemi Y, Nomoto A, Mitsui S, Murata H, Yokoyama I, Komiya Y, Arihara K (2022) Research Note: Expression of IGF-1 and IGF-1 receptor proteins in skeletal muscle fiber types in chickens with hepatic fibrosis. Poultry Sci 101:102045. https://doi.org/10.1016/j.psj.2022.102045

Nedergaard A, Vissing K, Overgaard K, Kjaer M, Schjerling P (2007) Expression patterns of atrogenic and ubiquitin proteasome component genes with exercise: effect of different loading patterns and repeated exercise bouts. J Appl Physiol 103(5):1513–1522. https://doi.org/10.1152/japplphysiol.01445.2006

Newham DJ, Mcphail G, Mills KR, Edwards RHT (1983) Ultrastructural-changes after concentric and eccentric contractions of human-muscle. J Neurol Sci 61(1):109–122. https://doi.org/10.1016/0022-510x(83)90058-8

Ni YG, Berenji K, Wang N, Oh M, Sachan N, Dey A, Cheng J, Lu GR, Morris DJ, Castrillon DH, Gerard RD, Rothermel BA, Hill JA (2006) Foxo transcription factors blunt cardiac hypertrophy by

inhibiting calcineurin signaling. Circulation 114(11):1159–1168. https://doi.org/10.1161/Circulationaha.106.637124
Novosyadlyy R, Lelbach A, Sheikh N, Tron K, Pannem R, Ramadori G, Scharf J-G (2009) Temporal and spatial expression of IGF-I and IGFBP-1 during acute-phase response induced by localized inflammation in rats. Growth Hormon IGF Res 19(1):51–60
Ochi E, Ishii N, Nakazato K (2010) Time course change of IGF1/Akt/mTOR/p70s6k pathway activation in rat gastrocnemius muscle during repeated bouts of eccentric exercise. J Sports Sci Med 9(2):170
Ogawa K, Sanada K, Machida S, Okutsu M, Suzuki K (2010) Resistance exercise training-induced muscle hypertrophy was associated with reduction of inflammatory markers in elderly women. Mediators Inflamm 2010(1):171023
Ohanna M, Sobering AK, Lapointe T, Lorenzo L, Praud C, Petroulakis E, Sonenberg N, Kelly PA, Sotiropoulos A, Pende M (2005) Atrophy of S6K1−/− skeletal muscle cells reveals distinct mTOR effectors for cell cycle and size control. Nat Cell Biol 7(3):286–294. https://doi.org/10.1038/ncb1231
Oishi Y, Ogata T, Ohira Y, Roy RR (2019) Phosphorylated ERK1/2 protein levels are closely associated with the fast fiber phenotypes in rat hindlimb skeletal muscles. Pflugers Arch-Eur J Physiol 471(7):971–982. https://doi.org/10.1007/s00424-019-02278-z
O'Neil TK, Duffy LR, Frey JW, Hornberger TA (2009) The role of phosphoinositide 3-kinase and phosphatidic acid in the regulation of mammalian target of rapamycin following eccentric contractions. J Physiol-Lond 587(14):3691–3701. https://doi.org/10.1113/jphysiol.2009.173609
Osório Alves J, Matta Pereira L, Cabral Coutinho do Rêgo Monteiro I, Pontes dos Santos LH, Soares Marreiros Ferraz A, Carneiro Loureiro AC, Calado Lima C, Leal-Cardoso JH, Pires Carvalho D, Soares Fortunato R (2020) Strenuous acute exercise induces slow and fast twitch-dependent NADPH oxidase expression in rat skeletal muscle. Antioxidants 9(1):57
Pagès G, Guérin S, Grall D, Bonino FD, Smith A, Anjuere F, Auberger P, Pouysségur J (1999) Defective thymocyte maturation in p44 MAP kinase (Erk 1) knockout mice. Science 286(5443):1374–1377. https://doi.org/10.1126/science.286.5443.1374
Parise G, Brose AN, Tarnopolsky MA (2005) Resistance exercise training decreases oxidative damage to DNA and increases cytochrome oxidase activity in older adults. Exp Gerontol 40(3):173–180
Park C, Lee S, Cho IH, Lee HK, Kim D, Choi SY, Oh SB, Park K, Kim JS, Lee SJ (2006) TLR3-mediated signal induces proinflammatory cytokine and chemokine gene expression in astrocytes: differential signaling mechanisms of TLR3-induced IP-10 and IL-8 gene expression. Glia 53(3):248–256
Parkington JD, Siebert AP, LeBrasseur NK, Fielding RA (2003) Differential activation of mTOR signaling by contractile activity in skeletal muscle. Am J Physiol-Regul Integr Comp Physiol 285(5):R1086–R1090. https://doi.org/10.1152/ajpregu.00324.2003
Pellegrino MA, D'Antona G, Bortolotto S, Boschi F, Pastoris O, Bottinelli R, Polla B, Reggiani C (2004) Clenbuterol antagonizes glucocorticoid-induced atrophy and fibre type transformation in mice. Exp Physiol 89(1):89–100. https://doi.org/10.1113/expphysiol.2003.002609
Peñailillo L, Blazevich A, Numazawa H, Nosaka K (2013) Metabolic and muscle damage profiles of concentric versus repeated eccentric cycling. Med Sci Sports Exerc 45(9):1773–1781. https://doi.org/10.1249/MSS.0b013e31828f8a73
Pende M, Um SH, Mieulet V, Sticker M, Goss VL, Mestan J, Mueller M, Fumagalli S, Kozma SC, Thomas G (2004) mice exhibit perinatal lethality and rapamycin-sensitive 5′-terminal oligopyrimidine mRNA translation and reveal a mitogen-activated protein kinase-dependent S6 kinase pathway. Mol Cell Biol 24(8):3112–3124. https://doi.org/10.1128/Mcb.24.8.3112-3124.2004
Perrey S, Betik A, Candau R, Rouillon JD, Hughson RL (2001) Comparison of oxygen uptake kinetics during concentric and eccentric cycle exercise. J Appl Physiol 91(5):2135–2142. https://doi.org/10.1152/jappl.2001.91.5.2135
Philp A, Hamilton DL, Baar K (2011) Signals mediating skeletal muscle remodeling by resistance exercise: PI3-kinase independent activation of mTORC1. J Appl Physiol 110(2):561–568. https://doi.org/10.1152/japplphysiol.00941.2010
Rahbek SK, Farup J, Moller AB, Vendelbo MH, Holm L, Jessen N, Vissing K (2014) Effects of divergent resistance exercise contraction mode and dietary supplementation type on anabolic signalling, muscle protein synthesis and muscle hypertrophy. Amino Acids 46(10):2377–2392. https://doi.org/10.1007/s00726-014-1792-1
Raingeaud J, Gupta S, Rogers JS, Dickens M, Han JH, Ulevitch RJ, Davis RJ (1995) Pro-Inflammatory cytokines and environmental-stress cause P38 mitogen-activated protein-kinase activation by dual phosphorylation on tyrosine and threonine. J Biol Chem 270(13):7420–7426. https://doi.org/10.1074/jbc.270.13.7420
Rasmussen BB (2009) Phosphatidic acid: a novel mechanical mechanism for how resistance exercise activates mTORC1 signalling. J Physiol-Lond 587(14):3415–3416. https://doi.org/10.1113/jphysiol.2009.176453
Raue U, Jemiolo B, Conley T, Louis E, Trappe S (2007) Fiber type specific myogenic and proteolytic gene expression after acute resistance exercise in young women. Wiley Online Library
Ribeiro MBT, Guzzoni V, Hord JM, Lopes GN, Marqueti RD, de Andrade RV, Selistre-de-Araujo HS, Durigan JLQ (2019) Resistance training regulates gene expression of molecules associated with intramyocellular lipids, glucose signaling and fiber size in old rats (vol 7, 8593, 2017). Sci Rep 9:6383. https://doi.org/10.1038/s41598-019-42462-w
Risson V, Mazelin L, Roceri M, Sanchez H, Moncollin V, Corneloup C, Richard-Bulteau H, Vignaud A, Baas D, Defour A, Freyssenet D, Tanti JF, Le-Marchand-Brustel Y, Ferrier B, Conjard-Duplany A, Romanino K, Bauché S, Hantaï D, Mueller M, Gangloff YG (2009) Muscle inactivation of mTOR causes metabolic and dystrophin defects leading to severe myopathy. J Cell Biol 187(6):859–874. https://doi.org/10.1083/jcb.200903131
Roberts M, Dalbo V, Sunderland K, Poole C, Hassell S, Bemben D, Cramer J, Stout J, Kerksick C (2010) IGF-1 splice variant and IGF-1 peptide expression patterns in young and old human skeletal muscle prior to and following sequential exercise bouts. Eur J Appl Physiol 110:961–969. https://doi.org/10.1007/s00421-010-1588-2
Sabouri M, Taghibeikzadehbadr P, Shabkhiz F, Izanloo Z, Shaghaghi FA (2022) Effect of eccentric and concentric contraction mode on myogenic regulatory factors expression in human vastus lateralis muscle. J Muscle Res Cell Motil 43(1):9–20. https://doi.org/10.1007/s10974-021-09613-x
Sadri S, Sharifi G, Dehkordi KJ (2021) Nano branched-chain amino acids enhance the effect of uphill (concentric) and downhill (eccentric) treadmill exercise on muscle gene expression of Akt and mTOR on aged rats. Sport Sci Health. https://doi.org/10.1007/s11332-021-00828-6
Sakamoto K, Hirshman MF, Aschenbach WG, Goodyear LJ (2002) Contraction regulation of Akt in rat skeletal muscle. J Biol Chem 277(14):11910–11917. https://doi.org/10.1074/jbc.M112410200
Saliou C, Kitazawa M, McLaughlin L, Yang J-P, Lodge JK, Tetsuka T, Iwasaki K, Cillard J, Okamoto T, Packer L (1999) Antioxidants modulate acute solar ultraviolet radiation-induced NF-kappa-B activation in a human keratinocyte cell line. Free Radical Biol Med 26(1–2):174–183

Sanchez AM (2015) FoxO transcription factors and endurance training: a role for FoxO1 and FoxO3 in exercise-induced angiogenesis. J Physiol 593(2):363–364. https://doi.org/10.1113/jphysiol.2014.285999

Sanchez AMJ, Csibi A, Raibon A, Cornille K, Gay S, Bernardi H, Candau R (2012) AMPK promotes skeletal muscle autophagy through activation of forkhead FoxO3a and interaction with Ulk1. J Cell Biochem 113(2):695–710. https://doi.org/10.1002/jcb.23399

Sandri M, Sandri C, Gilbert A, Skurk C, Calabria E, Picard A, Walsh K, Schiaffino S, Lecker SH, Goldberg AL (2004) Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. Cell 117(3):399–412. https://doi.org/10.1016/S0092-8674(04)00400-3

Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, Goldberg AL, Spiegelman BM (2006) PGC-1α protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. Proc Natl Acad Sci 103(44):16260–16265

Sardeli AV, Tomeleri CM, Cyrino ES, Fernhall B, Cavaglieri CR, Chacon-Mikahil MPT (2018) Effect of resistance training on inflammatory markers of older adults: a meta-analysis. Exp Gerontol 111:188–196

Schachter TN, Shen T, Liu Y, Schneider MF (2012) Kinetics of nuclear-cytoplasmic translocation of Foxo1 and Foxo3A in adult skeletal muscle fibers. Am J Physiol Cell Physiol 303(9):C977–C990

Schenk H, Klein M, Erdbrügger W, Dröge W, Schulze-Osthoff K (1994) Distinct effects of thioredoxin and antioxidants on the activation of transcription factors NF-kappa B and AP-1. Proc Natl Acad Sci 91(5):1672–1676

Schröfelbauer B, Polley S, Behar M, Ghosh G, Hoffmann A (2012) NEMO ensures signaling specificity of the pleiotropic IKKβ by directing its kinase activity toward IκBα. Mol Cell 47(1):111–121

Shi H, Scheffler JM, Pleitner JM, Zeng C, Park S, Hannon KM, Grant AL, Gerrard DE (2008) Modulation of skeletal muscle fiber type by mitogen-activated protein kinase signaling. FASEB J 22(8):2990–3000. https://doi.org/10.1096/fj.07-097600

Sil AK, Maeda S, Sano Y, Roop DR, Karin M (2004) IκB kinase-α acts in the epidermis to control skeletal and craniofacial morphogenesis. Nature 428(6983):660–664

Song WK, Wang W, Foster RF, Bielser DA, Kaufman SJ (1992) H36-alpha 7 is a novel integrin alpha chain that is developmentally regulated during skeletal myogenesis. J Cell Biol 117(3):643–657. https://doi.org/10.1083/jcb.117.3.643

Song XM, Ryder JW, Kawano Y, Chibalin AV, Krook A, Zierath JR (1999) Muscle fiber type specificity in insulin signal transduction. Am J Physiol-Regul Integr Comp Physiol 277(6):R1690–R1696

Southgate RJ, Neill B, Prelovsek O, El-Osta A, Kamei Y, Miura S, Ezaki O, McLoughlin TJ, Zhang W, Unterman TG, Febbraio MA (2007) FOXO1 regulates the expression of 4E-BP1 and inhibits mTOR signaling in mammalian skeletal muscle (Retracted Article. See vol 284, pg 20440, 2009). J Biol Chem 282(29):21176–21186. https://doi.org/10.1074/jbc.M702039200

Spiering BA, Kraemer WJ, Anderson JM, Armstrong LE, Nindl BC, Volek JS, Judelson DA, Joseph M, Vingren JL, Hatfield DL, Fragala MS, Ho JY, Maresh CM (2008) Effects of elevated circulating hormones on resistance exercise-induced Akt signaling. Med Sci Sports Exerc 40(6):1039–1048. https://doi.org/10.1249/MSS.0b013e31816722bd

Stefanetti RJ, Lamon S, Rahbek SK, Farup J, Zacharewicz E, Wallace MA, Vendelbo MH, Russell AP, Vissing K (2014a) Influence of divergent exercise contraction mode and whey protein supplementation on atrogin-1, MuRF1, and FOXO1/3A in human skeletal muscle. J Appl Physiol 116(11):1491–1502. https://doi.org/10.1152/japplphysiol.00136.2013

Stefanetti RJ, Zacharewicz E, Della Gatta P, Garnham A, Russell AP, Lamon S (2014b) Ageing has no effect on the regulation of the ubiquitin proteasome-related genes and proteins following resistance exercise. Front Physiol 5:30. https://doi.org/10.3389/fphys.2014.00030

Stefanetti RJ, Lamon S, Wallace M, Vendelbo MH, Russell AP, Vissing K (2015) Regulation of ubiquitin proteasome pathway molecular markers in response to endurance and resistance exercise and training. Pflugers Arch-Eur J Physiol 467(7):1523–1537. https://doi.org/10.1007/s00424-014-1587-y

Stitt TN, Drujan D, Clarke BA, Panaro F, Timofeyva Y, Kline WO, Gonzalez M, Yancopoulos GD, Glass DJ (2004) The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. Mol Cell 14(3):395–403. https://doi.org/10.1016/s1097-2765(04)00211-4

Suetta C, Clemmensen C, Andersen J, Magnusson S, Schjerling P, Kjaer M (2010) Coordinated increase in skeletal muscle fiber area and expression of IGF-I with resistance exercise in elderly post-operative patients. Growth Horm IGF Res 20(2):134–140. https://doi.org/10.1016/j.ghir.2009.11.005

Sullivan BP, Weiss JA, Nie YH, Garner RT, Drohan CJ, Kuang SH, Stout J, Gavin TP (2020) Skeletal muscle IGF-1 is lower at rest and after resistance exercise in humans with obesity. Eur J Appl Physiol 120(12):2835–2846. https://doi.org/10.1007/s00421-020-04509-z

Sumi K, Higashi S, Natsume M, Kawahata K, Nakazato K (2014) Temporal changes in ERK phosphorylation are harmonious with 4E-BP1, but not p70S6K, during clenbuterol-induced hypertrophy in the rat gastrocnemius. Appl Physiol Nutr Metab 39(8):902–910

Sun SC (2011) Non-canonical NF-κB signaling pathway. Cell Res 21(1):71–85. https://doi.org/10.1038/cr.2010.177

Szelenyi ER, Urso ML (2012) Time-course analysis of injured skeletal muscle suggests a critical involvement of ERK1/2 signaling in the acute inflammatory response. Muscle Nerve 45(4):552–561. https://doi.org/10.1002/mus.22323

Taghibeikzadehbadr P, Shirian S, Sabouri M (2020) Effect of different muscle contraction mode on the expression of Myostatin, IGF-1, and PGC-1 alpha family members in human Vastus Lateralis muscle. Mol Biol Rep 47(12):9251–9258. https://doi.org/10.1007/s11033-020-06017-x

Takagi R, Ogasawara R, Tsutaki A, Nakazato K, Ishii N (2016) Regional adaptation of collagen in skeletal muscle to repeated bouts of strenuous eccentric exercise. Pflugers Arch-Eur J Physiol 468(9):1565–1572. https://doi.org/10.1007/s00424-016-1860-3

Takegaki J, Ogasawara R, Tamura Y, Takagi R, Arihara Y, Tsutaki A, Nakazato K, Ishii N (2017) Repeated bouts of resistance exercise with short recovery periods activates mTOR signaling, but not protein synthesis, in mouse skeletal muscle. Physiol Rep 5(22):e13515. https://doi.org/10.14814/phy2.13515

Takegaki J, Ogasawara R, Kotani T, Tamura Y, Takagi R, Nakazato K, Ishii N (2019a) Influence of shortened recovery between resistance exercise sessions on muscle-hypertrophic effect in rat skeletal muscle. Physiol Rep 7(13):e14155. https://doi.org/10.14814/phy2.14155

Takegaki J, Sase K, Fujita S (2019b) Repeated bouts of resistance exercise attenuate mitogen-activated protein-kinase signal responses in rat skeletal muscle. Biochem Biophys Res Commun 520(1):73–78

Tang WW, Yuan J, Chen XY, Gu XT, Luo KT, Li J, Wan B, Wang YL, Yu L (2006) Identification of a novel human lysophosphatidic acid acyltransferase, LPAAT-theta, which activates mTOR pathway. J Biochem Mol Biol 39(5):626–635

Tannerstedt J, Apró W, Blomstrand E (2009) Maximal lengthening contractions induce different signaling responses in the type I and type II fibers of human skeletal muscle. J Appl Physiol

106(4):1412–1418. https://doi.org/10.1152/japplphysiol.91243.2008

Taylor LW, Wilborn CD, Kreider RB, Willoughby DS (2012) Effects of resistance exercise intensity on extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase activation in men. J Strength Cond Res 26(3):599–607

Terzis G, Georgiadis G, Stratakos G, Vogiatzis I, Kavouras S, Manta P, Mascher H, Blomstrand E (2008) Resistance exercise-induced increase in muscle mass correlates with p70S6 kinase phosphorylation in human subjects. Eur J Appl Physiol 102(2):145–152. https://doi.org/10.1007/s00421-007-0564-y

Thirupathi A, Wang M, Lin JK, Fekete G, István B, Baker JS, Gu Y (2021) Effect of different exercise modalities on oxidative stress: a systematic review. Biomed Res Int 2021(1):1947928

Thomson DM, Fick CA, Gordon SE (2008) AMPK activation attenuates S6K1, 4E-BP1, and eEF2 signaling responses to high-frequency electrically stimulated skeletal muscle contractions. J Appl Physiol 104(3):625–632

Townsend JR, Stout JR, Jajtner AR, Church DD, Beyer KS, Oliveira LP, La Monica MB, Riffe JJ, Muddle TWD, Baker KM, Fukuda DH, Roberts MD, Hoffman JR (2016) Resistance exercise increases intramuscular NF-κb signaling in untrained males. Eur J Appl Physiol 116(11–12):2103–2111. https://doi.org/10.1007/s00421-016-3463-2

Tremblay F, Brûlé S, Hee Um S, Li Y, Masuda K, Roden M, Sun XJ, Krebs M, Polakiewicz RD, Thomas G (2007) Identification of IRS-1 Ser-1101 as a target of S6K1 in nutrient- and obesity-induced insulin resistance. Proc Natl Acad Sci 104(35):14056–14061

Tsai S, Sitzmann JM, Dastidar SG, Rodriguez AA, Vu SL, McDonald CE, Academia EC, O'Leary MN, Ashe TD, La Spada AR, Kennedy BK (2015a) Muscle-specific 4E-BP1 signaling activation improves metabolic parameters during aging and obesity. J Clin Investig 125(8):2952–2964. https://doi.org/10.1172/Jci77361

Tsukiyama-Kohara K, Poulin F, Kohara M, DeMaria CT, Cheng A, Wu ZD, Gingras AC, Katsume A, Elchebly M, Spiegelman BM, Harper ME, Tremblay ML, Sonenberg N (2001) Adipose tissue reduction in mice lacking the translational inhibitor 4E-BP1. Nat Med 7(10):1128–1132. https://doi.org/10.1038/nm1001-1128

Um SH, Frigerio F, Watanabe M, Picard F, Joaquin M, Sticker M, Fumagalli S, Allegrini PR, Kozma SC, Auwerx J (2004) Absence of S6K1 protects against age-and diet-induced obesity while enhancing insulin sensitivity. Nature 431(7005):200–205

Utsugi M, Dobashi K, Ono A, Ishizuka T, Matsuzaki S-I, Hisada T, Shimizu Y, Kawata T, Aoki H, Kamide Y (2009) PI3K p110β positively regulates lipopolysaccharide-induced IL-12 production in human macrophages and dendritic cells and JNK1 plays a novel role. J Immunol 182(9):5225–5231

Vaughan EM, You JS, Yu HYE, Lasek A, Vitale N, Hornberger TA, Bement WM (2014) Lipid domain-dependent regulation of single-cell wound repair. Mol Biol Cell 25(12):1867–1876. https://doi.org/10.1091/mbc.E14-03-0839

Veilleux A, Houde VP, Bellmann K, Marette A (2010) Chronic inhibition of the mTORC1/S6K1 pathway increases insulin-induced PI3K activity but inhibits Akt2 and glucose transport stimulation in 3T3-L1 adipocytes. Mol Endocrinol 24(4):766–778

Velásquez C, Cheng E, Shuda M, Lee-Oesterreich PJ, Pogge von Strandmann L, Gritsenko MA, Jacobs JM, Moore PS, Chang Y (2016) Mitotic protein kinase CDK1 phosphorylation of mRNA translation regulator 4E-BP1 Ser83 may contribute to cell transformation. Proc Natl Acad Sci 113(30):8466–8471

Vissing K, McGee S, Farup J, Kjølhede T, Vendelbo M, Jessen N (2013) Differentiated mTOR but not AMPK signaling after strength vs endurance exercise in training-accustomed individuals. Scand J Med Sci Sports 23(3):355–366. https://doi.org/10.1111/j.1600-0838.2011.01395.x

Wackerhage H, Schoenfeld BJ, Hamilton DL, Lehti M, Hulmi JJ (2019) Stimuli and sensors that initiate skeletal muscle hypertrophy following resistance exercise. J Appl Physiol 126(1):30–43. https://doi.org/10.1152/japplphysiol.00685.2018

Werner SL, Barken D, Hoffmann A (2005) Stimulus specificity of gene expression programs determined by temporal control of IKK activity. Science 309(5742):1857–1861

West DWD, Marcotte GR, Chason CM, Juo N, Baehr LM, Bodine SC, Baar K (2019) Normal ribosomal biogenesis but shortened protein synthetic response to acute eccentric resistance exercise in old skeletal muscle. Front Physiol 9:1915. https://doi.org/10.3389/fphys.2018.01915

Williamson D, Gallagher P, Harber M, Hollon C, Trappe S (2003) Mitogen-activated protein kinase (MAPK) pathway activation: effects of age and acute exercise on human skeletal muscle. J Physiol-Lond 547(3):977–987. https://doi.org/10.1113/jphysiol.2002.036673

Williamson DL, Raue U, Slivka DR, Trappe S (2010) Resistance exercise, skeletal muscle FOXO3A, and 85-year-old women. J Gerontol Ser A Biol Sci Med Sci 65(4):335–343. https://doi.org/10.1093/gerona/glq005

Witard OC, Tieland M, Beelen M, Tipton KD, Van Loon LJ, Koopman R (2009) Resistance exercise increases postprandial muscle protein synthesis in humans. Med Sci Sports Exerc 41(1):144–154

Wolfe RR (2006) The underappreciated role of muscle in health and disease. Am J Clin Nutr 84(3):475–482

Wymann MP, Pirola L (1998) Structure and function of phosphoinositide 3-kinases. Biochim Biophys Acta (BBA) Mol Cell Biol Lipids 1436(1–2):127–150

Yang SY, Alnaqeeb M, Simpson H, Goldspink G (1997) Changes in muscle fibre type, muscle mass and IGF-I gene expression in rabbit skeletal muscle subjected to stretch. J Anat 190:613–622. https://doi.org/10.1046/j.1469-7580.1997.19040613.x

Yang Y, Jemiolo B, Trappe S (2006a) Proteolytic mRNA expression in response to acute resistance exercise in human single skeletal muscle fibers. J Appl Physiol 101(5):1442–1450

Yang YF, Jemiolo B, Trappe S (2006b) Proteolytic mRNA expression in response to acute resistance exercise in human single skeletal muscle fibers. Med Sci Sports Exerc 38(5):S546–S546. https://doi.org/10.1249/00005768-200605001-03147

Yao Y, Li W, Wu JW, Germann UA, Su MSS, Kuida K, Boucher DM (2003) Extracellular signal-regulated kinase 2 is necessary for mesoderm differentiation. Proc Natl Acad Sci USA 100(22):12759–12764. https://doi.org/10.1073/pnas.2134254100

Yin L, Lu L, Lin X, Wang X (2020) Crucial role of androgen receptor in resistance and endurance trainings-induced muscle hypertrophy through IGF-1/IGF-1R- PI3K/Akt- mTOR pathway. Nutr Metab (Lond) 17:26. https://doi.org/10.1186/s12986-020-00446-y

Yoshida T, Delafontaine P (2020) Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy. Cells 9(9):1970. https://doi.org/10.3390/cells9091970

You JS, Frey JW, Hornberger TA (2012) Mechanical stimulation induces mTOR signaling via an ERK-independent mechanism: implications for a direct activation of mTOR by phosphatidic acid. PLoS ONE 7(10):e47258. https://doi.org/10.1371/journal.pone.0047258

You JS, Lincoln HC, Kim CR, Frey JW, Goodman CA, Zhong XP, Hornberger TA (2014) The role of diacylglycerol kinase ζ and phosphatidic acid in the mechanical activation of mammalian target of rapamycin (mTOR) signaling and skeletal muscle hypertrophy. J Biol Chem 289(3):1551–1563. https://doi.org/10.1074/jbc.M113.531392

You JS, Dooley MS, Kim CR, Kim EJ, Xu W, Goodman CA, Hornberger TA (2018) A DGKζ-FoxO-ubiquitin proteolytic axis controls fiber size during skeletal muscle remodeling. Sci Signal 11(530):eaao6847. https://doi.org/10.1126/scisignal.aao6847

Yu JS, Cui W (2016) Proliferation, survival and metabolism: the role of PI3K/AKT/mTOR signalling in pluripotency and cell fate determination. Development 143(17):3050–3060. https://doi.org/10.1242/dev.137075

Yu J, Hu Y, Li Y, Han T, Zhu R, Fu P (2022) Resistance training relieves skeletal muscle atrophy induced by hypoxia via the Akt-FoxO1-MuRF1/Atrogin-1 signaling pathway

Zeng ZZ, Liang JL, Wu LW, Zhang H, Lv J, Chen N (2020) Exercise-induced autophagy suppresses sarcopenia through Akt/mTOR and Akt/FoxO3a signal pathways and AMPK-mediated mitochondrial quality control. Front Physiol 11:583478. https://doi.org/10.3389/fphys.2020.583478

Zhang J, Gao Z, Yin J, Quon MJ, Ye J (2008) S6K directly phosphorylates IRS-1 on Ser-270 to promote insulin resistance in response to TNF-α signaling through IKK2. J Biol Chem 283(51):35375–35382

Zheng B, Ohkawa S, Li H, Roberts-Wilson TK, Price SR (2010) FOXO3a mediates signaling crosstalk that coordinates ubiquitin and atrogin-1/MAFbx expression during glucocorticoid-induced skeletal muscle atrophy. FASEB J 24(8):2660

Zhong H, Roy RR, Woo J, Kim JA, Edgerton VR (2007) Differential modulation of myosin heavy chain phenotype in an inactive extensor and flexor muscle of adult rats. J Anat 210(1):19–31. https://doi.org/10.1111/j.1469-7580.2006.00665.x

Zick M, Stroupe C, Orr A, Douville D, Wickner WT (2014) Membranes linked by trans-SNARE complexes require lipids prone to non-bilayer structure for progression to fusion. Elife 3:e01879. https://doi.org/10.7554/eLife.01879