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Perspective

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The effect of physical exercise on anticancer immunity

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Abstract

Regular physical activity is associated with lower cancer incidence and mortality, as well as with a lower rate of tumour recurrence. The epidemiological evidence is supported by preclinical studies in animal models showing that regular exercise delays the progression of cancer, including highly aggressive malignancies. Although the mechanisms underlying the antitumorigenic effects of exercise remain to be defined, an improvement in cancer immunosurveillance is likely important, with different immune cell subtypes stimulated by exercise to infiltrate tumours. There is also evidence that immune cells from blood collected after an exercise bout could be used as adoptive cell therapy for cancer. In this Perspective, we address the importance of muscular activity for maintaining a healthy immune system and discuss the effects of a single bout of exercise (that is, 'acute' exercise) and those of 'regular' exercise (that is, repeated bouts) on anticancer immunity, including tumour infiltrates. We also address the postulated mechanisms and the clinical implications of this emerging area of research.

Sections

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Introduction

The global burden of cancer — a leading cause of death worldwide — continues to grow, accounting for approximately 10 million deaths in 2020 (one in six of all deaths)[1]. About half of all cancer deaths could be prevented by modifying lifestyle and environmental-related risk factors[2]. Physical inactivity, which has reached pandemic proportions, is a modifiable risk factor that is gaining increasing attention[2]. Indeed, nearly one in three adults worldwide[3] fail to meet the minimum World Health Organization (WHO) recommendations for aerobic physical activity, which is defined as ≥150 min per week of moderate activities (such as walking) or ≥75 min per week of vigorous activities (such as brisk or very brisk walking), or a combination thereof[4]. Physical inactivity starts early in life, with approximately 80% of children aged 11–17 years currently inactive[5]. In turn, regular physical activity is associated with lower cancer incidence[6–8], lower cancer recurrence[9] and reduced mortality[8–11]. This association is independent of important confounders (such as body mass index or smoking status)[6] and is potentially dose–response dependent, with a benefit threshold for mortality at approximately 3–5 times the minimum WHO dose and no excess risk at 10 times or more of the minimum dose[11].

The identification of the mechanisms underlying the potential antitumorigenic effects of exercise or physical activity, which remain largely unknown, will deepen our understanding of cancer biology. The stimulation of immune function is a strong candidate to at least partly explain these effects. The fact that the immune system is highly responsive to exercise-induced stimuli has been known for more than a century[12] (Box 1). The concept of 'exercise-induced leucocytosis', whereby a single bout of dynamic, moderate–vigorous (but not necessarily exhausting) exercise (typically running or bicycling for approximately 1 hour) elicits a profound mobilization of all major leucocyte subtypes into the peripheral circulation, was subsequently validated[13–16]. However, it was found that exercise-induced leucocytosis is not uniform and that immune cell subtypes with higher cytotoxicity, antigen experience and potential for migration into tissues (such as natural killer (NK) cells, γδ T cells and $CD8^+$ T cells[17], as well as $CD14^+CD16^+$ monocytes[18] and $CD16^-$ neutrophils[19]) are preferentially mobilized[16]. Moreover, there is evidence for a stimulating effect of exercise on immune effectors (particularly NK cells and $CD8^+$ T cells) against tumours[20] and that optimal systemic immunity is critical for durable clinical responses to immunotherapy[21,22], as well as for prolonging the survival of patients with cancer in general[23].

Here we argue that the contracting muscle can be considered a modulator of immunity that can boost anticancer immune responses. We first discuss immune modulation by muscle tissue and the effects of acute and regular exercise (that is, a single exercise bout and repeated bouts, respectively) on the immune system, and then examine how the 'exercise milieu' can stimulate different immune cell subsets to infiltrate tumours and impair cancer growth. Throughout, we discuss the mechanisms — both at the systemic and tumour level — that may mediate these exercise effects and the potential clinical implications of the evidence available.

Muscle tissue and immunity

Skeletal muscle is an endocrine organ that releases a plethora of signalling molecules into the bloodstream. These include mainly proteins or small peptides (for example, cytokines, such as interleukin-6 (IL-6), IL-7 and IL-15), but also nucleic acids, lipids and metabolites (such as lactate). These can be freely circulating or packaged in exosomes and/or microvesicles and are collectively referred to as 'myokines'[24]. In addition to pleiotropic effects at the metabolic and multisystem level, myokines mediate immune-specific effects[25]. For example, the contracting muscle releases IL-6, which rises exponentially with exercise intensity and duration, potentially reaching an approximately 100-fold increase over baseline circulating levels[26]. Although IL-6 derived from other sources (such as immune cells) has a predominantly pro-inflammatory role, when released in the exercise milieu, it elicits an overall anti-inflammatory effect — notably, by inducing the release of other circulating cytokines that have anti-inflammatory properties, specifically IL-1 receptor antagonist (IL-1RA, a natural inhibitor of the potent pro-inflammatory cytokine IL-1β) and IL-10[27], while decreasing circulating levels of TNF[28]. Additionally, beyond non-immune (mostly metabolic) functions[29], exercise-induced IL-6 can bind to NK cells and stimulate their acute mobilization to the bloodstream[30] and their homing into tumours[31].

IL-7 and IL-15 are members of the common cytokine receptor γ-chain family of cytokines and are also highly expressed or secreted by contracting muscles[32–35]. IL-7 helps to maintain thymic mass and promotes the output of naive T cells[36], and both cytokines have major roles in αβ and γδ T cell survival and in $CD8^+$ T cell homoeostasis, to replenish (acutely or chronically) naive and memory subsets[36–40]. Notably, naive and memory $CD8^+$ T cells require IL-7Rα signalling and both IL-7Rα-mediated and IL-15-mediated signals, respectively, for proliferation in a lymphopenic host[37]. Furthermore, in vitro treatment of naive T cells with low doses of IL-7 and IL-15, in combination with anti-CD3-mediated and anti-CD28-mediated T cell receptor activation, results in the generation of cells resembling memory stem T cells, a subset of long-lived cells that can differentiate into virtually any type of T cell[41]. In turn, muscle-specific ablation of IL-15 in mice with a chronic viral infection lowers the levels of virus-specific $CD8^+$ T cells and increases the levels of exhausted T cells that express inhibitory checkpoint receptors such as PD1, CD244, LAG3 and TIGIT[39]. An increase in muscle mass (of note, muscle accretion is safely feasible with exercise in patients with cancer[42]) has essentially the opposite effect to muscle-specific IL-15 ablation on $CD8^+$ T cells[39]. Stimulation of peripheral $CD3^+CD4^-CD8^-$ T cells (a large proportion of which consists of γδ T cells) with IL-15 upregulates the expression of activating surface receptors such as NKG2D, NKp30 and NKp44, and increases the secretion of effectors such as IFNγ and soluble TRAIL, reflecting their enhanced tumouricidal activity[43]. Importantly, IL-15-stimulated γδ T cells are being investigated as an alternative to NK cells and αβ T cells in adoptive immunotherapy, owing to their ability to target tumour cells using both innate and T cell receptor-mediated mechanisms, their capacity to enhance antigen-specific T cell responses and their potential to be used in an autologous or allogeneic setting (for example, in acute myeloid leukaemia)[44]. Preclinical models have shown that ex vivo expansion of CAR-19 T cells with IL-7 and IL-15 contributes to superior cell proliferation, effector functions, trafficking, survival and antitumour activity of these cells compared with CAR-19 T cells grown in IL-2[45]. In patients with advanced-stage lymphoma who were treated with CAR-19 T cells, peak levels of IL-15 in the serum correlated with peak circulating levels of these cells and patients achieving remission showed higher levels of IL-15 than those who did not[46]. Furthermore, the IL-15–IL-15Rα axis was shown to be involved in the infiltration of 'exercise-mobilized' $CD8^+$ T cells in a mouse model of pancreatic cancer[47]. This was reflected by a higher expression of genes downstream of IL-15 engagement in the $CD8^+$ T cells of mice subjected to exercise training compared with their untrained controls, as well as by a significant increase in the fraction and number of IL-15Rα-positive $CD8\ T^+$ cells in the tumours of

Box 1

Exercise, cancer and immunity: early observations

In 1921, Siverten and Dahlstrom postulated a prophylactic effect of 'muscular activity' against carcinoma[144]. They based their theory on the observation that carcinoma incidence was higher in retired inactive farmers than in those remaining physically active until their seventies or eighties, as well as on the impression that carcinomas were rarely found in wildlife animals with high levels of spontaneous activity, such as rats. A proof-of-concept biological evidence for a protective association between physical exercise and cancer was reported in 1944 by Rush and Kline in albino mice that were inoculated with fibrosarcoma[145]. Forced exercise — accomplished by rotating the cages continuously — starting 1 week before tumour inoculation and applied for 2 or 16 hours per day, delayed tumour growth rate by approximately 34% or 25%, respectively, compared with controls on an isocaloric diet[145]. The potential for regular exercise to not only delay tumour growth (which was also shown in rat pups[146] or adult rats[147] implanted with a breast cancer cell line) but also reduce lung metastases in some mice injected with tumorigenic cells (H-ras-transformed fibroblasts known as CIRAS-1 cells)[148] was essentially replicated over the following decades. However, whether exercise effects were linked to immune function was not contemplated despite the fact that both the exercise-induced leucocytosis phenomenon[12] and the phenomenon of immunosurveillance against tumours had already been documented. Virchow had identified in 1863 that neoplastic tissues were often infiltrated with leucocytes[149], and William Coley (often referred to as the 'the father of immunotherapy') had attempted to leverage the immune system to treat cancer in 1891[150,151].

A study investigating whether the protective effect of exercise or physical activity against cancer was linked to an improved antitumorigenic function was published in 1993. Voluntary wheel running in mice for 9 weeks before the administration of CIRAS-1 cells increased splenic NK cell cytotoxic function for up to 3 weeks after the running intervention, although it did not impact tumour development[152].

exercised mice, together with an upregulation of markers of proliferation and activation in tumour-infiltrating IL-15Rα-positive $CD8^+$ T cells compared with their IL-15Rα-negative counterparts[47].

The progressive decrease in myokine secretion owing to the ageing-related decline in skeletal muscle mass (sarcopenia) is a critical mechanism for the development of immunosenescence[25,48], a condition linked to cancer immune evasion[49]. Here, tailored exercise — especially 'resistance training' — can attenuate sarcopenia even in patients of very advanced age (that is, over 85 years)[50].

The induction of muscle-derived cytokines through repeated bouts of exercise supports the maintenance of healthy immune effector cell populations[25] and promotes an overall anti-inflammatory milieu[51]. The latter is particularly important when considering that systemic, low-grade chronic inflammation — characterized by the activation of immune components that are often distinct from those engaged during acute immune response[52] — is a hallmark of ageing (the so-called inflammageing phenomenon[53]) and numerous chronic noncommunicable conditions, including cancer[52]. There is indeed meta-analytic evidence for an association between higher levels of chronic inflammation markers such as C-reactive protein and cancer risk[54]. Indeed, pharmacological blockade of pro-inflammatory factors (such as IL-1β) can reduce lung cancer incidence and mortality in individuals with a mean age above 60, with high levels of systemic inflammation at baseline[55]. At the mechanistic level, ageing-associated chronic inflammation favours oncogenesis not only by increasing cellular turnover[53] but also, at least partly, by favouring the accumulation of immunosuppressive cell types in the tumour microenvironment, as documented in mouse models for myeloid-derived suppressor cells (MDSCs), type 2 macrophages (M2) and $FOXP3^+$ regulatory T (T_{reg}) cells[56].

Advances in 'omics' technologies have led to the broad concept (beyond myokines) of 'exerkines' — which are signalling moieties that are released in response to exercise by several organs (not just muscle tissue) and exert their effects via endocrine, paracrine and/or autocrine pathways[24]. Some exerkines influence immune function, particularly adrenaline, the 'fight or flight' hormone released during exertion[57].

Immune effects of acute and regular exercise

Immune effects of acute exercise

In humans, acute dynamic exercise bouts lasting ≥20–60 min induce a biphasic response in lymphocytes. The initial response is characterized by dramatic lymphocytosis that affects mainly NK cells, which increase several-fold above baseline levels in the blood[58,59]. The most responsive NK cells are the mature KIR^+ or $NKG2A^-$ NK cells[60]. $CD8^+$ T cells and γδ T cells (which increase by approximately twofold[61] and threefold[17], respectively) are also mobilized in response to acute exertion. Acute exercise preferentially mobilizes subsets of $CD8^+$ T cells[61] and $CD3^+CD56^+$ NK T-like cells[62] that exhibit surface phenotypes associated with increased differentiation (for example, $KLRG1^+$, $CD57^+$ and $CD28^-$) and gene expression programmes associated with antitumour activity, and also mobilizes $CD14^+CD16^+$ monocytes over classical $CD14^+CD16^-$ monocytes[16,18,57,63]. Lymphocyte subtypes that are not typically involved in cytotoxicity (such as $CD4^+$ T cells and B cells) are recruited into the blood to a significantly lesser extent[16]. Within the T cell compartment, highly differentiated subsets of $CD4^+$ and $CD8^+$ T cells (such as effector memory (EM) and $CD45RA^+CCR7^-$ effector memory (EMRA) cells) are preferentially mobilized over their less differentiated counterparts (such as naive and central memory cells)[16].

Lymphocyte mobilization during exertion is proportional to effort intensity and is driven by increased blood pressure and shear forces that cause demargination from the vascular and tissue reservoirs (the lung, liver and spleen), which boosts the number of leucocytes travelling in the main axial blood flow of the peripheral circulation[16,64] (Fig. 1). Mobilization is also principally promoted by adrenaline stimulation of β_2-adrenergic receptors on the surface of lymphocytes, leading to endothelial detachment and recirculation of lymphocytes into the bloodstream[57,64–66]. The molecular mechanisms by which exercise and

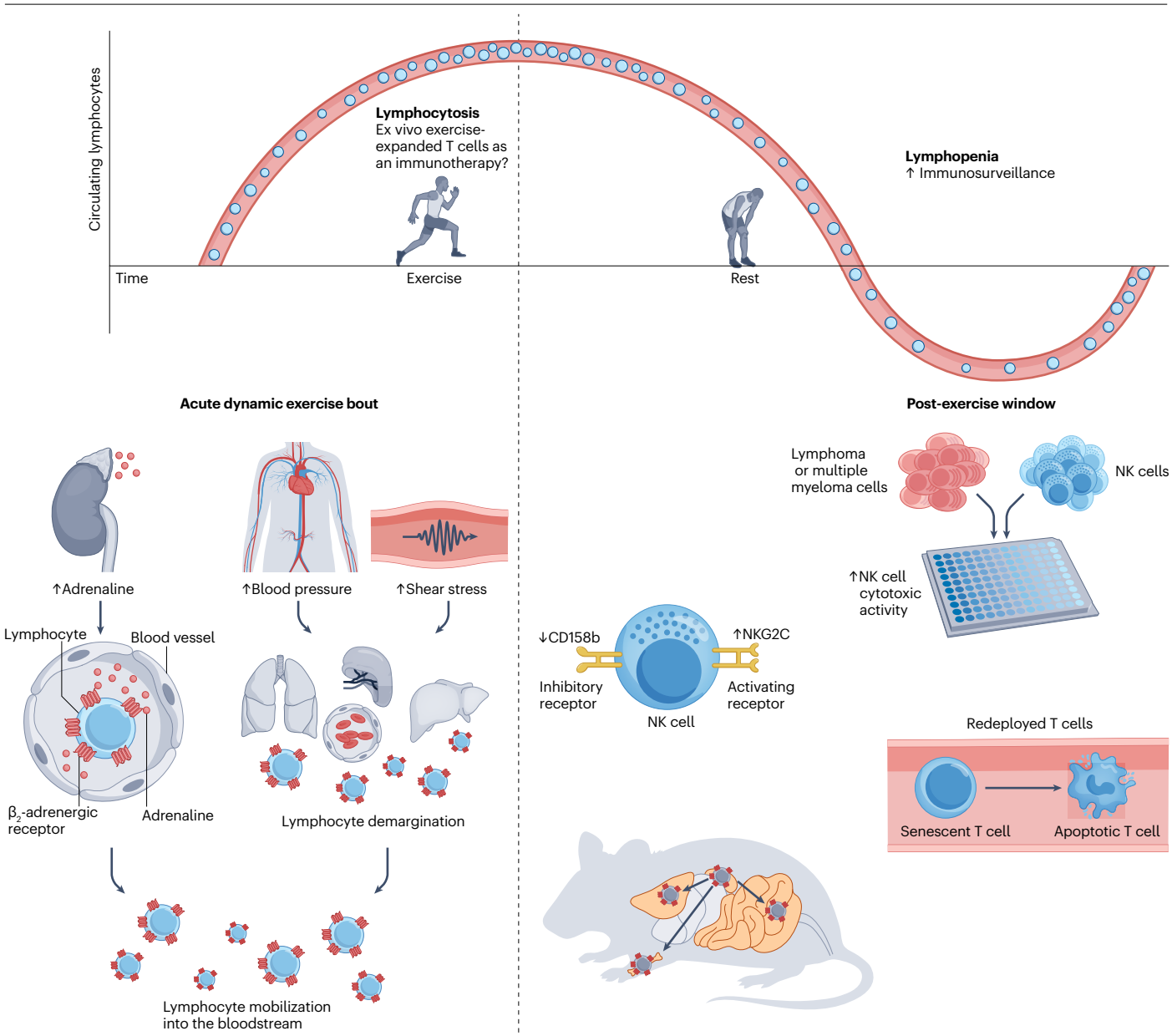

Fig. 1 | The biphasic immune cell response to dynamic (such as bicycling and running), acute exercise. Lymphocytosis — affecting mostly natural killer (NK) cells, $CD8^+$ T cells and γδ T cells — is driven by increased blood pressure and shear forces (causing demargination from the vascular or tissue reservoirs) and by adrenaline stimulation of β_2-adrenergic receptors on the surface of lymphocytes. This is followed by transient (within 24 hours) lymphopenia where previously mobilized cells are redeployed to target tissues, with this post-exercise window potentially improving immunosurveillance (higher NK cell cytotoxic capacity as assessed in vitro and decreased and increased proportion of NK cells expressing the inhibitory receptor CD158b and the activating receptor NKG2C, respectively). Because senescent T cells are mobilized into circulation to a greater extent than naive T cells, this could facilitate their apoptosis and create 'vacant space' for new naive T cells to take occupancy (see also Fig. 2).

catecholamine signalling affect immune cell mobilization, redistribution and function remain to be fully understood[57]. However, shedding of the adhesion molecule ICAM-1 from the lymphocyte surface upon stimulation via adrenergic pathways might be one mechanism, with subsequent detachment of these cells from the vascular endothelium in primary (the bone marrow and thymus) and secondary (such as the spleen and lymph nodes) lymphocyte reservoirs[67], where norepinephrine and adrenaline are released from nerve terminals or diffuse from the bloodstream[57]. In addition, there are indications that β-adrenergic stimulation can precipitate IL-6 release from skeletal muscle[68]. The exertional lymphocyte mobilization response reflects, at least partly, the differential expression of β_2-adrenergic receptors on lymphocyte subtypes — with the highest expression on NK cells, followed by γδ T cells, $CD8^+$ T cells, B cells and T_{reg} cells[58,69] — and is

inhibited by non-selective β-antagonists that bind β_2-receptors (nadolol and propranolol), but not by β_1-only blockers (bisoprolol and metoprolol)[18,65,70].

Blood lymphocyte counts start to decrease during recovery after exercise, with a nadir at approximately 1–2 hours after exertion. Transient lymphopenia below pre-exercise levels is frequent, affecting mostly NK and $CD8^+$ T cells and gradually returning to baseline levels, usually within 24 hours[58]. This acute, transient lymphopenia does not reflect immunosuppression and might occur in the context of an improved immunosurveillance[58]. Indeed, in healthy individuals, NK cell cytotoxic capacity against lymphoma and multiple myeloma cell lines increases by 60% at 1 hour after exertion, which is accompanied by a decrease in the proportion of NK cells that express the inhibitory receptor CD158b and an increase in NK cells that express the activating receptor NKG2C[60]. Fluorescent cell tracking studies in rodents revealed that T cells are largely redeployed from the spleen to target organs such as the lung, bone marrow and gut[69,71]. Additionally, acute physical exercise preferentially mobilizes highly differentiated T cells into the circulation, many of which display phenotypes associated with exhaustion and terminal differentiation[72]. Some of these mobilized cells appear to be more susceptible to exercise-induced apoptosis, which may create 'vacant space' (especially if acute exertion bouts are repeated frequently) for new naive T cells to take occupancy[73]. Through its ability to rapidly mobilize and increase circulating T cells, acute exercise has been postulated as a method to enrich T cells in the blood before leukapheresis, which will then be used for adoptive transfer immunotherapies that require ex vivo expansion (such as CAR T cells)[25] (Box 2).

Immune effects of regular exercise

The long-term beneficial effects of daily regular exercise might be due to the cumulative impact of 'repeated acute exercise bouts' and the subsequent salutary effects during a few hours per day (Fig. 2). Since each bout of exercise induces myokine or exerkine secretion and induces the redeployment of massive numbers of lymphocytes, the effects of regular exercise on immune function in general and on antitumour immune function in particular might be linked, at least partly, to the progressive accumulation of frequent acute episodes of mobilization or redistribution of effector lymphocytes[25], even if this is not necessarily reflected by noticeable changes in the blood or in in vitro assessments performed under resting conditions in humans (that is, after a 'washout' period of ≥24 hours from the last session). Immune adaptations to exercise training might be better observed using 'dynamic' endpoints such as the ability of NK cells or other immune cell populations to traffic to and infiltrate tumours[25].

Although a single exercise session mobilizes NK cells into the bloodstream, as corroborated for instance in patients with prostate cancer[74,75], this does not suffice to increase prostate NK cell infiltrates[74,76]. Yet, a higher number of training sessions over an 8-week period correlated with greater prostate NK cell infiltrates in patients with this malignancy, and good adherence to the programme (up to 4 days a week) led to higher increases in tumour infiltrates at end intervention (mean change of +1.60 cells mm^{-2}) compared with non-exercising controls (+0.44 cells mm^{-2})[77]. This finding is relevant because prostate tumours hijack host macrophages to form a barrier around the tumour, preventing effector lymphocyte infiltration[78,79]. Consequently, although a single exercise session does not change blood inflammatory markers in cancer survivors, there is a cumulative effect of subsequent sessions, with increases in IL-1RA[80].

In people with (or at risk of) cancer, exercise training interventions might not necessarily affect NK cell activity (as assessed in vitro with NK cells obtained from blood collected ≥1 day after the last exercise session)[81,82]. There is, however, evidence for a significant enhancement in NK cell activity after an 8-week aerobic exercise intervention

Box 2

The use of exercise to facilitate the expansion of cells used for adoptive transfer

The use of 'exercise-expanded' T cells could overcome manufacturing issues such as the low cell numbers collected from lymphopenic patients, prolonged culturing to produce sufficient numbers of T cells or poor ex vivo cell expansion[153–157]. Adoptive transfer of ex vivo expanded tumour-associated antigen (TAA)-specific cytotoxic T cells is a potential treatment strategy for several haematological and solid tumours and can reduce the risk of relapse following haematopoietic stem cell transplantation[157]. Yet, this method can be hampered by difficulties in priming and expanding sufficient numbers of TAA-specific cytotoxic T cells[25]. Here, the outcome of a study that collected blood lymphocytes from healthy adults at rest (baseline) and after a single bout of maximal-intensity exercise suggested that acute exercise might be used for immunotherapy with donor-derived T cells after allogeneic haematopoietic stem cell transplantation[158]. TAA-specific cytotoxic T cells were expanded using autologous monocyte-derived dendritic cells pulsed with melanoma-associated antigen 4 (MAGE-A4), with preferentially expressed antigen in melanoma (PRAME) and with Wilms' tumour protein[158]. Compared with baseline, post-exercise blood samples had a greater number of MAGE-A4-specific and PRAME-specific cells in 70% and 61% of participants (3.4-fold and 6.2-fold increase, respectively), and expanded TAA-specific cytotoxic T cells retained their antigen-specific cytotoxic activity[158]. A similar approach was used to increase the expansion and antitumour activity of γδ T cells, where cell products that were expanded from exercise-mobilized lymphocytes showed enhanced cytotoxic effects against a range of haematological tumours, which correlated with increases in the surface expression of activating receptors such as NKG2D[70]. In summary, there is preliminary clinical evidence that immune cells from blood collected after an exercise bout could be used as adoptive T cell therapy for cancer.

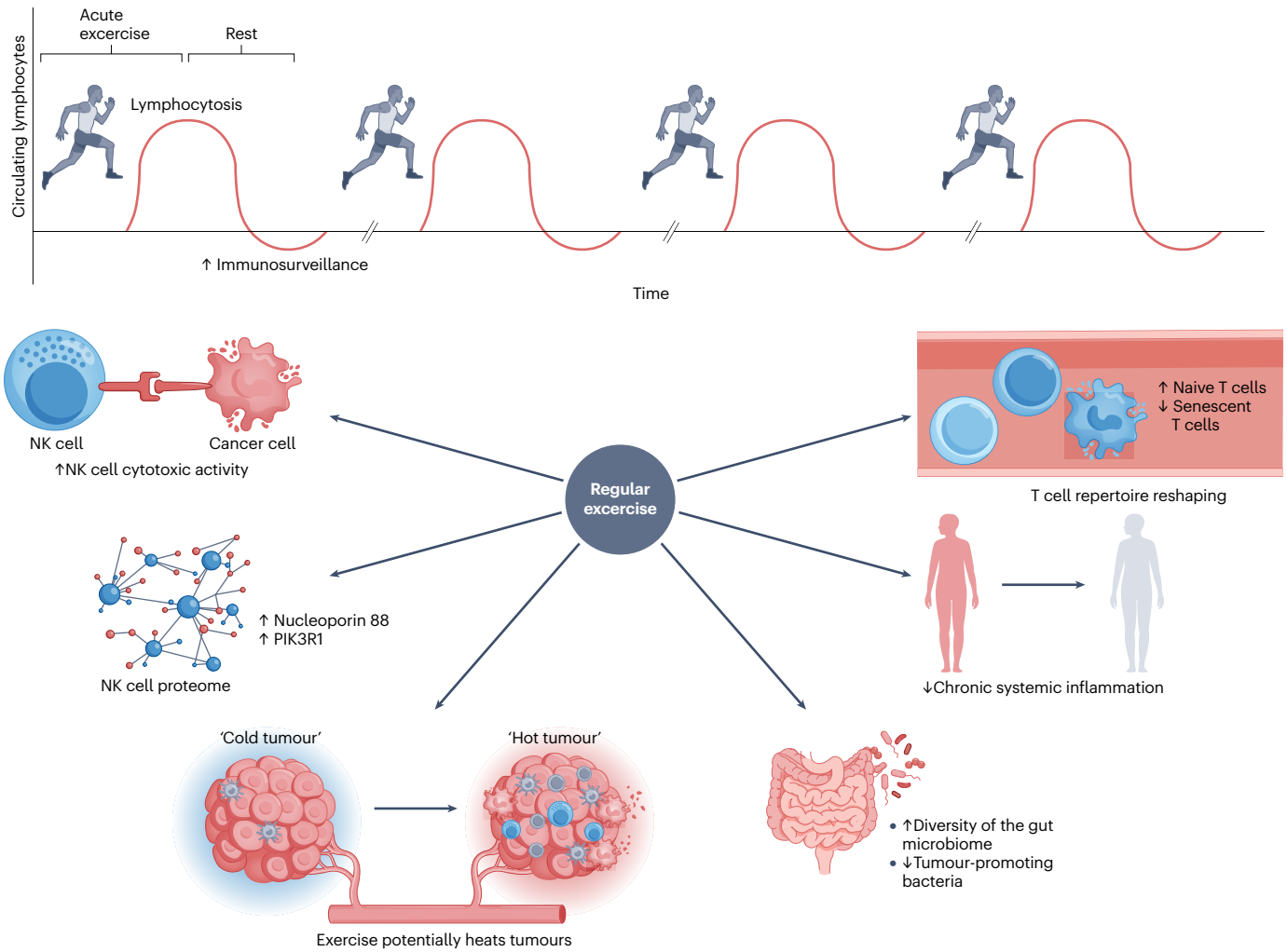

Fig. 2 | The immune cell response to regular exercise (that is, accumulation of repeated exercise bouts). Regular exercise can increase natural killer (NK) cell cytotoxic activity (as assessed in vitro) against tumour cells, which can be accompanied by changes at the NK cell proteome level. Regular exercise might reshape the T cell repertoire by potentially increasing the proportion of naive $CD8^+$ T cells while also increasing immune cell infiltrates in tumours (see also Fig. 3). In addition, regular exercise attenuates chronic systemic inflammation — a condition associated with higher cancer risk — and increases gut microbiota diversity, while also potentially reducing the levels of tumour-promoting bacteria.

(including high-intensity interval training (HIIT)) in healthy adults[83], after a 12-week HIIT and resistance training intervention in patients with chronic lymphocytic leukaemia[84] and after an aerobic and resistance training programme performed during the first 9–12 weeks of (neo) adjuvant chemotherapy in women with resectable breast or colon cancer[85]. Of note, training-induced increases in NK cell activity have been associated with changes at the proteome level, including the upregulation of PIK3R1[83], which is required for the maturation, homing, priming and function of NK cells[86], and nucleoporin 88 (ref. 83), which selectively mediates the nucleocytoplasmic transport of NF-κB, an ubiquitous transcription factor involved in immune responses[87]. Regular exercise — or at least high aerobic fitness levels that usually result from exercise training — can also reshape the T cell repertoire by reducing the proportion of dysfunctional and senescent T cells that have an impaired ability to mediate antitumour responses[25], while increasing the proportion of naive $CD8^+$ T cells ($CD45RA^+CD27^+$ $CD62L^+CCR7^+$) that are capable of recognizing and responding to new antigens[88].

Beyond the direct effects of exercise on immune cells, a recent study that compared individuals with colorectal cancer who followed WHO guidelines of physical activity (179 participants, stages I–IV) with individuals who were inactive or obese has concluded that the beneficial effect of physical activity is associated with an enhancement of the alpha diversity (a measure of microbiome diversity) of the gut microbiota[89]. Moreover, exercise also appeared to increase the abundance of bacteria that are associated with a retardation of tumour growth (such as *Faecalibacterium*) and reduced bacterial strains that have been associated with a promotion of tumour growth[89]. The finding that higher microbial diversity is associated with regular physical activity or exercise is consistent with previous observations in athletes[90,91] and is potentially important given that alpha diversity is a general indicator of good health[92]. Individuals with colorectal cancer have

previously been shown to have lower microbial diversity than healthy controls[93]. In addition, there is evidence that the composition of the gut ecosystem markedly affects immune responses to cancer and the efficacy of antitumour immunotherapies[94,95]. For example, a higher alpha diversity with a high abundance of *Faecalibacterium* has been associated with enhanced systemic and local antitumour immunity, mediated through increased antigen presentation and improved effector T cell function in the blood and the tumour microenvironment[96].

Effects on tumour immune cell infiltration

Several studies have specifically addressed the effects of exercise on the anticancer responses of different immune cell subsets. A large number of these studies have focused on NK cells, but others have also investigated exercise effects on myeloid cells, T cells and B cells.

NK cells

A seminal study led by Hojman showed that exposure of mice to regular voluntary wheel running (approximately 4–7 km per day from 4 weeks before to 2–3 weeks after tumour cell inoculation) reduced tumour incidence and growth by approximately 60% across five different tumour models (including B16-F10 melanoma)[31]. This was attributed, at least partly, to the combined effects of each of the repeated exercise bouts on catecholamine-induced mobilization of NK cells into the circulation and the subsequent binding of muscle-released IL-6 on NK cell surface receptors, ultimately driving NK cell homing to tumours[31]. Here, the amount of infiltrates was inversely linked to tumour burden, and NK cell depletion with antibodies abolished the suppressive effect of exercise on tumour growth[31] (Fig. 3).

Another study confirmed higher tumour NK cell infiltrates in mice that performed forced treadmill running for 20 days before being orthotopically transplanted with breast cancer cells compared with control mice[97]. Although running might not necessarily enhance NK cell cytotoxicity in mice per se, it might enhance NK cell infiltration into the tumour environment by upregulating the expression of genes encoding chemokines (such as *Ccl3*, *Cxcl10* and *Cx3cl1*) and increase tumour immunogenicity via the upregulation of ligands for the NK cell-activating receptor NKG2D (such as *Mult1* and *H60a*)[31]. In a study where athymic mice (which lack functional T cells but retain NK cells) were challenged with prostate cancer cells and then treated with radiotherapy, a 2-week forced treadmill running intervention stimulated antitumour immune responses by enhancing NK cell tumour infiltration and upregulated gene expression of receptors required for NK cell cytotoxic activity (*Klrk1*, which encodes NKG2D, and *Il2rb*)[98]. In a recent proof-of-concept randomized controlled trial in the setting of preoperative prostatectomy, where patients were divided into a control (standard of care) or 8-week HIIT intervention group, NK cell infiltrates in prostatic tissue were analysed in diagnostic core needle biopsies before the intervention and upon prostatectomy (post-intervention)[77]. This revealed increased NK cell infiltration in the exercise group compared to the control group[77]. These findings are likely relevant when considering the important role that NK cells have in antitumour immunity[99–102], and that increased NK cell infiltrates inside tumours are associated with higher response to chemotherapy[103] and higher survival[103] in gastric cancer, and also with improved response to anti-PD1 immunotherapy treatment[104] and survival in metastatic melanoma[105].

NK cells have been traditionally viewed as the main effectors of the exercise-related immunosurveillance against tumour development, partly because they are the immune cell subset that is the most responsive to the acute mobilizing effect of a single exercise bout and thus have been the most studied. However, this may not always be the case. For example, a study of mice with B16-F10 melanoma has found that when the exercise intervention started after the implantation of the tumour, no changes in intratumoural NK cell infiltrates were observed[106]. This stands in contrast to the findings by Hojman's group as discussed above and might suggest that a 'pre-conditioning' exercise effect before tumour onset may be needed to enhance NK cell infiltration. On the other hand, the study by Hojman's group reported larger tumours in athymic mice than in wild-type mice[31], indicating that T cells had a major role (potentially beyond NK cells) in controlling tumour growth independently of exercise state and that all immune cells must work together to orchestrate an efficient antitumour response. Although there is overall preclinical and clinical evidence that regular exercise can increase tumour NK cell infiltration, whether this translates into actual clinical benefits remains to be determined.

Myeloid cells

Studies of the effects of exercise on myeloid anticancer responses have mainly focused on MDSCs, the polarization of tumour-associated macrophages (TAMs) and tumour infiltrates of dendritic cells. For example, two studies have reported that exercise training in a mouse model of breast cancer reduced the tumour-induced accumulation of MDSCs after 6 weeks of voluntary wheel running or approximately 3 weeks of treadmill running starting at different timepoints after the inoculation with cancer cells[107,108]. This is potentially important because MDSCs (especially $CD14^{+}HLA\text{-}DR^{lo/neg}$ monocytes) can have a role in cancer-induced immunosuppression, notably by inhibiting the antitumour activities of T cells and NK cells at the same time as stimulating T_{reg} cells[109–111]. The reduction of intratumoural MDSC infiltrates after exercise training in mice was accompanied by a relative increase in NK and $CD8^{+}$ T cell activation and improved responses to combination therapy with PD1 blockade and radiotherapy[108]. There is also evidence for an improved response to PD1 blockade when treadmill running was combined with resistance training in a patient-derived xenograft mouse model of lung cancer, albeit with no significant differences in total tumour MDSC infiltrates[112]. Another study in a mouse model of melanoma (B16), however, has found no additive effect of exercise (wheel running) on the efficacy of immunotherapy (PD-1 or PD-L1 blockade)[113].

Macrophages can be polarized towards a pro-inflammatory (M1) phenotype or an immunosuppressive (M2) phenotype. M1-polarized TAMs induced by IFNγ and lipopolysaccharide are considered antitumorigenic owing to the expression of inducible nitric oxide synthase (iNOS) and the secretion of cytotoxic reactive oxygen species and pro-inflammatory cytokines[114]. By contrast, TAMs activated by IL-4 (M2-TAMs) can be considered pro-tumorigenic owing to their expression of growth-promoting, proangiogenic and extracellular matrix remodelling signals via vascular endothelial factor, among other factors[114]. M2-TAMs also show elevated expression of CCL22 (also known as monocyte chemoattractant protein-1)[115] which facilitates the recruitment of immunosuppressive T_{reg} cells[116]. In a mouse model of invasive breast cancer, wheel-running training (especially above 150 km per week) had a dose–response effect on tumour growth, together with a significant reduction in *Ccl22* transcription[117]. A study in a mouse model of intestinal tumorigenesis has found that, compared with sedentary controls, mucosal scrapings of treadmill-exercised mice (1 hour per day, 6 days per week for 12 weeks) had lower levels of transcripts of *Ccl22*, as well as of *Cd206* and *Arg1* – two other genes

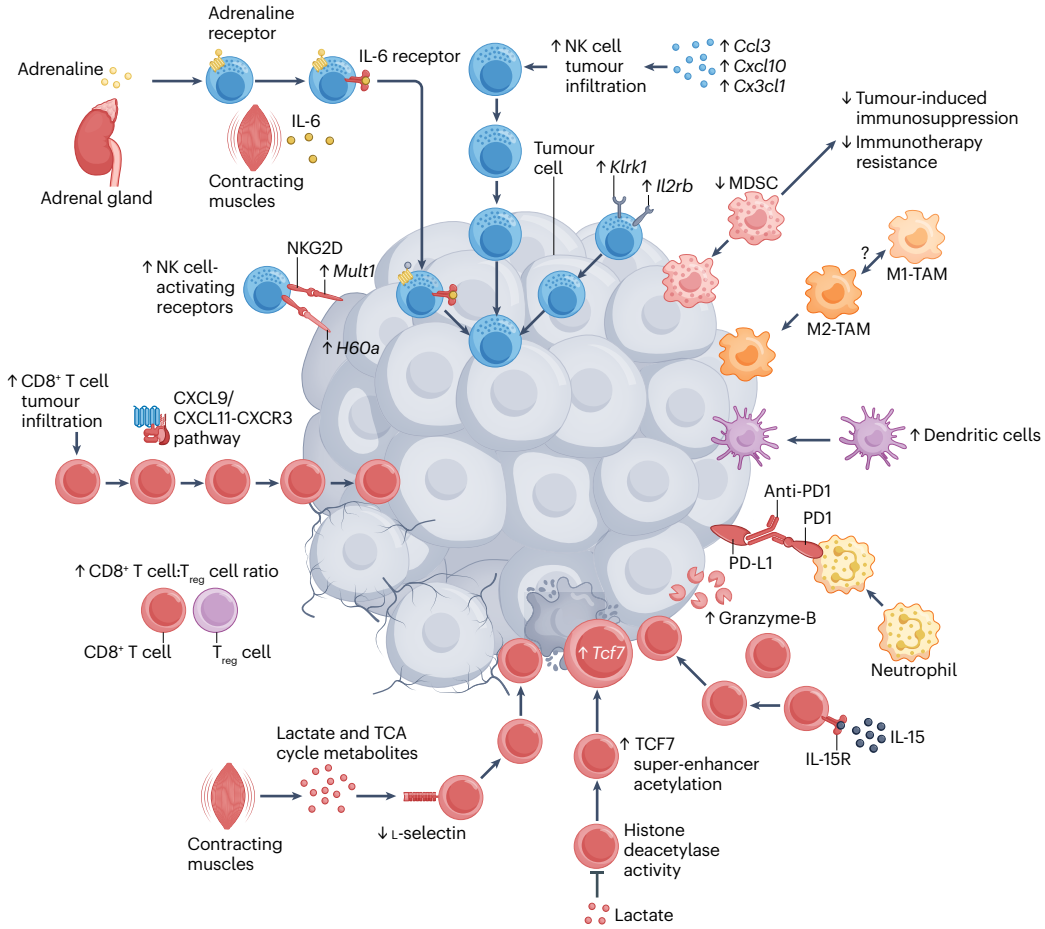

Fig. 3 | Regular exercise has the potential to 'heat' tumours. Exercise-primed immune cell infiltrates in tumours have mainly been studied with regard to natural killer (NK) cells, with the evidence indicating enhanced gene expression of chemokines that stimulate NK cell infiltration into the tumour bed (*Ccl3*, *Cxcl10* and *Cx3cl1*), increased tumour expression of ligands (*H60a*, *Mult1*) for the NK cell-activating receptor NKG2D, and gene upregulation of receptors required for NK cell cytotoxic activity (*Klrk1*, encoding NKG2D, and *Il2rb*). In addition, during each exercise bout, β_2-adrenergic-driven NK cell mobilization into the blood is followed by myokine (IL-6)-mediated infiltration into tumours. Exercise training can reduce tumour infiltrates of an immune subset that has been linked to immunotherapy resistance and tumour progression: the myeloid-derived suppressor cells (MDSCs). There is more controversy regarding the potential infiltration by tumour-associated macrophages (TAMs). Regular exercise can also increase tumour infiltrates of dendritic cells (this was shown in a mouse model of high-risk neuroblastoma, one of the most aggressive paediatric tumours[121]). There is evidence for a CXCL9–CXCR3 and CXCL11–CXCR3 pathway-mediated increase in tumour infiltrates — and effector functions — of CD8$^+$ T cells with exercise training, together with an inhibition of FOXP3$^+$ regulatory T (T$_{reg}$) cells. Some myokines might prime CD8$^+$ T cells against tumours by decreasing the expression of the cell adhesion molecule L-selectin (lactate and tricarboxylic acid (TCA) metabolites), by epigenetic mechanisms (lactate released from muscles can inhibit histone deacetylase in T cells, which, in turn, leads to higher acetylation of H3K27 of the *Tcf7* super enhancer locus, leading to increased *Tcf7* gene expression) or by stimulating the release of granzyme-B (IL-15). Finally, neutrophils can infiltrate lung tumours in response to exercise training, with these cells acting as potential effector cells of PD1 inhibition.

that are upregulated in M2-TAMs — together with lower expression of FOXP3, a marker for T$_{reg}$ cells[118]. By contrast, transcriptome analysis in a mouse model of lung cancer showed that a 12-week endurance (treamill exercise) regimen decreased the proportion of M1-TAMs (that is, lower mRNA levels of the M1 markers *Cd86*, *Tnf* and *Nos2* compared with controls)[119]. In a similar vein, other studies of breast tumour transcriptome analyses[120] or flow cytometry of high-risk neuroblastoma tumours[121] indicated that wheel running in the 2 weeks before tumour engraftment[120] or treadmill running combined with resistance exercise for 5 weeks after tumour implantation[121] led to higher M2-like TAM infiltrates in the tumours as compared with control mice. However, the inhibitory effect of exercise on tumour growth might be independent of its effect on total TAM infiltrates, as antitumorigenic immune activity can occur on a background of decreasing levels of TAM infiltration[119]. Consequently, TAMs extracted from exercised lymphoma-bearing mice had a higher antitumour activity in vitro and production of tumouricidal molecules (such as TNF and nitric oxide) than those from non-exercised controls[122].

Dendritic cells stimulate and expand tumour-specific effector T cells through IL-12 signalling, and a high number of dendritic cells are detected in spontaneous regressing tumour models, suggesting a critical role in tumour control[123,124]. A 5-week treadmill running

and resistance intervention in a mouse model of high-risk neuroblastoma increased the presence of myeloid cells, and in particular dendritic cells, in tumours[121]. This finding is potentially relevant since the high-risk neuroblastoma tumour environment is often referred to as 'cold' or 'immune-deserted'[125] and strategies to increase dendritic cells represent a potential immunotherapeutic approach to promote tumour regression[126]. Moreover, an 8-week moderate-intensity training regimen (treadmill aerobic exercise and resistance training) in a patient-derived xenograft mouse model of early-stage non-small-cell lung carcinoma decreased the tumour growth rate compared to controls, and also tended to increase intratumoural neutrophil infiltrates (that is, quasi-significant *P* value of 0.060) when combined with immunotherapy (PD1 blockade)[112]. This finding is also of potential interest given that, although myeloid subsets have been less studied than lymphocytes in the context of immunotherapy, neutrophil infiltrates might exert a cytotoxic effect and act as effector cells (involved in necrotic tumor regression) in response to PD1 inhibition[127].

T cells

An 8-week forced running intervention in a mouse model of breast cancer slowed tumour growth and increased the ratio of intratumoural $CD8^+$ T cells to T_{reg} cells[128]. Similarly, exercise training for 1–2 weeks delayed the growth of breast cancer in an orthotopic rodent model by increasing tumour infiltration and effector functions of $CD8^+$ T cells via CXCL9–CXCR3-mediated and CXCL11–CXCR3-mediated pathways[129]. Beyond the finding that a delay in the growth of breast cancer tumours was observed in exercised wild-type mice but not in equivalent athymic mice[128], there is additional mechanistic evidence supporting a $CD8^+$ T cell-dependent reduction in tumour growth in response to exercise: skeletal muscle-derived lactate and tricarboxylic acid cycle metabolites, which are released into circulation during exertion (and reach virtually all tissues including lymphoid organs), appear to enhance the antitumour effector profile of $CD8^+$ T cells, notably by driving the loss of the cell adhesion molecule CD62L (also known as L-selectin)[130]. Similarly, the administration of sodium lactate for 2–3 weeks in mice inoculated with MC-38 colon adenocarcinoma cells resulted in an immune-dependent decline in tumour expansion by enhancing the stemness of $CD8^+$ T cells through epigenetic regulation; specifically, lactate inhibited histone deacetylase activity, resulting in increased acetylation (at H3K27) of a T cell-specific transcription factor (*Tcf7*) super enhancer locus, leading to increased *Tcf7* gene expression[131]. Furthermore, there is recent evidence that lactate represents a bioenergetic and biosynthetic fuel for $CD8^+$ effector T cells and also has an effect on their transcriptome, including the expression of key effector differentiation markers such as granzyme B (a serine protease secreted by these cells to mediate apoptosis in target cells) and IFNγ[132,133].

Pancreatic ductal adenocarcinoma (PDA) is the third leading cause of cancer-related death in the USA with 5-year survival of <10% and no effective treatment for advanced disease[134,135]. Furthermore, PDA remains resistant to immunotherapies, probably because of the modest T cell infiltrate and highly immunosuppressive tumour microenvironment[134,135]. Some studies have found no changes with exercise in the tumour infiltrates of mice that were subcutaneously inoculated with PDA cells[136]. Yet, a notable recent study has shown that 6-week treadmill running restricted tumour growth in several different mouse models of PDA, which was accompanied at the intratumoural level by a significant expansion of lymphocyte clusters, particularly $CD8^+$ T cells, and a contraction of MDSCs[47]. The authors have noted that only $CD8^+$ T cells induced by exercise, particularly those responsive to IL-15 signalling, were responsible for the observed reductions in tumour growth[47]. In addition, individuals with PDA who participated in a pre-operative exercise training programme showed significantly higher tumour $CD8^+$ T cell infiltrates and a trend towards higher expression of granzyme-B when compared with matched historical controls, in which higher levels of these infiltrates or granzyme-B were positively associated with survival in the exercise cohort[47]. This study has provided mechanistic evidence for an exercise-primed immune effect and biological support for novel therapeutic targets, such as IL-15 signalling. Indeed, treatment with an IL-15 superagonist enhanced the efficacy of immunotherapy (PD1 blockade) and promoted durable responses in mice[47].

B cells

The concept of tumour-infiltrating lymphocytes (TILs) has evolved to include not only T or NK cells but also B cells and plasma cells, collectively referred to as TIL-Bs[137]. TIL-Bs can perform important functions in the tumour microenvironment, including antigen presentation and antibody production, to support both T cell responses and innate immune mechanisms[137,138]. The presence of high B cell infiltration inside tumours has been associated with improved response to immunotherapy and longer survival in patients with melanoma and sarcoma[139,140]. However, TIL-Bs have rarely been studied in the context of exercise, with no significant differences reported in B cell infiltrates between exercised and control mice in models of high-risk neuroblastoma, PDA or several other tumour types[31,47,121]. More research is, therefore, needed on this topic.

Cancer progression despite immune cell infiltration

The findings of exercise-induced tumour infiltrates are promising. Nevertheless, it is important to note that, although tumours can be recognized by the immune system (which can delay their growth before they become clinically apparent), cancer can still develop[141]. Indeed, tumour cells can progressively change their phenotype through genetic and epigenetic adaptations to escape from immunosurveillance and advance to a clinically detectable state either by 'hiding' from immune recognition ('immunoselection', also known as 'immunoediting', a process where non-immunogenic tumour cell variants have a selective advantage) or actively suppressing immune effectors ('immunosubversion')[49]. In this context, although tumours in humans are often infiltrated by TILs, they may not exert significant antitumour activity[141]. Thus, it is conceivable that increasing the numbers of TILs alone does not necessarily allow for meaningful immune responses.

Glossary

Exercise (or 'exercise training')
A form of structured leisure-time physical activity with the purpose of improving or maintaining health — training for a 10-km running race, or resistance training (for example, weight lifting) to increase muscle mass. Although physical activity and exercise are often used interchangeably, the bulk of observational epidemiological evidence is based on physical activity data, whereas exercise is frequently used in intervention trials and preclinical studies.

Physical activity
Any bodily movement produced by skeletal muscles that requires energy expenditure and includes the domains of occupational, domestic, transportation and leisure time (such as walking to work or walking the dog).

An increase in TILs mediated by exercise in combination with immune checkpoint inhibitor therapy might, however, help to attenuate tumour growth — at least theoretically.

Conclusion

There is biological evidence for an immune-stimulating effect of regular physical activity or exercise, notably, by stimulating immune cell mobilization (and, at least potentially, homing into tumours) in the few hours after each acute bout of exercise. As opposed to immunotherapeutic approaches, the beneficial immune effects of exercise are not accompanied by detrimental side effects, and carefully adapting exercise programmes to the individual characteristics of each patient can have a positive impact on health status, even in those with advanced-stage cancer[142]. These observations support the recommendation of experts that 'all people living with and beyond cancer should be as active as is possible for them'[143]. More research is, however, needed for testing the 'bench-to-bed' translation of recent preclinical findings, as well as new designs to unveil the potential mechanisms behind the preventive benefits of exercise against tumour establishment (that is before a tumour is already visible and assessable). In addition to expanding preclinical research, it would seem necessary to assess potential (co)adjuvant exercise effects in the context of immunotherapy trials and in the prehabilitation setting (that is, preoperative interventions, such as exercise training, aimed at increasing the physiological reserve of patients with cancer so that they can better withstand the stress of surgery on body systems). Some other questions regarding specific exercise modalities remain open, such as the potential effects of resistance exercise (which has been scarcely studied compared with endurance exercise) on anticancer immune function.

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