Impact of physical activity on immune cell populations and potential for synergy with immune checkpoint inhibitors (Review)

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Abstract. Over the last decade, immune checkpoint inhibitors have revolutionized cancer patient treatment. However, not all patients benefit from these therapies. A major predictive factor of response to immune checkpoint inhibitors is immune infiltration at the tumor site. Although immune infiltration is dictated mostly by intrinsic tumor attributes, particularly the tumor mutational burden, intense research is ongoing to identify approaches to increase the homing of immune cells, especially of T cells, to the tumor. The aim of the present review was to provide an overview of the impact of physical activity on immune cell populations and on the perspectives of synergy with immune checkpoint inhibitors in cancer treatment. Physical activity is known to induce peripheral leukocytosis and has been shown to increase T and NK cell infiltration at the tumor site, suggesting that its combination with immune checkpoint inhibitors could be beneficial. Available literature on exercise immunity lacks homogeneity and this is identified as a gap for establishing strong evidence.

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1. Introduction

It is now well established that physical activity decreases the incidence of several types of cancer, this protective effect being intensity-dependent (1). Exercise is also showing promising results during different phases of oncologic treatments. In a randomized trial assessing the impact of exercise on patients with early breast cancer receiving neoadjuvant chemotherapy, women in the intervention group were more likely to have a pathologic complete response (2). Physical activity during neoadjuvant radio-chemotherapy before surgery for rectal cancer was associated with reduction in surgical complications (3,4). More recently, the CHALLENGE trial showed that a 3-year structured physical activity program in patients with colon cancer having completed adjuvant treatment was associated with longer disease-free survival (5).

In that regard, the immunomodulatory effect of exercise has become a subject of high interest in the last decade. The advent of immune checkpoint inhibitors (ICIs) has been a breakthrough in oncology, although not all patients respond to these therapies (6). ICIs act on invigorating antitumor immune responses and the potential of exercise to mobilize the immune system is explored to potentiate the effects of ICIs (6). The central hypothesis explored in the present review is that physical activity leads to immune cell mobilization and remodeling of the tumor microenvironment (TME) through increased CD8 T-cell and natural killer (NK) cell infiltration in tissues, together with a reduction in myeloid-derived suppressor cells (MDSCs). With response to ICIs being correlated with immune infiltration (7,8), there is a clear biological rationale to hypothesize that exercise can improve ICI efficacy.

The aim of the present review was to provide an overview of the existing evidence on the possible synergistic effect of physical activity in patients receiving ICIs. The concept of antitumor immunity and treatment with ICIs is first introduced. The impact of physical activity on immune cell populations in healthy individuals, mouse models of cancer and in patients with cancer is then described, together with the current evidence for the benefit of combining exercise and immunotherapy with ICIs. Finally, ongoing randomized

clinical trials that have the potential to address the identified research gaps are listed.

Several reviews detailed later in the text (9-13) already cover the immunological effects of exercise, the determinants of response to ICIs, or the preclinical and clinical evidence of the effects of physical activity on ICI efficacy, each covering one segment of the reasoning. The present review assembles the current knowledge in a single narrative chain. This narrative review is based on a non-exhaustive literature search performed in PubMed (https://pubmed.ncbi.nlm.nih.gov/) database. Search terms combined 'exercise' or 'physical activity', 'cancer', with 'immune system' or 'tumor microenvironment' or 'ICI' or 'immunotherapy'. No restriction of date was applied; the last search was performed in April 2024, and clinical trial registries were last searched in April 2024. Recent results from two randomized trials (CHALLENGE and ERICA) (5,14) were added later. Studies were eligible if they reported immune cell populations or immune-related outcomes in the context of physical activity, in healthy individuals, preclinical tumor models or patients with cancer. Case reports, abstracts or articles that were not available in English were not included. Evidence is listed in three different settings: Healthy individuals, murine tumor models and patients with cancer, which have not been formally linked together. No published prospective trial has yet evaluated the benefit of physical activity on ICI efficacy as a primary endpoint, and the rationale that was explored in the present review is therefore hypothetical.

2. The immune system and cancer

The immune system. The immune system relies on two facets of immunity, innate and adaptative immunity. Innate immunity readily activates upon pathogen encounter by recognizing pathogen-specific motifs, whereas adaptative immunity generates a pathogen-specific response as well as a memory response that can persist for life (15). Adaptative immunity relies mostly on T and B lymphocytes, both being elicited to be highly specific for their target.

The immune system is educated to react to the non-self, namely foreign motifs borne by pathogens, and to ignore the self. T lymphocytes only get activated when they encounter peptide motifs [presented by major histocompatibility complex (MHC) molecules on antigen-presenting cells] to which they have never been exposed. Recognition of foreign antigens in secondary lymphoid organs induces T-cell activation, which requires two signals, one mediated by the interaction between the MHC/peptide complex and the T-cell receptor (TCR) and the other mediated through interaction between CD28 with CD80 or CD86 ligands on antigen-presenting cells. Once activated, T lymphocytes are able to mediate their cytotoxic or helper effector function and help control infection. During this process, T lymphocytes upregulate co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD1), which, upon binding to their respective ligands [CD80/86 and programmed death ligand 1/2 (PD-L1/2)], leads to T-cell inhibition, a normal process of regulation of the immune system (16).

Antitumor immunity. In addition to being able to recognize pathogens, the immune system is also able to recognize and destroy emerging tumor cells. Antitumor immunity is elicited upon uptake of tumor antigens by dendritic cells (DCs), which traffic to secondary lymphoid organs to prime T lymphocytes. Antitumor B cells are also elicited, but their role in antitumor immunity is less well described (17). Although T cells can recognize tumor cells, tumor eradication is in most cases not efficient, as the tumor has the capacity to counteract immune responses, a process known as immunoediting (18). This concept proposes that, whereas tumor cells are initially eliminated by the immune system, a phase of equilibrium between the immune system and the tumor then takes place, where mutations continuously accumulated by tumor cells are selected by immune pressure, eventually leading to tumor escape, a phase in which the immune system is no longer able to contain tumor growth (18). Evasion of immunosurveillance by the tumor includes mechanisms such as alteration of the antigen presentation pathway, secretion of soluble immunosuppressive factors, as well as attraction of immunosuppressive cells (18). This altogether creates an immunosuppressive TME, in which tumor, stromal and immune cells are reprogrammed to an immune inhibitory phenotype. In particular, macrophages found at the tumor site, also known as tumor-associated macrophages (TAMs), are polarized by TME cytokines into an immunosuppressive phenotype, which promotes angiogenesis and tumor growth. Macrophages can also be promoted to become MDSCs, which are pro-tumoral cells with immune suppressive activity (18,19). Finally, CD4 T-cells can be induced to become immunosuppressive T regulatory (Treg) cells in the TME. Altogether, by inducing a TME, the tumor generates a milieu where infiltrating antitumor T cells are prevented from exerting their effector function. In that regard, overexpression of T-cell inhibitory ligands such as PD-L1 plays a major role (Fig. 1) (20).

The nature of the immune infiltrate itself varies from one tumor to the other and three types of immune phenotypes have been identified (16). In an immune-inflamed environment, CD4 and CD8 T cells are present in abundance and both tumor cells and infiltrating immune cells (mostly TAMs) express PD-L1. In the immune-excluded type, immune cells are unable to penetrate the tumor and are limited to the stroma surrounding the tumor bulk. Finally, in immune-desert tumors, no immune infiltrate is found (16). The different types of immune infiltrates result mostly from the number of mutations accumulated by the tumor, which varies for each tumor type. Notably, mutated proteins contain epitopes (neoantigens) that have the potential to be recognized as non-self by the immune system and to induce antitumor T-cell responses. Thus, tumors with high mutational loads are inherently more immunogenic and contain elevated T-cell numbers. As outlined below, in addition to influencing the nature of the immune infiltrate, the tumor mutational burden (TMB) is positively associated with response to ICIs (21).

Immune checkpoint inhibition. The recognition that immune checkpoint molecules (CTLA4 and PD1, among others) are used by tumors to escape antitumor T-cell responses led to the development of a new type of cancer immunotherapy, ICIs, which has been implemented in the clinic in the last decade. ICIs are monoclonal antibodies that specifically bind to T-cell inhibitory molecules such as CTLA4, PD1 or PD-L1. By inhibiting the negative regulation of T lymphocytes, these

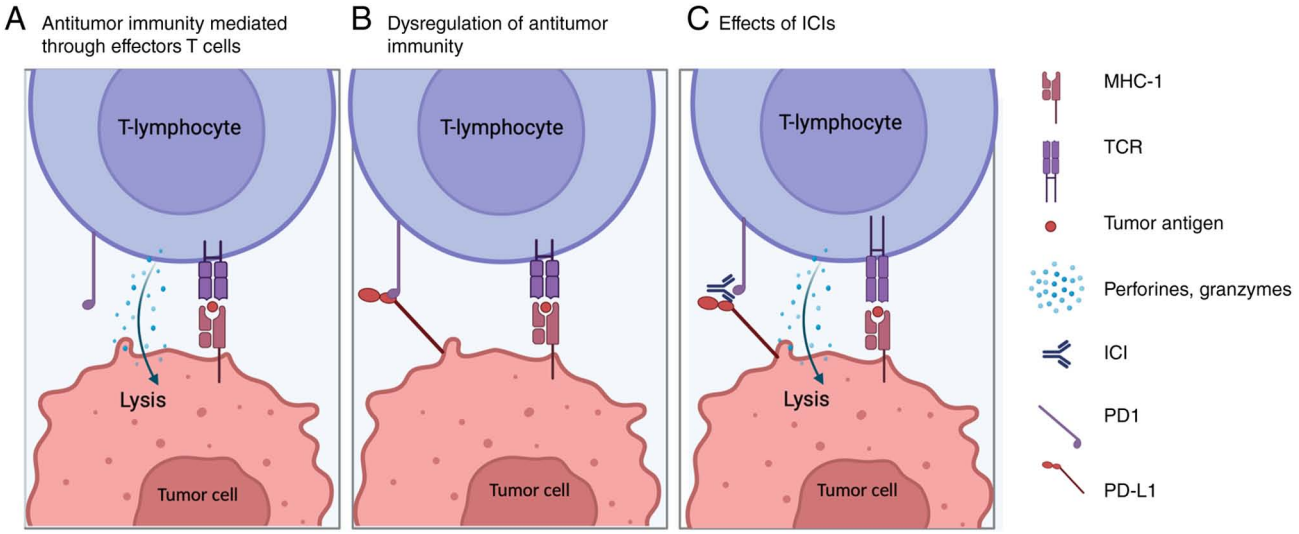


Figure 1. Mechanism of action of immune checkpoint inhibitors. (A) Effective antitumor immunity occurs when cytotoxic T lymphocytes recognize tumor antigens presented by MHC-I, leading to tumor cell lysis via perforin and granzyme release. (B) Dysregulation of antitumor immunity occurs when tumor cells express PD-L1, which engages PD1 on T lymphocytes and suppresses their cytotoxic function, thereby preventing effective tumor cell lysis. (C) Immune checkpoint inhibitors restore T-cell effector function by blocking inhibitory pathways, thereby restoring cytotoxic activity and tumor cell lysis. MHC-I, major histocompatibility complex-I, PD-L1, programmed death-ligand 1; PD1, programmed cell death protein 1; TCR, T-cell receptor; ICIs, immune checkpoint inhibitors. Created with BioRender.

antibodies restore antitumor immunity, resulting in improved patient survival, as observed in several malignancies (Fig. 1). Anti-PD1 antibodies are the first line of treatment for *BRAF* wild type metastatic melanoma and ICIs targeting the PD1/PD-L1 axis are now recommended as first- or second-line therapies for numerous cancer types including lymphoma, lung, renal cell, head and neck squamous cell, bladder, liver and gastro-esophageal cancers (22).

Determinants of response to ICIs. Whereas ICIs have revolutionized the treatment of numerous malignancies, response to ICIs is inconsistent, as only a fraction of patients experience durable clinical benefit (23). Identifying the determinants of response to ICIs and finding biomarkers able to predict response are currently the next important stake. Thus far, only two predictive factors for ICI response have been validated in phase III clinical trials: The TMB and PD-L1 expression (16). The TMB is defined as the number of somatic mutations per megabase of interrogated genomic sequence (24). As aforementioned, it is highly variable among tumor types, with cancers caused by mutagenic exposure such as lung cancer and melanoma having a markedly high TMB and leukemia and some childhood cancers having the lowest TMB (25). In addition, some malignancies such as colon or bladder cancer show a high interpatient TMB variability whereas others, such as lung and head and neck cancers, have lower variability. Tumors having >10 mutations per megabase are usually considered TMB-high tumors, following association with ICI efficacy in metastatic solid tumors treated with anti-PD1 (26). PD-L1 expression is being measured using various scoring methods; the tumor proportion score, which refers to PD-L1 expression by neoplastic cells, the combined positive score, illustrating expression of PD-L1 by tumor cells, lymphocytes and macrophages, and the immune cell scoring, which refers to the area occupied by PD-L1-positive immune cells (lymphocytes, DCs, macrophages, and granulocytes) as a percentage of the whole tumor area (27).

A positive association between the TMB and response to ICIs has been reported for 27 types of cancers (21). This association is explained by the fact that tumors with higher TMB produce higher numbers of neoepitopes which can be detected by T cells, inducing spontaneous T-cell responses that can be invigorated by ICIs. Notably, ICIs (when used as monotherapy) act only on pre-existing T-cell responses and are thus not efficient in TMB-low tumors. Within a given cancer type, the TMB is not able to discriminate between responders and non-responders (21). Some malignancies show a response rate different from the one predicted by TMB alone, suggesting that other factors are involved. The use of the TMB alone is therefore not sufficient to select patients who will benefit from ICIs.

PD-L1 expression by tumor cells has been extensively investigated as a predictive factor of response to ICIs. In the TME, tumor-infiltrating lymphocytes release interferon (IFN)-γ as part of their antitumor activity, and IFN-γ production in turn stimulates PD-L1 expression by tumor cells (as well as by other cells present in the TME) (28). Thus, considering that PD-L1 expression is positively associated with immune infiltration, analyzing PD-L1 levels will likely identify tumors that will respond to ICIs (21). Although this explanation suggests that PD-L1 expression and the TMB are directly linked, they have been shown to be largely independent (29) and PD-L1 expression is currently clinically used as a biomarker in non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma and urothelial carcinoma (30). However, whereas multiple studies describe a positive association between PD-L1 expression and overall survival or response to ICIs (31-35), others show no association (16,36-39). These discordant results may be explained by the use of different assays for the determination of PD-L1

expression, non-standardized criteria to assess positivity, or by intratumoral heterogeneity (16). It has been shown that selected patients displaying low or non-detectable PD-L1 expression still benefited from pembrolizumab administration (16). Overall, it is not surprising that the type of TME is predictive of response to PD1/PD-L1 blockade. Immune-desert and -excluded tumors are associated with low response to ICIs, whereas immune-inflamed tumors are associated with better response to PD1/PD-L1 blockade (16,21). Nonetheless, PD-L1 expression remains an imperfect biomarker and some patients are treated irrespectively of it (9). Finally, other factors such as immune infiltration at the tumor site and microbiota are considered as playing a predictive role in response to ICIs (40). All in all, it is still difficult to predict which patient is going to respond to ICI therapy across different malignancies, but combining predictive factors might enable a better selection of patients benefiting from ICIs.

3. Impact of physical activity on immune cell populations

Healthy individuals. The benefits of physical activity on health are widely demonstrated, and a large body of evidence describes the impact of exercise on the immune system. Exercise induces secretion of cortisol, adrenaline, growth hormones and prolactin, which lead to immunomodulatory effects on leukocyte trafficking and function (41). Physical activity also increases levels of anti-inflammatory myokines (muscle-derived cytokines) (41). The effect of exercise on body homeostasis in general and on the immune system in particular depends on exercise frequency, type and intensity and the magnitude of the effect also depends on measurement time in relation to the training session. In this first part, the effects described in the literature according to those parameters are classified.

Exercise is characterized by its type, frequency and intensity. The main types of physical activity studied in the literature are resistance and endurance training. Resistance training implies a series of exercise repetitions designed to improve muscular fitness. Endurance training, on the other hand, implies performing activities such as running or cycling at a moderate intensity to train the cardiorespiratory system (42). Frequency is defined according to the number of repetitions of the training: Acute exercise refers to one single bout whereas chronic exercise involves repeated physical activity sessions. Intensity of exercise can be quantified according to the percentage of maximal oxygen consumption (VO_2 max) or according to metabolic equivalent of task (MET). VO_2 max measures the maximal rate of oxygen consumption that an individual can have during a progressive exercise (43). It reflects the cardiorespiratory fitness of an individual and allows standardization of exercise intensity among a heterogenous group. On the other hand, MET is the ratio of energy expenditure due to exercise over basic metabolism at rest (44). This unit is standardized based on the type of activity and not on individual fitness, ranging from sedentary (<2 MET) to vigorous (>6 MET) (44).

Impact of frequency. In healthy individuals performing acute bouts of endurance activity, exercise induces an immediate and robust immune cell mobilization in the blood, reflected by increase of NK cells, CD8 and CD4 T cells as well as B cells immediately after the effort, with NK cells displaying the greatest relative change (10). Lymphocyte increase is temporary, with a return to basal levels 3 h after exercise, whereas neutrophils peak 3 h after exercise (45), this not being due to cell death but to redistribution of immune cells to tissues and organs. Immune cell-effector function, including cell proliferation, cytokine secretion and cytotoxicity, is also altered with the same kinetics, potentially leading to redistribution in tissues of highly functional immune cells and improving immune surveillance against pathogens and tumor cells (46). Regular exercise is meant to be beneficial to immunity through the cumulative effects of repeated acute bouts (11). However, their lasting effect is not necessarily noticed in blood counts with a phenomenon of 'wash out' period described in the literature after 24 h (11).

Impact of exercise type. In studies where healthy men performed either resistance or endurance training at moderate intensity, endurance activity was found to be more efficient at inducing leukocytosis than resistance training (45,47).

Impact of exercise intensity. Moderate intensity exercise has been shown to improve immune responses to vaccines (48). Acute bouts of low to moderate intensity exercise also mediate immunomodulatory effects through transient secretion by contracting muscles of small amounts of IL-6 (10). Although IL-6 is a pro-inflammatory cytokine, it mediates anti-inflammatory effects on immune cells when secreted by skeletal muscles through the induction of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (41,49). In contrast to exercise of moderate intensity, prolonged and intensive physical activity such as that performed by athletes is thought to provoke immune dysfunction lasting from a few hours to a few days (50). Although debated, the concept of the 'open window' describes how extremely intense exercise temporarily leads to immunosuppression, leading to an increased risk of contracting upper respiratory tract infections (51). However, it remains unclear whether this effect is due to the intensity or the duration of exercise. In a study where 15 healthy individuals were cycling at either maximal intensity or moderate one, immune populations showed different kinetics. Both were able to induce significant increase in granulocyte populations, but only maximal intensity significantly mobilized lymphocytes (52). Thus, the optimal frequency and intensity of exercise to potentialize immunity remains to be determined.

Preclinical cancer models. A narrative overview of the mechanisms behind exercise impact on immunity is provided. A systematic listing of these has not been undertaken, as they have already been covered in several reviews. The preclinical effects of physical activity on tumor incidence, growth and progression are covered in Ashcraft *et al* (53), while preclinical findings on the effects of physical activity on tumor and immune outcomes are covered in Xu and Rogers (12). The ability of physical activity to mobilize immune effector cells has been explored in mouse models to study cancer immunosurveillance, based on the observation that exercise was associated with decreased tumor incidence, growth or metastasis in the majority of preclinical cancer models (53,54). It was observed across multiple mouse tumor models that exercise induces accumulation of effector cells at the tumor site. Voluntary wheel running induced catecholamine-mediated

mobilization and redistribution of NK cells, leading to reduced tumor growth and incidence (46). Wheel running was also shown to increase the intratumoral CD8 T-cell to Treg cell ratio in a breast cancer tumor model (55), which might be due to the ability of exercise to decrease the levels of the Treg chemoattractant molecule C-C motif chemokine ligand 22 (CCL22) (56). In parallel, T- and NK-cell chemoattractants were shown to be increased by exercise (46). In a mouse melanoma model, voluntary wheel running was also shown to increase expression of immune checkpoint molecules (57), which could be secondary to immune infiltration and activation (28). Additionally, exercise was shown to be beneficial in priming antitumor CD8 T cells in secondary lymphoid organs (58).

Other research has shown the potential of exercise to modulate the TME (59). Studies in mouse breast carcinoma models showed that MDSC levels at the tumor site were reduced in mice performing voluntary wheel running (60,61), which was associated with increased CD8 T-cell and NK-cell activation (62). In a murine model of breast cancer, swimming resulted in the polarization of macrophages towards an antitumor phenotype as a result of pro-inflammatory cytokine secretion (63). As antitumor immune cells have to function in a usually highly suppressive TME, reduction in immunosuppressive MDSC levels in the TME has the potential to be beneficial for efficient antitumor immune responses.

Finally, it has been shown that exercise is able to modulate the tumor vasculature. In mouse breast, melanoma and prostate cancer models, exercise promoted normalization of the tumor vasculature and led to increased tumor vessel perfusion and reduced hypoxia (64-67). This, in addition to enabling better delivery of chemotherapeutic drugs, has the potential to increase accessibility of immune cells at the tumor, while reducing hypoxia, leading to better antitumor immune cell function. In summary, in murine models, physical activity modifies the TME towards a proinflammatory phenotype by promoting immune cell infiltration and reducing levels of immunosuppressive myeloid cells. Of note, the different mouse model studies discussed above present considerable methodological heterogeneity, preventing definitive conclusions to be drawn.

Patients with cancer. The impact of exercise on immune cell modulation has been tested in patients with cancer, but the heterogeneity in methodology (exercise type, regimen and timing with regard to cancer treatment), type of neoplasia (organ, histology, and stage) and cancer treatments (surgery, radiotherapy, and chemotherapy) makes it difficult to draw definitive conclusions, with some studies also lacking internal sedentary controls (12,68-70). In general, the existing literature lacks statistical power and reproducibility in exercise protocols and target populations and, to date, fails to provide consistent results.

Studies analyzing the effect of exercise on serum inflammatory markers and cytokines did not find consistent results, with most studies showing no impact (12). The same was observed regarding circulating T, NK and B cells, monocytes and neutrophils as well as regarding T- and NK-cell function. Only a limited number of studies were able to analyze the tumor tissue after exercise intervention (69,71,72). In a randomized study implementing a 1-month exercise period before surgery in patients with localized breast cancer who were not receiving any treatment during the study period, upregulation of immune cell function and inflammatory signaling pathways was observed in the exercise group compared with the sedentary group, but no changes in T-cell or macrophage abundance at the tumor site were noted (72). In a prospective single-arm study, where a combination of aerobic and resistance training before surgery in patients with pancreatic ductal adenocarcinoma receiving neoadjuvant chemotherapy or chemoradiotherapy was tested, higher CD8 T-cell infiltration at the tumor site was observed in the exercise group compared with historical matched controls (71). Within this cohort, patients displaying the highest CD8 T-cell infiltration were found to have improved overall survival. However, a randomized controlled trial (n=30) in patients with prostate cancer assessing whether high-intensity aerobic exercise performed before surgery could increase NK-cell infiltration was negative, with no intergroup differences observed (69). In the latter study, adherence to the exercise program was heterogenous, ranging from 4 to 30 sessions and, in patients attending at least 75% of sessions, an increase in NK-cell infiltration was observed, with a dose-response gradient between the number of sessions attended and the change in NK cell infiltration (69).

Most of the inconsistency in the results obtained in clinical trials can likely be explained by four confounding factors. First, adherence to exercise protocols is directly linked to the magnitude of the effect observed, as depicted by the study showing positive results only in patients regularly attending the exercise sessions and by a gradient of response between the number of sessions attended and the change in NK-cell infiltration (69). This notion is supported by evidence that regular exercise in healthy individuals is associated with increased benefit through the cumulative effects of acute bouts (11). Second, as detailed in the next section, physical fitness likely influences the frequency and intensity of the exercise practice of patients (70). Third, concurrent treatments differ markedly across studies. Among the studies cited, only two analyzed the effect of physical activity in patients not receiving any oncological treatment (69,72). Beyond oncological treatments, β-adrenergic receptor antagonists such as propranolol can inhibit lymphocyte mobilization mediated by exercise (73) and these treatments were only excluded in one study (69). Finally, only two studies explicitly detail cancer stages, and both included localized and locally advanced cancers (69,72). As adherence to physical activity programs is likely to be more difficult in symptomatic metastatic patients, this parameter is also likely to influence the results obtained.

Potential synergy with ICIs. Considering that exercise can promote increased T-cell and NK-cell infiltration while reprogramming the TME into a pro-inflammatory environment, there is a rationale to hypothesize that response to ICIs could be amplified by exercise (10). Using exercise as an adjuvant to ICI therapy is therefore a promising research path. In a previous review compiling murine studies testing the impact of exercise as an adjuvant treatment to ICI (13), exercise combined with ICI therapy was found to decrease tumor growth compared

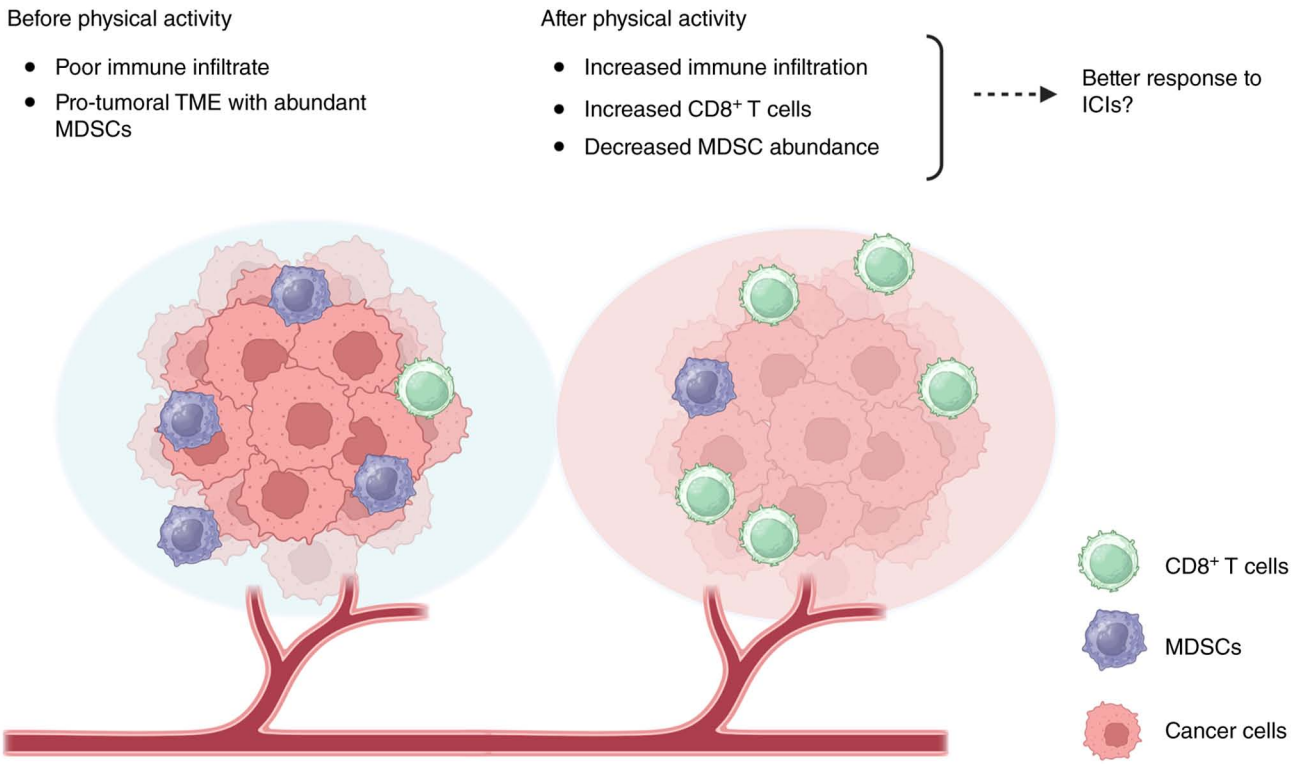


Figure 2. Hypothesized mechanism of synergy between physical activity and immune checkpoint inhibitors, mainly based on preclinical data. Physical activity remodels the tumor microenvironment by increasing immune infiltration and reducing immunosuppressive MDSCs, potentially enhancing responsiveness to ICIs. MDSCs, myeloid-derived suppressor cells, ICIs, immune checkpoint inhibitors; TME, tumor microenvironment. Created with BioRender.

with ICI treatment alone in two murine models (62,74), but no effect was observed in two other preclinical studies (57,75). The two former studies chose shorter exercise regimen (1-3 weeks) whereas the latter ones had longer regimens (5-8 weeks). The comparison of these models is thus limited by the heterogeneity of exercise regimens and the lack of data on their intensity. Nevertheless, in the two studies showing a positive impact of the ICI/exercise combination, both using a breast cancer model, the TME was found to be modified after exercise, with reduced MDSC infiltration (62) and increased infiltration of activated CD8 T cells (74) (Fig. 2). Similarly, in murine models of pancreatic ductal adenocarcinomas, known as poor responders to ICIs due to their low immunogenicity, aerobic exercise increased intratumor CD8 T cells, leading to improved response to anti-PD1 and survival (71), suggesting that exercise could sensitize poor immunogenic tumors to ICIs. In studies showing no effect of the combination, exercise alone was able to reduce tumor growth in a B16 melanoma model (57) and in an NSCLC model, in which increased infiltration of neutrophils was observed (75), but no additional benefit of ICI treatment was observed. In other breast tumor or melanoma model studies, no impact of exercise, ICIs or their combination on tumor growth was observed, but an impact of the combination on tumor CD8 T-cell infiltration was observed in the breast tumor model (76). These studies suggest that there may be a benefit in combining exercise with ICIs, but further research is required to be able to use rodent studies as a guide to incorporate exercise in ICI regimens. The lack of protocoled physical activity is identified as a major gap in this literature.

4. Physical activity in patients receiving ICI treatment

Until now, no prospective published human study investigated implementation of exercise as an approach to improve response to ICIs as a primary endpoint. Studies in patients receiving physical activity as adjuvant to ICIs are covered in Handford *et al* (13). A retrospective study analyzed influence of aerobic exercise on overall survival in patients with unresectable hepatocellular carcinoma treated with the tyrosine kinase inhibitor lenvatinib and anti-PD1 (77). Exercise was not proposed to patients, but patients (n=59) were categorized depending on their physical activity status. Regular physical activity was associated with improved overall and progression-free survival as well as with an improved overall response rate, but no immune analysis was performed. Other studies investigated the impact of exercise on quality of life in patients receiving ICIs but did not analyze immune markers nor patient outcome (68,78,79). In a cohort of patients with melanoma receiving pembrolizumab (n=28), an overall adherence rate to a physical activity program of 85% was reached (68). Similarly, two studies demonstrated a 75% (78) to 88% (80) adherence rate for videoconference-based physical activity programs in patients (n=16 and 11, respectively) receiving ICIs, suggesting that performing physical activity during treatment was safe and feasible. Notably, a recent study showed that moderate and high levels of patient-reported physical activity at the start of ICI treatment (n=251) were associated with a lower risk of severe immune-related adverse events and prolonged survival. However, once overall survival was adjusted for performance status, the association was no longer significant, suggesting that

the tendency observed may be biased by the physical fitness of a patient (70). No analysis of immune markers was performed, but, although confirmation is warranted, this study suggests that exercise used with the aim of potentiating ICI therapy will not result in higher rates of occurrence of immune-related adverse events.

Based on these results, studies are now starting to assess the effect of exercise on response to ICIs as well as on its influence on inflammatory markers, immune mobilization or immune tumor infiltration when combined with ICI. The ERICA randomized trial demonstrated the safety and feasibility of a resistance exercise regimen performed within 1 h before anti-PD1 immunotherapy/chemotherapy administration in patients with NSCLC (81). The ongoing HI-AIM randomized trial (NCT04263467) included 54 patients with NSCLC receiving anti-PD1 with or without chemotherapy or under oncological surveillance and evaluated the potential of a 6-week medium- to high-intensity training program to mobilize the immune system (82). Notably, this trial will monitor immune cells and inflammation markers in the blood as well as at the tumor site using paired pre- and post-training biopsies. Preliminary results report a high adherence (94%) as well as an increase in the VO_2 peak in the intervention group, and a trend towards improved survival was observed in patients receiving ICIs alone (83). The EX-BOOST randomized trial (NCT06008977) will assess feasibility and impact of physical activity proposed prior to each cycle of ICI administration on response to ICIs in patients with cutaneous cancers. Patients in the adjuvant treatment setting will be followed for recurrence-free survival whereas, in patients in the neoadjuvant treatment setting, pathological response will be assessed; however, no monitoring of immune markers will be performed. Another randomized trial with a similar design (NCT05358938) will in addition assess the impact of exercise on immune markers in the blood longitudinally in patients in the adjuvant setting. Additional trials are assessing the effect on exercise on quality of life, without immune markers or impact on patient outcome being analyzed (NCT03171064 and NCT06026111).

5. Conclusions

The rationale for the use of exercise as an approach to potentiate ICI therapy is based on the observation that physical activity mediates transient immune cell mobilization in the blood and redistribution to tissues in healthy individuals and promotes cancer immunosurveillance and remodeling of the TME in rodent models, although these effects have been observed only in a fraction of studies, probably due to the heterogeneity in the models and methodology used. Preclinical studies combining exercise and ICIs are limited and show contrasting results, some studies nevertheless showing an additive effect on tumor growth. In humans, results regarding the ability of physical activity to increase intratumoral immune infiltrates are inconsistent due to confounding factors and study heterogeneity.

Thus far, no clinical trial has tested the implementation of exercise as a combination therapy with ICIs as a primary endpoint in a prospective randomized manner, although assessment of the potential co-adjuvant effect of exercise appears essential (73). Several clinical trials are assessing the impact of implementing exercise in patients receiving ICI treatment on immune markers and clinical outcome. To date, physical activity has been shown to be feasible and safe, and to augment patient quality of life. However, successful translation of physical activity protocols into clinics will rely on an improved understanding of the underlying immune mechanisms. In addition, the heterogeneity of the studies makes it difficult to define a therapeutic exercise dose and protocol to optimally benefit from the effects of exercise on immunity. In that regard, the use of standardized activity protocols will increase result reproducibility. The exercise protocol of the CHALLENGE trial has been shown to be safe and feasible and to maintain favorable adherence rates over 3 years (5). Regardless of the type of physical activity (aerobic or resistance), the trial focused on increasing patient basal physical activity by 10 MET hours per week, combining supervised sessions and behavioral interventions and observed an adherence of 83% in the most intensive phase of the program. This protocol could be used as a standardized intervention to prospectively evaluate the impact of physical activity on response to ICIs in patients with cancer, concomitantly to ICI treatment. In addition, immune biomarkers should also be standardized in studies assessing the combination of ICIs with exercise and should, when possible, include both peripheral and tumor biomarkers. However, as biopsies are needed to investigate immune composition at the tumor site, they are less likely to be accepted by patients and might limit patient recruitment in clinical studies. Although a definitive priority still needs to be defined, peripheral blood biomarkers should include the proportion of NK, T, and B cells as well as their phenotype (45,47), whereas tumor biomarkers should, in addition, include the intratumoral proportion of MDSCs, TAMs and DCs. In that regard, the protocol of the HI-AIM study (83) assesses immune populations in both compartments and represents an excellent basis for further standardization of studies.

A limitation of the present review is its narrative rather than systematic nature. Study selection may thus reflect authors' assessment of relevance. The scope of the review was limited to physical activity and does not include other interventions that may affect the effect of ICIs (such as nutrition or modification of the microbiota). Notably, certain data suggest that diet, while modulating the microbiota of a patient, increases immune cell activation and tumor infiltration in a similar fashion to exercise (84). Finally other immunotherapy approaches, using, for example, adoptive cell therapy, could benefit from combination with exercise. In this context, in these approaches, T (or NK) cells are collected from the peripheral blood of patients and modified to generate a cell product with antitumor activity, and mobilization of immune cells with increased effector function in the bloodstream before cell collection should be explored.

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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