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Review

The exercise IL-6 enigma in cancer

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Interleukin (IL)-6 elicits both anticancer and procancer effects depending on the context, which we have termed the 'exercise IL-6 enigma'. IL-6 is released from skeletal muscles during exercise to regulate short-term energy availability. Exercise-induced IL-6 provokes biological effects that may protect against cancer by improving insulin sensitivity, stimulating the production of anti-inflammatory cytokines, mobilising immune cells, and reducing DNA damage in early malignant cells. By contrast, IL-6 continuously produced by leukocytes in inflammatory sites drives tumorigenesis by promoting chronic inflammation and activating tumour-promoting signalling pathways. How can a molecule have such opposing effects on cancer? Here, we review the roles of IL-6 in chronic inflammation, tumorigenesis, and exercise-associated cancer prevention and define the factors that underpin the exercise IL-6 enigma.

Highlights

Interleukin (IL)-6 can prevent or promote cancer development, depending on the context.

IL-6 is released from skeletal muscles during exercise.

IL-6 is also secreted by leukocytes and stromal cells at sites of inflammation and in the tumour microenvironment.

Muscle-derived IL-6 enhances insulin sensitivity in glycogen-storing tissues, stimulates the appearance of anti-inflammatory cytokines in the blood, mobilises cytotoxic immune cells, and reduces DNA damage in cancer cells. These biological effects may help protect against cancer formation and progression.

By contrast, sustained IL-6 signalling at sites of inflammation and in the tumour microenvironment promotes chronic low-grade inflammation and activates tumour-promoting signalling pathways.

Paradoxical role of IL-6 in cancer

Participating in 150–300 min per week of structured physical activity (i.e., exercise) reduces the risk of at least seven types of cancer: breast, colon, endometrial, kidney, and liver cancer, myeloma, and non-Hodgkin's lymphoma [1]. The size of the relative risk reduction ranges from 10% to 27%, depending on the cancer site [1]. Exercise is associated with lower recurrence rates and improved survival in people diagnosed with colon, breast, and prostate cancers [2].

A breakthrough in the field will be to identify the exercise-induced bioactive material that underlies the association between exercise and cancer risk and survival. A notable candidate is the cytokine IL-6 [3]. IL-6 is released from contracting skeletal muscle during exercise to regulate short-term energy availability and is quickly eliminated from plasma upon exercise cessation [4]. Muscle-derived IL-6 enhances insulin sensitivity [5], stimulates the production of anti-inflammatory cytokines [6], reduces proliferation and DNA damage in cancer cells [7], and stimulates tumour infiltration of cytotoxic immune cells in mice [8]. Based on these findings, we propose that IL-6 plays a key role in the multiple health benefits of exercise, including protection against cancer.

A large body of evidence suggests that IL-6 promotes **tumorigenesis** [9] (see Glossary). IL-6 is secreted by leukocytes and **stromal cells** for up to 15 h at local inflammatory sites [10] and controls the switch from acute to chronic inflammation, which is linked to the development of many cancers [11]. IL-6 produced in the **tumour microenvironment (TME)** activates tumour-intrinsic signalling pathways and regulates the protumour behaviour of infiltrating stromal and immune cells [12].

We have termed the opposing effects of IL-6 in cancer the 'exercise IL-6 enigma'. Here, we review the roles of IL-6 in chronic inflammation, tumorigenesis, and exercise-associated cancer prevention. We then define the factors that can explain the exercise IL-6 enigma and explore their mechanistic bases.

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IL-6 signalling

The IL-6 receptor complex consists of the IL-6 receptor α (IL-6Rα) and **glycoprotein 130 (gp130)**. IL-6Rα exists in a transmembrane and soluble form. **Classic signalling** is initiated when IL-6 binds to the membrane-bound form of IL-6Rα (mbIL-6Rα), forming a complex of IL-6 and mbIL-6Rα. This complex then binds to two molecules of gp130, which triggers gp130 **dimerization** and formation of a complex consisting of IL-6, mbIL-6Rα, and gp130. Classic signalling occurs in cell types that express mbIL-6Rα, including skeletal muscle fibres, hepatocytes, and neutrophils [13]. Many cancer cell lines and human tumours have mbIL-6Rα, although there is high variability in mRNA expression within and between cancer sites (Figure 1) [14,15].

IL-6 elicits biological effects on cell types that do not express mbIL-6Rα by binding to the soluble form of IL-6Rα (sIL-6Rα) in extracellular fluids, such as in blood plasma [16]. The IL-6/sIL-6Rα complex binds to gp130 on the plasma membrane of target cells, promoting gp130 dimerization.

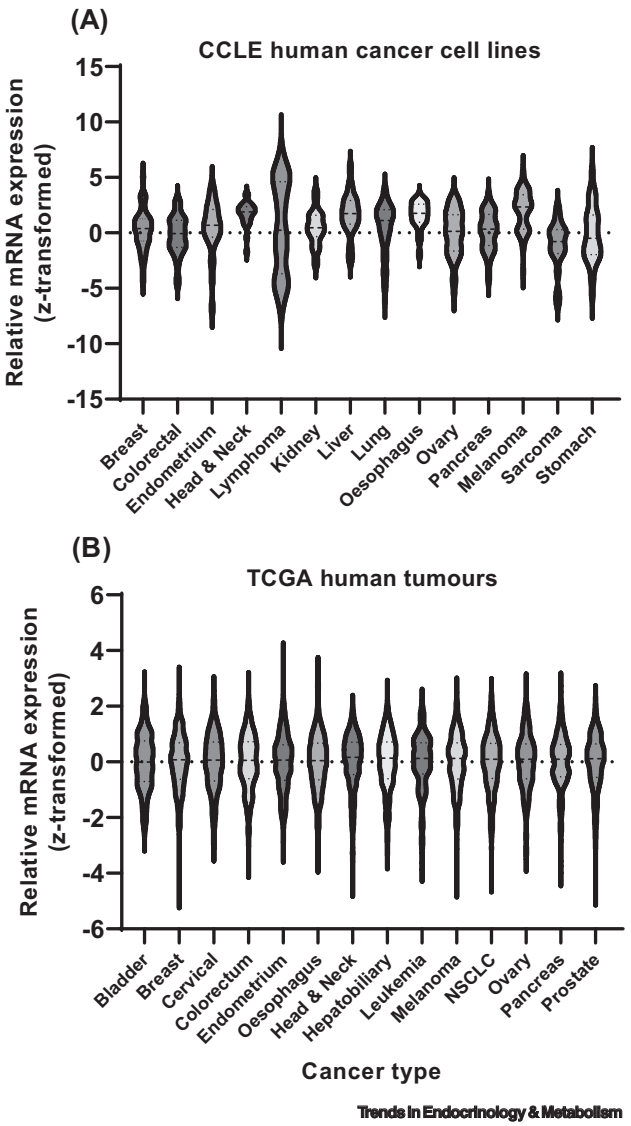

Figure 1. Interleukin-6 receptor (IL6R) expression in cancer cell lines and human tumours. Relative IL-6R mRNA expression data for (A) ~800 cancer cell lines across 14 cancer types retrieved from the Cancer Cell Line Encyclopedia (CCLE) [14] and (B) ~7000 human cancer samples across 14 cancer types retrieved from The Cancer Genome Atlas (TCGA) via cBioPortal [15].

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This form of IL-6 signalling – known as **trans-signalling** – enables IL-6 signalling in diverse cell types because gp130 is expressed on the surface of most cells.

Two more IL-6 signalling modes have recently been identified: **trans-presentation** and **joint reconstituted signalling**. In trans-presentation, IL-6 binds to mbIL-6Rα on a transmitting cell membrane and the IL-6/mbIL-6Rα complex is presented to a receiving cell expressing gp130, triggering gp130 dimerization and downstream signalling in the receiving cell [17]. In joint reconstituted signalling, mbIL-6Rα on **extracellular vesicles (EVs)** are transported and fused with cells that lack mbIL-6Rα, enabling delayed classic signalling on cells that otherwise would only respond to trans-signalling or trans-presentation [18].

All IL-6 signalling modes activate the **JAK/STAT3 signalling pathway**. Formation of the entire IL-6 receptor complex (IL-6/IL-6Rα/gp130) activates JAK and subsequently induces the phosphorylation of tyrosine residues within the cytoplasmic part of gp130. These phosphorylated tyrosine residues recruit a variety of molecules with **Src homology domain 2 (SH2 domain)** including STAT3, which is phosphorylated, dimerized, and consequently translocates to the nucleus to activate target genes including *c-myc, bcl2, cyclin D1*, and *MCP-1* [19]. gp130 phosphorylation also serves as a recruitment site for SH2-containing protein tyrosine phosphatase (SHP)-2, which promotes activation of PI3K/Akt and MAPK/ERK signalling [20].

IL-6, inflammation, and cancer

IL-6 in acute inflammation

Acute inflammation is a normal biological response to tissue damage and acts to restore tissue homeostasis. IL-6 is produced by macrophages, fibroblasts, and endothelial cells at sites of inflammation and controls the extent of tissue inflammatory responses. IL-6 induces the hepatic synthesis of **acute phase proteins** and stimulates the recruitment of neutrophils and lymphocytes to the inflammatory site by activating endothelial and smooth muscle cells to express **adhesion molecules** and release **chemokines** IL-8 and monocyte chemoattractant protein (MCP)-1 (also known as CCL2) [21,22]. Neutrophils and some lymphocyte subsets express mbIL-6Rα and thus are responsive to IL-6 classic signalling. The mbIL-6Rα can also be shed from neutrophil and lymphocyte membranes as a soluble form [23,24].

IL-6 in chronic inflammation

IL-6 trans-signalling in stromal cells induces a transition from neutrophilic recruitment in the early stages of acute inflammation to a more sustained monocyte influx by regulating a shift in chemokine production. The activation of neutrophils by IL-8 and other chemokines triggers mbIL-6Rα shedding [25]. The sIL-6Rα combines with IL-6 to enable binding to gp130 on the endothelial cell membrane, increasing IL-6 and MCP-1 secretion but not IL-8, which favours monocyte recruitment [26]. Monocytes differentiate into macrophages at the site of inflammation, which secrete proinflammatory cytokines [e.g., IL-1β, tumour necrosis factor (TNF)-α, and IL-1]. Additionally, although the phagocytosis of apoptotic neutrophils by macrophages is important for the resolution of inflammation, this process increases MCP-1 and inhibits IL-8 production by macrophages [27,28], further favouring monocyte recruitment.

Chronic inflammation and cancer

Chronic inflammation associated with sustained IL-6 signalling can promote the transformation of normal cells into premalignant or malignant cells. Macrophages and neutrophils produce reactive oxygen species (ROS) that induce DNA damage in normal tissues, increasing genetic instability and the propensity of acquiring mutations in cancer-related genes. For instance, chronic exposure to myeloid cell-derived ROS molecules leads to DNA damage and *Tp53* mutations in

Glossary

Acute phase proteins: blood proteins produced by the liver in response to inflammation or infection, helping to stimulate the immune system and aid tissue repair. Examples of key acute phase proteins include C-reactive protein, serum amyloid A protein, and fibrinogen.
ADAM17: an enzyme involved in the shedding of membrane-bound proteins from cell surfaces, such as the IL-6 receptor, releasing their extracellular domains into the surrounding environment.
Adhesion molecules: cell surface proteins that mediate the interaction between cells, or between cells and the extracellular matrix. Adhesion molecules play a major role in the recruitment of neutrophils to the site of inflammation. An example of an adhesion molecule is the intercellular adhesion molecule 1 (ICAM-1).
Chemokines: small signalling proteins secreted by cells that control the movement of white blood cells to specific sites in the body, such as to sites of inflammation.
Classic signalling: mode of IL-6 signalling initiated when IL-6 binds to the membrane-bound IL-6 receptor on the surface of a cell.
Dedifferentiation: process by which specialised cells lose their specific characteristics and return to a less specialised state, often occurring during tissue repair and regeneration.
Dimerization: process of two molecules joining together to form a two-part complex (called a dimer). This often triggers downstream signal transduction.
Epithelial–mesenchymal transition (EMT): process in which epithelial cells lose their characteristic properties and acquire mesenchymal-like characteristics, leading to increased cell mobility and invasive capabilities, often associated with tissue development and cancer metastasis.
Extracellular vesicles (EVs): lipid-bound particles secreted by cells into the extracellular space. EVs carry a cargo of various molecules (e.g., proteins, lipids, and nucleic acids) and play a crucial role in cell-to-cell communication, allowing cells to exchange information and molecules with neighbouring or distant cells.
Glycoprotein 130 (gp130): cell surface receptor used by several cytokines to

inflamed intestinal epithelial cells [29]. Inflammatory signalling can also stimulate **dedifferentiation** of normal epithelial cells into tumour-initiating stem cells through a nuclear factor (NF)-κB-dependent mechanism [30]. Moreover, prolonged IL-6 trans-signalling causes premature cellular senescence in fibroblasts [31] and promotes **senescence associated secretory phenotype (SASP)** signalling, which can drive epithelial plasticity and stemness [32], thus supporting the dedifferentiation and self-renewal of epithelial tissue.

Following the transformation of cells, inflammation-associated IL-6 may support progression into a fully developed tumour. IL-6 signalling in premalignant cells leads to the hyperactivation of JAK/STAT3 signalling, resulting in the upregulation of target genes that stimulate cell survival [33]. Persistent activation of STAT3 by IL-6 in tumour regulatory T cells helps transformed epithelium evade $CD8^+$ T cell cytotoxicity [34]. IL-6 released by **myeloid-derived suppressor cells (MDSCs)** prevents functional differentiation of tumour-specific $CD4^+$ T cells into effector T helper cells, leading to tumour progression in fibrosarcoma-bearing mice [35]. In slow proliferating tissues, such as liver and skin cells, necrosis and apoptosis caused by inflammation leads to compensatory proliferation of neighbouring transformed cells and triggers tumorigenesis [36].

IL-6 in the TME

The main sources of IL-6 in the TME are tumour cells, stromal cells and infiltrating immune cells, including fibroblasts, MDSCs, tumour-associated macrophages (TAMs), and $CD4^+$ T cells [12]. mbIL-6Rα is overexpressed in tumours compared to normal tissue [37–40] and cancer cells can shed mbIL-6Rα from their cell surface, partly through the actions of **ADAM17** [41], and thus are responsive to both classic and trans IL-6 signalling. Chronic IL-6 signalling in the TME promotes tumour progression by activating tumour-intrinsic signalling pathways and eliciting protumour effects on infiltrating stromal cells. In contrast to chronic IL-6 signalling, acute activation of IL-6 in the TME may promote antitumour adaptive immunity by inducting the migration of cytotoxic T cells to tumour-draining lymph nodes and tumour vasculature (Figure 2).

Protumour mechanisms of IL-6 in the TME

Activation of STAT3 by IL-6 trans-signalling regulates gene expression resulting in cell cycle progression, proliferation, and survival [42]. Persistent IL-6/STAT3 signalling inactivates p53 in human multiple myeloma cells, in part by increasing the expression of DNA methyltransferase (DNMT)-1 [43], allowing cells to bypass crucial cell cycle checkpoints. Acting through STAT3, IL-6 upregulates vascular endothelial growth factor (VEGF) to promote angiogenesis in a range of solid tumours and primes cancer cells for metastatic spread by upregulating matrix metalloproteinase (MMP)-2 [44,45]. IL-6/STAT3 signalling also promotes **epithelial–mesenchymal transition (EMT)** by decreasing the expression of EMT-associated marker e-cadherin and increasing expression of vimentin [46]. IL-6 secreted by cancer-associated fibroblasts induces cancer stem cell expansion in early colorectal tumours through HES1 activation [47]. IL-6/STAT3 signalling promotes local immunosuppression via several mechanisms, including regulatory T cell and B cell expansion and recruiting immunosuppressive MDSC [48].

Antitumour mechanisms of IL-6 in the TME

There is some evidence that acute activation of IL-6 signalling promotes antitumour adaptive immunity by regulating T cell priming in lymphoid organs and stimulating lymphocyte trafficking [49]. IL-6 produced by dendritic cells in lymph nodes engenders the activation, expansion, and survival of T cells during an immune response [50]. IL-6 is important for the differentiation of naïve $CD4^+$ T cells into Th17 cells and protects T cells from apoptosis [51]. IL-6 trans-signalling stimulates lymphocyte trafficking to tumour-draining lymph nodes by increasing intercellular adhesion molecule

trigger intracellular signalling. The binding of the IL-6/IL-6 receptor complex to gp130 forms a dimer and triggers downstream JAK/STAT3 signalling.

High endothelial venules: specialised blood vessels found in lymph nodes that facilitate the entry of immune cells from the blood to the lymphatic system.

JAK/STAT3 signalling pathway: important intracellular signalling cascade that is activated by various cytokines (including IL-6) and induces the transcription of target genes involved in cell cycle progression, proliferation, and survival.

Joint reconstituted signalling: process by which the membrane-bound IL-6 receptor on EVs is transported to, and fused with, cells that lack the IL-6 receptor on their surface. This process enables IL-6 classic signalling in cells that would otherwise only respond to trans-signalling or trans-presentation.

Myeloid-derived suppressor cells (MDSCs): diverse group of immune cells from the myeloid linage that are able to suppress the activity of other immune cells, particularly T cells and natural killer cells. MDSC expand under pathological conditions such as chronic inflammation and cancer.

Senescence associated secretory phenotype (SASP): phenotype of senescent cells whereby those cells secrete high levels of proinflammatory cytokines and growth factors into their surrounding environment, which can reinforce the senescent state in neighbouring cells and promote chronic inflammation.

Src homology domain 2 (SH2 domain): region of a protein (called protein domain) that binds to specific phosphorylated tyrosine residues in other proteins, facilitating intracellular signalling. STAT3 contains the SH2 domain and it is essential for activating the JAK/STAT3 signalling pathway.

Stromal cells: diverse group of connective tissue cells of any organ, providing structural support and contributing to tissue organization, immune responses, and tissue repair. The most common type of stromal cells are fibroblasts, found abundantly in the connective tissues.

Trans-presentation: mode of IL-6 signalling in which IL-6 binds to the membrane-bound IL-6 receptor on a transmitting cell and subsequently engages and binds with gp130 on a neighbouring receiving cell.

(ICAM)-1 expression on **high endothelial venules**, which are the main entry site for naïve and central memory T cells [52].

Despite that IL-6 trans-signalling is constitutively active in pancreatic and colonic tumour types [52], vessels in these tumours typically express a low level of trafficking molecules (such as ICAM-1) and do not support the extravasation of circulating effector and naïve $CD8^+$ T cells [52,53], suggesting that tumour endothelial cells are insensitive to chronic IL-6 activity. However, acute activation of IL-6 trans-signalling in murine models of colon and pancreatic cancer stimulates intratumoral $CD8^+$ T cell infiltration by increasing tethering and rolling behaviour of $CD8^+$ T cells and upregulating ICAM-1 density in tumour vessels [52]. Recombinant IL-6 also increases expression of ICAM-1 on intratumoral vessels in stage IV colorectal patient tumour explants, despite the presence of IL-6 in tumour lesions [52]. When combined with adoptive transfer of effector $CD8^+$ T cells, acute IL-6 stimulation enhances apoptosis of tumour cells and delayed tumour growth [52].

Regular exercise reduces resting levels of intratumoral IL-6 in breast cancer-bearing mice, which correlates to reduced tumour size [54]. An acute bout of exercise induces the release of IL-6 into the systemic circulation [55], which may acutely activate IL-6 signalling in the TME because

Trans-signalling: mode of IL-6 signalling initiated when IL-6 binds to the soluble form of the IL-6 receptor in extracellular fluids, such as in blood plasma.
Tumorigenesis: formation of cancer, whereby normal cells are transformed into cancer cells.
Tumour microenvironment (TME): complex environment around a tumour, including the surrounding blood vessels, immune cells, stromal cells, signalling molecules and the extracellular matrix, all of which interact with the tumour and influence tumour growth and behaviour.

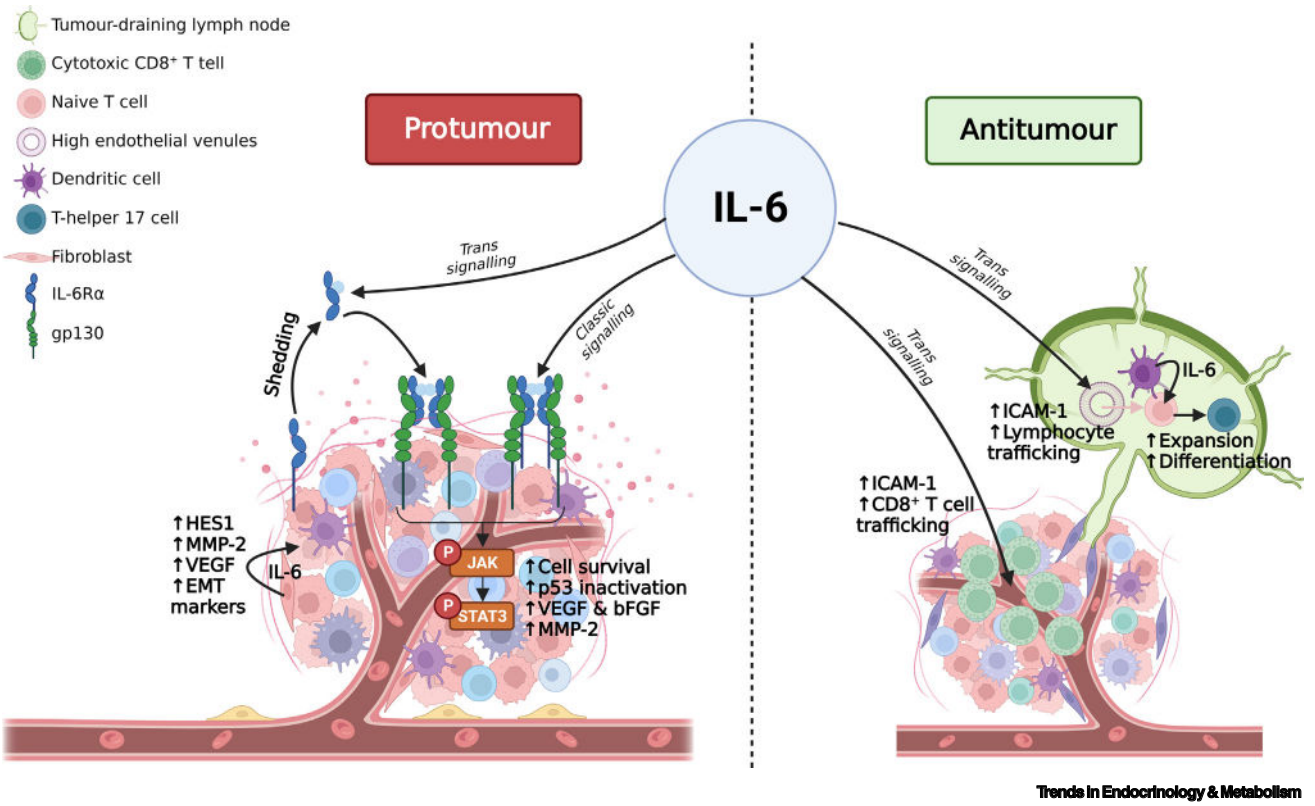

Figure 2. Protumour and antitumour actions of IL-6 in the tumour microenvironment (TME). Persistent IL-6 signalling in the TME promotes all stages of tumorigenesis by supporting cell survival, angiogenesis, EMT, and metastatic spread through activation of the JAK/STAT3 pathway and regulation of tumour-infiltrating stromal and immune cells. Conversely, acute IL-6 signalling may promote antitumour adaptive immunity by regulating T cell priming in lymphoid organs and inducting the migration of cytotoxic T cells to tumour-draining lymph nodes and tumour vessels. Abbreviations: bFGF, basic fibroblast growth factor; EMT, epithelial–mesenchymal transition; HES1, transcription factor HES1; IL-6, interleukin-6; ICAM-1; intercellular adhesion molecule 1MMP-2, matrix metalloproteinase-2; VEGF, vascular endothelial growth factor. Created with BioRender.com.

plasma IL-6 is able to penetrate into the interstitial fluid bathing vascularised tumours [56]. Thus, exercise may shift the balance of IL-6 signalling in the TME away from chronic activation (protumour) and toward acute activation (antitumour).

Exercise, IL-6, and cancer protection

IL-6 response to acute exercise

IL-6 is released by skeletal muscle into the interstitium and systemic circulation during exercise and acts in autocrine/paracrine and endocrine fashions to shunt energy towards the contracting muscle [4]. Plasma IL-6 concentrations increase exponentially during a bout of exercise and reach their peak at exercise cessation [57]. Exercise bouts performed for longer durations, at higher intensities, and recruiting large muscle groups, result in the greatest increases in circulating IL-6 [55,58,59]. Muscle-derived IL-6 has a half-life of ~5 min and is quickly eliminated from plasma after exercise cessation due to increased hepatic clearance and cessation of skeletal muscle secretion [60,61].

An acute bout of exercise upregulates mbIL-6Rα mRNA in skeletal muscle and there is evidence that myofibers do not shed mbIL-6Rα [62]. Plasma levels of soluble gp130 (sgp130) increase following acute exercise [63,64]. sgp130 forms a ternary complex with IL-6/sIL-6Rα in plasma to inhibit IL-6 trans-signalling [65]. Therefore, acute exercise may shift the IL-6 signalling axis away from trans-signalling and towards classic signalling.

Exercise-induced IL-6 in cancer prevention

Cancer prevention efforts can broadly be split into primary prevention (i.e., reducing the risk of developing cancer) and secondary or tertiary prevention (i.e., controlling the progression of precancerous or cancerous lesions).

IL-6 in primary cancer prevention

Putative biological mechanisms linking exercise to the primary prevention of site-specific cancers include improved insulin sensitivity, reduced bioavailability of exogenous sex hormones, and resolution of chronic low-grade inflammation [66]. Acute exercise has widespread effects on multiple organ systems and results in the rise and fall of thousands of bioactive molecules [67]. Therefore, many exercise-regulated biological processes are likely to impact on these pathways. As we describe below, there is good evidence that the biological actions of muscle-derived IL-6 directly or indirectly affect these pathways, and thus may play an important role in the exercise-associated prevention of cancer (Figure 3).

Evidence from *in vitro*, murine, and human studies suggests that IL-6 improves insulin resistance in glycogen-storing tissues. IL-6 infusion increases basal and insulin-stimulated glucose clearance in humans [5,68,69]. IL-6-deficient mice develop glucose intolerance, insulin resistance, and obesity [70–73], and the exercise-dependent increase in insulin sensitivity and GLUT4 expression is abolished by IL-6 knockout or IL-6 neutralizing antibodies [74,75]. IL-6 is required to elicit the exercise-dependent decrease in liver ectopic fat and browning of white adipose tissue *in vivo* [76,77]; both of which are characteristics of an insulin sensitive phenotype. Underlying these effects may be the IL-6-dependent upregulation of lipolytic and insulin-sensitizing genes, including peroxisome proliferator-activated receptor (PPAR)-γ and PPAR-γ coactivator (PGC)-1α [76]. IL-6 increases insulin-stimulated glucose in skeletal muscle cells and adipocytes through AMPK activation [78,79], and improves glucose-stimulated insulin secretion in pancreatic beta cells [80]; likely by triggering GLP-1 secretion from intestinal L cells and pancreatic alpha cells, or enhancing insulin-degrading enzyme expression in skeletal muscle [72,81].

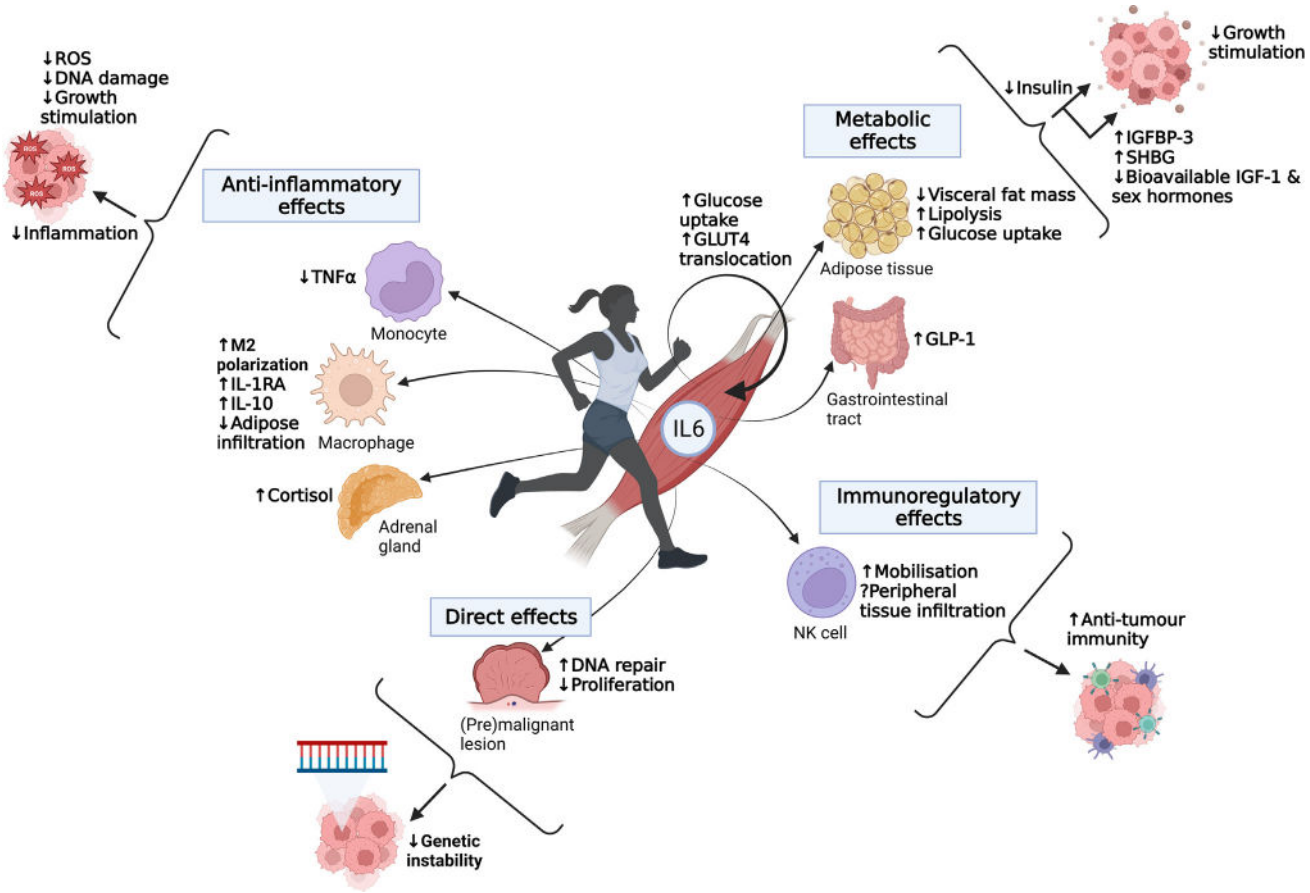

Figure 3. Hypothesized biological mechanisms underlying the role of exercise-induced IL-6 in primary and secondary cancer prevention. *Metabolic effects.* IL-6 promotes GLUT4 translocation and glucose uptake in skeletal muscle, reduces visceral fat mass, increases lipolysis and glucose uptake in adipocytes, and stimulates GLP-1 secretion from intestinal L cells. *Anti-inflammatory effects.* IL-6 stimulates release of IL-10 and IL-1RA from macrophages and cortisol from adrenal glands, inhibits TNFα release from monocytes, reduces macrophage infiltration in adipose tissue, and promotes polarization of macrophages towards the anti-inflammatory M2 phenotype. *Immunoregulatory effects*. IL-6 contributes to the mobilisation of cytotoxic NK cells in humans and stimulates tumour infiltration of NK cells in mice, although exercise effects on NK cell tumour infiltration in humans is unclear. *Direct effects.* IL-6 directly inhibits cell proliferation and reduces DNA damage in early-stage colon cancer cells. Abbreviations: GLP-1, glucagon-like peptide 1; IGF, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; IL, interleukin; IL-1RA, IL-1 receptor antagonist; NK cell, natural killer cell; ROS, reactive oxygen species; SHBG, sex hormone binding globulin; TNFα, tumour necrosis factor α. Created with BioRender.com.

However, some studies *in vitro* [82,83] and in mice [84,85] suggest that IL-6 causes insulin resistance, mainly in the liver. These opposing effects may depend on the duration of IL-6 exposure [86]. Chronic exposure to IL-6 for >24 h causes insulin resistance in adipose and hepatic tissue [87,88], whereas acute administration of IL-6 for ≤60 min improves insulin sensitivity [78,89–91]. Time-course studies show that chronic (2–24 h) but not acute (30–60 min) exposure to IL-6 induces insulin resistance in adipocytes and hepatocytes [82,88].

Enhanced insulin sensitivity induced by IL-6 may lower cancer risk by increasing production of insulin-like growth factor binding protein (IGFBP)-3 and consequently reducing IGF-1 bioavailability [92]. Overstimulation of IGF-1 signalling is associated with an increased risk of several cancers, particularly breast, prostate, and colorectal cancers [93]. Improved insulin sensitivity also reduces the bioavailability of sex steroid hormones because insulin inhibits hepatic secretion of sex

hormone binding globulin (SHBG) and stimulates aromatase activity [94]. Exercise-induced reductions in the bioavailability of oestrogen and androgens protect against some hormone sensitive cancers, such as postmenopausal breast cancer [95].

In addition to improving insulin sensitivity, regular exercise may reduce cancer risk by resolving chronic low-grade inflammation. Each bout of exercise stimulates the induction of anti-inflammatory cytokines [96], and regular exercise leads to a reduction in visceral fat [97]; there is evidence that muscle-derived IL-6 mediates both of these mechanisms. IL-6 is required to elicit the exercise-dependent decrease in visceral fat in humans and mice [76,98]. Infusing physiological concentrations of IL-6 in humans mimics the anti-inflammatory effects of an exercise bout by inducing the appearance of anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1RA) into the circulation and suppressing production of the proinflammatory cytokine TNF-α [6,99]. IL-6 infusion also stimulates cortisol release into the circulation – a potent anti-inflammatory hormone – by acting directly on the adrenal medulla [100] and triggering release of adrenocorticotropic hormone from the pituitary gland [101], replicating the impact of exercise on the hypothalamic–pituitary–adrenal axis. IL-6 promotes the polarization of macrophages towards the M2 (anti-inflammatory) phenotype rather than the M1 (proinflammatory) phenotype [102].

IL-6 in secondary/tertiary cancer prevention

The biological mechanisms underlying the effects of exercise on secondary/tertiary cancer prevention may occur through the same pathways as primary prevention, in addition to direct effects on cancer cells and modulation of the TME [103].

Growing evidence suggests that bioactive molecules released into the systemic circulation during exercise act directly on cancer cells to reduce proliferation [104]. Our meta-analysis showed that exposing breast, prostate, colon, and lung cancer cell lines to serum obtained immediately after an exercise bout reduces cell proliferation by ~9% compared to nonexercise serum [105]. Many of the bioactive molecules regulated by acute exercise have capacity to impact biological processes related to cell cycle progression and proliferation [106]. Given that the biological actions of IL-6 contribute to the maintenance of tissue homeostasis [107], IL-6 is a notable candidate. Indeed, our research and work by others show that directly stimulating cancer cells with IL-6 reduces cell growth or proliferation in colon, oestrogen-receptor-positive breast cancer, prostate, and meningioma cell lines [7,108–110]. IL-6 reduces colon cancer cell proliferation in a dose–response manner up to 10 pg/ml [7], which is the typical postexercise plasma concentration found in human studies [55].

We have recently shown that exercise-induced IL-6 reduces colon cancer cell proliferation by regulating cellular DNA damage [7]. In line with findings from our meta-analysis [105], stimulating colon cancer cells with post-exercise serum reduced cell proliferation by 6% compared to nonexercise control serum [7]. This effect was accompanied by decreased expression of the DNA double-strand break marker γ-H2AX. Acute exercise also increased serum IL-6, and exposing colon cancer cells to recombinant IL-6 reduced cell proliferation and DNA damage in a dose-dependent manner, mimicking the effect of exercise [7]. These observations are consistent with evidence showing that IL-6 reduces DNA damage in cancer cells following exposure to DNA damaging agents [111], and activates DNA repair enzymes and improves liver repair after partial hepatectomy *in vivo* [112].

How might a reduction in DNA damage inhibit colon cancer cell proliferation? According to the oncogene-induced DNA damage model for cancer development, DNA damage (specifically DNA double-strand breaks) drives the early stages of carcinogenesis [113]. Aberrant cell

proliferation prompted by activated oncogenes induces DNA double strand breaks, and the sustained formation of DNA damage contributes to genomic instability, which is a hallmark of cancer cells and increases the propensity of acquiring additional genetic mutations favouring cancer progression [114]. Therefore, given that cancer cell lines are known to rapidly attain new genetic variants in culture, which accelerate proliferation [115], the IL-6-dependent reduction in DNA damage may inhibit cancer cell proliferation by shifting the cells towards a more genetically stable phenotype, reducing the acquisition of further genetic mutations [3].

There is evidence that IL-6 partially controls the innate immune response to acute exercise, which may inhibit cancer progression through the recognition and elimination of cancer cells [116]. A single bout of exercise mobilises $CD8^+$ cytotoxic T cells and natural killer (NK) cells into the circulation in patients with prostate cancer and lymphoma [117,118]. Although β-adrenergic signalling and vascular wall shear stress are key to NK cell mobilisation, blocking IL-6 signalling (using tocilizumab) attenuated the increase in circulating NK cells by 53% and dendritic cells by 66% during an acute bout of exercise in humans [119]. Exercise selectively mobilises mbIL-6Rα-positive NK cells in mice [8] and treatment of NK cells with IL-6 increases their surface expression of adhesion molecules [120].

Voluntary wheel running in mice has been shown to increase the infiltration of cytotoxic NK cells in tumours, resulting in a 60% reduction in tumour growth across five different tumour models [8]. IL-6-blocking antibodies decreased the number of NK cells in the tumour and blunted the tumour-suppressive effect of wheel running, suggesting that exercise-induced IL-6 mediated these anticancer effects [8]. However, human studies have shown little evidence of an effect of exercise on NK tumour infiltration [121,122].

Factors that explain the exercise IL-6 enigma

As we have described, IL-6 acutely released from contracting skeletal muscle during exercise elicits different biological effects to IL-6 released for sustained periods at inflammatory sites. Below, we present five factors that can explain the exercise IL-6 enigma in cancer and draw on evidence to explore their mechanistic bases.

Duration of IL-6 exposure

Muscle-derived IL-6 is quickly eliminated from plasma upon exercise cessation with a half-life of ~5 min [60], whereas the half-life of IL-6 produced during acute inflammation is ~15 h [10,123] and plasma IL-6 is chronically elevated in people with cancer [124]. Acute IL-6 signalling induces biological responses that intercept carcinogenesis, whereas persistent IL-6 signalling predisposes tissues to cancer development. For instance, acute IL-6 signalling during exercise inducts an anti-inflammatory environment and enhances insulin sensitivity in glycogen-storing tissues, whereas sustained IL-6 signalling promotes chronic inflammation and insulin resistance. Short-term IL-6 administration improves liver regeneration and repair following partial hepatectomy, but chronic exposure sensitizes the liver to injury and death [125]. Directly exposing prostate cancer cells to IL-6 inhibits cell growth in the short term (<28 passages), but increases growth in the longer term (>42 passages) [109]. Further research is needed to understand the molecular mechanisms underlying the transition of IL-6 from an anticancer to procancer agent as the duration of exposure increases.

In the TME, continuous IL-6 production is needed to support tumorigenesis in several tumour models. IL-6 facilitates epigenetic gene silencing of p53 in the IL-6-dependent myeloma cell line KAS 6/1 by increasing the activity of DNMT-1, but IL-6 only begins to inhibit p53 expression after 4 days of exposure [43]. Additionally, depriving KAS 6/1 cells of IL-6 results in continued p53

expression and cell death [43], suggesting that persistent IL-6 signalling is required to maintain enhanced expression of DNMT-1 and epigenetic gene silencing of p53. Despite chronically elevated IL-6 signalling in pancreatic and colonic TMEs [52], the tumour vessels express a low expression of adhesion molecules and $CD8^+$ T cells are poorly represented, yet acute activation of IL-6 trans-signalling increases ICAM-1 density in tumour vessels and intratumoral infiltration of $CD8^+$ T cells [52].

IL-6 signalling mode

IL-6 classic signalling is generally considered anti-inflammatory and IL-6 trans-signalling is considered proinflammatory, although the underlying mechanisms have remained elusive. IL-6 trans-signalling induces a stronger phosphorylation of STAT3 than classic signalling in endothelial cells and cancer cells [41,126]. When human vascular endothelial cells are exposed to IL-6 and sIL-6Rα together, low concentrations of IL-6 are required to evoke STAT3 phosphorylation (1 ng/ml), whereas higher concentrations of IL-6 (50 ng/ml) are needed to induce a similar degree of STAT3 phosphorylation when sIL-6Rα is not present [126]. Moreover, trans-signalling, but not classic signalling, leads to activation of the PI3K/Akt and MAPK/ERK signalling pathways in endothelial cells [126]. Simultaneous activation of the JAK/STAT3 and PI3K/Akt pathways is required to induce an IL-6-mediated proinflammatory response, characterised by the expression and release of MCP-1 [126]. Thus, concurrent JAK/STAT3, PI3K/Akt, and MAPK/ERK pathway activation, MCP-1 induction, and stronger STAT3 signalling seems to explain why trans-signalling is proinflammatory and classic signalling is anti-inflammatory. These differences may also explain why IL-6 exposure increases proliferation in oestrogen-receptor-negative breast cancer cells that do not express mbIL-6Rα (i.e., acting via trans-signalling), but has growth-inhibitory effects on oestrogen-receptor-positive breast cancer cells that have mbIL-6Rα (acting via classic signalling) [127].

IL-6 trans-signalling dominates in the TME; cancer cells shed mbIL-6Rα from their cell surface and thus, in some cases, respond to trans but not classic IL-6 signalling [41]. T cells lose mbIL-6Rα expression in inflamed microenvironments [128] and TAMs shed mbIL-6Rα in the presence of ADAM17, which drives tumorigenesis [129,130]. IL-6 trans-signalling, but not classic signalling, decreases expression of tumour suppression gene maspin in prostate cancer cells [131].

It is not known whether exercise impacts the balance of trans- to classic signalling in the TME by, for example, increasing the ratio of mbIL-6Rα to gp130 on the tumour membrane. The recent discovery of joint reconstituted signalling – involving mbIL-6Rα on EVs fusing with cells that lack mbIL-6Rα – opens up the possibility that cells could respond to IL-6 classic signalling without actually expressing the surface receptor [18]. This is especially important in the context of exercise given that EVs are liberated during acute exercise and carry protein cargo to distant organs [132].

Upstream regulation of IL-6

Signals of energetic stress during strenuous exercise, such as accumulation of Ca^{2+}, lactate, and ROS, and activation of AMPK and p38 MAPK [133–136], stimulate the secretion of IL-6 from skeletal muscle, which occurs in the absence of NF-κB signalling and TNF-α/IL-1β secretion [137,138], and in the presence of anti-inflammatory cytokines IL-10 and IL-1RA [6]. By contrast, IL-6 released from inflammatory cells such as macrophages, stromal cells, and cancer cells largely depends on upstream NF-κB signalling and occurs concurrently with TNF-α production [139]. Thus, when IL-6 release is triggered by upstream inflammatory signalling, IL-6 signalling occurs in microenvironments rich in DNA-damaging agents, genetic instability, growth factors, and activated stroma. IL-6/STAT3 signalling alone does not cause cancer, but persistent activation of

STAT3 in a milieu of inflammation and DNA damage can promote malignant transformation and progression [140].

Cell source of IL-6

The source of IL-6 influences its biological actions. Adipocyte-derived IL-6 promotes macrophage infiltration in mouse adipose tissue, but IL-6 released from skeletal muscles during exercise suppresses adipose tissue macrophage infiltration [141]. Others have shown that adipocyte-derived IL-6 decreases hepatic expression of the adapter protein IRS1 [142], while IL-6 derived from Kupffer cells (liver resident macrophages) increases the expression of the adapter protein IRS2 [143]. The underlying mechanisms are unresolved, but may be related to a switch between IL-6 classic- and trans-signalling due to differences in the expression of ADAM10/17 that

Key figure

The exercise IL-6 enigma in cancer

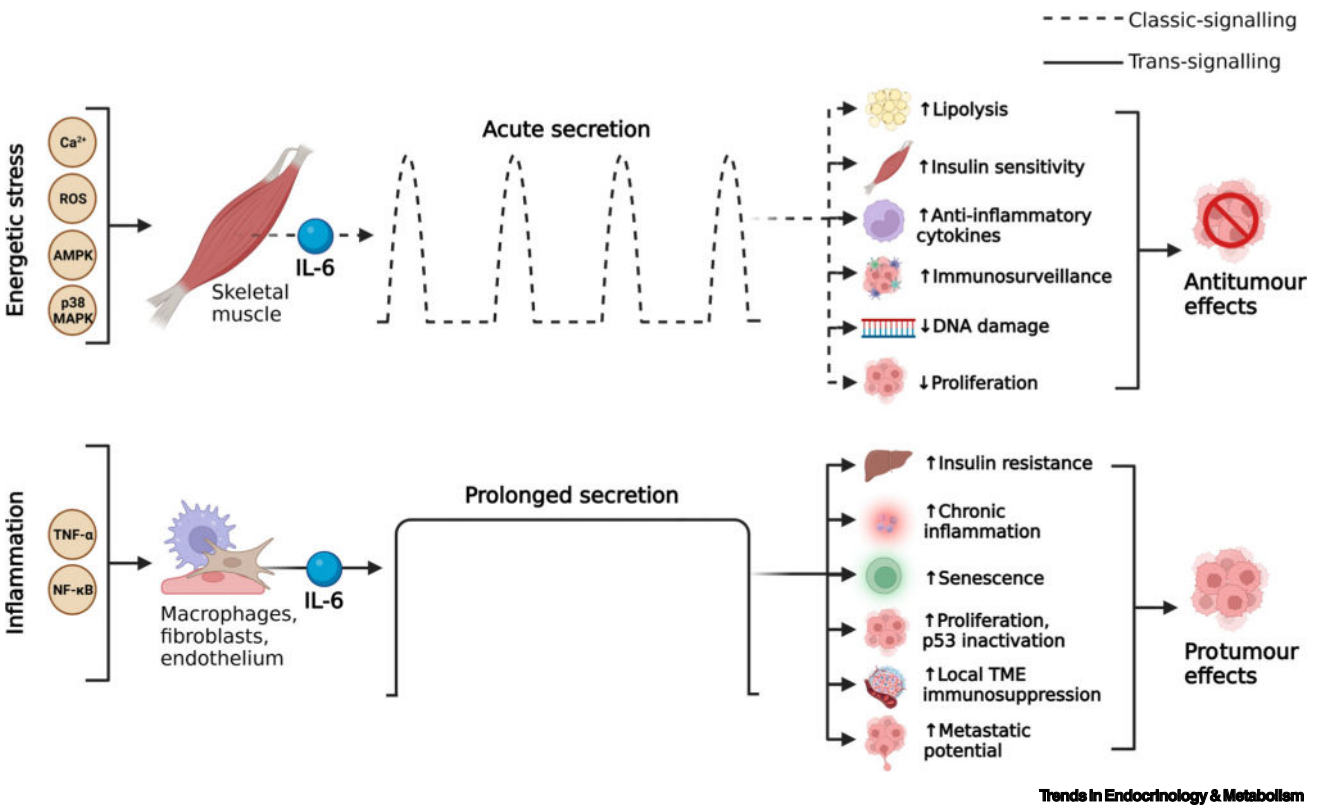

Figure 4. Signals of energetic stress during strenuous exercise induce the acute release of IL-6 from skeletal muscle to regulate energy availability. Acting via IL-6 classic-signalling, muscle-derived IL-6 may elicit antitumour effects by stimulating lipolysis in adipose tissue, increasing insulin sensitivity in glycogen storing tissues such as skeletal muscle, triggering the release of anti-inflammatory cytokines from monocytes and macrophages, mobilising cytotoxic immune cells, regulating DNA damage in malignant cells, and reducing cancer cell proliferation. By contrast, inflammatory signalling induces the prolonged release of IL-6 from macrophages, fibroblasts, and endothelial cells. IL-6 continuously secreted by inflammatory cells activates the trans-signalling pathway to elicit protumour effects by promoting insulin resistance in hepatocytes, inducing sustained monocyte recruitment to local inflammatory sites to control the switch from acute to chronic inflammation, provoking senescence and a senescence-associated secretory phenotype in stromal cells, stimulating proliferation, p53 inactivation, and metastatic potential in malignant cells, and supporting an immunosuppressive TME. Abbreviations: IL-6, interleukin-6; NF-κB, nuclear factor κB; ROS, reactive oxygen species; TME- tumour microenvironment; TNF-α, tumour necrosis factor-α. Created with BioRender.com.

promotes mbIL-6Rα shedding [141]. Unlike leukocytes and cancer cells, there is evidence that skeletal muscle cells do not shed mbIL-6Rα [62]. It is hence biologically plausible that muscle-derived IL-6 acts partially through IL-6 classic signalling to elicit anticancer effects in tissues (e.g., increased insulin resistance, reduced chronic inflammation), while IL-6 released from tumour cells, fibroblasts, and TAMs in the TME acts through IL-6 trans-signalling to promote tumorigenesis.

Cell targeted by IL-6

Cells respond differently to IL-6; this is partly determined by the ratio of mbIL-6Rα to gp130 on the cell surface and thus the balance of classic versus trans-signalling [144]. However, other cell-intrinsic factors are likely to be relevant, such as the expression of suppressor of cytokine signalling (SOCS)3, the primary negative regulator of IL-6 signalling. IL-6 inhibits the growth of M1 leukaemia cells, which completely lack expression of SOCS3 [145]. In addition, IL-6 induces an anti-inflammatory response in macrophages lacking the SOCS3 gene [146]. Site-specific cancer cells also respond differently to autocrine IL-6 stimulation; IL-6 is an autocrine growth stimulator in prostate cancer cells [109,147], whereas autocrine production of IL-6 inhibits proliferation in oestrogen-receptor-negative breast cancer cells [148].

Concluding remarks

Exercise scientists typically see IL-6 as a cytokine that prevents disease, whereas cancer researchers generally consider IL-6 to drive tumorigenesis. The evidence suggests both disciplines are correct because the biological effects of IL-6 are context dependent. IL-6 acutely released from skeletal muscle during exercise coordinates short-term energy allocation via IL-6 class-signalling and elicits biological effects that may contribute to cancer prevention, including increasing insulin sensitivity, inducing an anti-inflammatory environment, and reducing DNA damage. By contrast, chronically elevated IL-6 trans-signalling due to continuous release of IL-6 by stromal cells and macrophages promotes chronic inflammation and cancer formation (Figure 4, Key figure). The context-specific effects of IL-6 may explain why Phase 1/2 trials have reported limited clinical efficacy for the anti-IL-6 antibody siltuximab in patients with advanced solid tumours [149]. Factors that explain the paradoxical effects of IL-6 in cancer include the duration of IL-6 exposure, signalling mode, upstream regulation, cell source, and target cell. Future work should aim to better understand the mechanistic basis for these moderating factors. Doing so will help define the role of IL-6 in cancer and ultimately guide the development of more precise IL-6 therapies, through behavioural and pharmacological approaches, targeted to moderators and their underlying mechanistic pathways (see Outstanding questions).

Outstanding questions

Several factors can explain the context-dependent effects of IL-6 in cancer, including the duration of IL-6 exposure, signalling mode, upstream regulation, cell source, and cell target. What are the precise mechanisms of action underlying these factors? Can the underlying pathways be precisely targeted through behavioural, pharmacological, or immunological approaches to improve cancer control outcomes?

Exercise-induced IL-6 reduces DNA damage and proliferation in cancer cell lines and stimulates the tumour infiltration of cytotoxic immune cells in mice. Can these findings be replicated in humans and, if so, do they translate into improved patient outcomes?

Does maximising the amount of IL-6 released during acute exercise through manipulation of exercise characteristics (type, duration, and intensity) optimise the protective effect of exercise on cancer? If so, is this a casual effect or does the amount of IL-6 released during exercise simply reflect the overall exercise dose?

What effect does exercise have on IL-6 signalling in the tumour microenvironment? For example, does exercise modify mbIL-6Rα or SOCS3 expression in tumours?

Do tumour subtypes respond differently to exercise-induced IL-6 signalling?

Declaration of interests

No interests are declared.

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