# The Effects of Exercise on the Tumor Immune Microenvironment

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## ABSTRACT

This review explores the current understanding of the immunomodulatory effects of exercise, and the effectiveness of utilizing exercise as a therapy for cancer. Physical exercise has been shown to reduce the risk of developing cancer and appears to possess tumor-suppressive capabilities in existing solid tumors by modulating the tumor immune microenvironment. The current literature suggests exercise to enhance intra-tumoral tumor-suppressive immune cell activity through multiple pathways. The immunomodulating capabilities of exercise are likely dependent on anti-tumor immunity pathways. Exercise appears to be a viable tumor-suppressive strategy, depending on the state of anti-tumor immunity.

**Keywords**
Cancer, immunesystem, exercise, anti-tumor immunity

## INTRODUCTION

The tumor microenvironment has been characterized by the presence of tumor and non-tumor cells, including immune cells[1]. Essentially all solid tumors have adjacent or infiltrating subsets of immune cells[2], implicating the immune system to be an excellent target for tumor-suppressing therapy. Although clinical trials confirm the efficacy of immunomodulating therapies, they also show high inter-patient variability[3]. The differences in efficacy have been attributed to variables affecting the tumor immune microenvironment (TIME) composition[4].

Exercise is one of the most well-studied lifestyle variables and shown to be associated with decreased risk of cancer development[5]. The protective effect of exercise can be, amongst others, attributed to its effect on immune function[6]. Although exercise itself is not capable of eradicating existing tumors, the current literature suggests a possible tumor-suppressive effect[7]. To establish a better understanding of the relationship between exercise and the TIME this review will provide an overview of the exercise-induced changes on the TIME and their implications for future utilization of exercise as a therapy for cancer patients.

## METHODS

The literature search was conducted through PubMed, which offers biomedical- and life-sciences-related literature. Search queries included terms related to exercise, immunology and microenvironment. The usability of articles was judged on the subsequent reading of title, abstract and contents.



*SRC 2019*, December 5, 2019, The Netherlands.

## RESULTS

### Tumor immune microenvironment characterization

Immune cells interact with tumor cells, displaying both tumor-promoting and tumor-suppressive effects[8]. Although the TIME is considered to be a context-dependent dynamic environment, parts of the immune presence can be characterized based on their distinct tumor-suppressive or tumor-promoting effects.

Three different types of immune cells have been characterized to elicit tumor-suppressive effects. Monocytes are recruited to the tumor microenvironment and differentiate into tumor-associated macrophages (TAM), which are able to induce tumor-suppressive signaling in case they are M1-polarized by for example IFN-$\gamma$[8–11]. Cytotoxic T-lymphocytes (CTL) display the greatest tumor-suppressing capabilities of the adaptive immune system through their granular secretion of cytotoxic compounds, which are able to induce apoptosis in tumor-cells[12]. The presence of T-lymphocytes has been associated with a good prognosis of cancer in many tumors[13]. Lastly, natural-killer cells (NK-cells) display specific tumor-suppressive effects due to their ability to lyse tumor cells[14].

Similarly, three types of immune cells have been characterized to elicit tumor-promoting effects. The previously mentioned macrophages are also able to polarize towards M2 macrophages in response to cytokines, like IL-4, IL-10, IL-13, and glucocorticoids, which are associated with tumor-promoting signaling[10,11,15]. Myeloid-derived suppressor cell (MDSC) presence has been associated with poor prognosis and decreased treatment efficacy, rendering them tumor-promoting[16]. Finally, regulatory T-cells (T-reg) have been shown to attenuate the cytotoxicity of CTLs and NK-cells, and reduce the antigen presentation by dendritic cells[16,17]. The presence and characteristics of all these immune cells in the tumor microenvironment makes them an excellent target for immunomodulation.

### Tumor immune microenvironment variability

Categorization of tumors based on their TIME might predict the effectiveness of immunomodulating therapies[4]. The infiltrated-excluded tumor immune microenvironment (IE-TIME) is characterized by the lack of CTL infiltration into the tumor, which is suggested to be the result of TAM signaling[4,18]. These types of tumors are considered to display a low reactivity to immunomodulating therapies[8]. In contrast, infiltrated-included tumor immune microenvironments (II-TIME) are characterized by a high number of infiltrating CTLs into the tumor core[4]. Given the ability of immune cells to infiltrate the tumor microenvironment of II-TIMEs, these tumors are likely more responsive to exercise-induced immunomodulation.

### Tumor immune microenvironment differentiation

Understanding the possible causes of the variability in immune cell infiltration into the tumor microenvironment could have implications for estimating the effectiveness of exercise as an immunomodulating-therapy. A lot of research emerged showing genotypical or phenotypical discrepancies between tumors[4]. These discrepancies result in a state of anti-tumor immunity which might be responsible for the TIME-regulation and variability. An example of anti-tumor immunity is the expression of Programmed death-ligand 1 by tumor cells, which downregulated CTL activity, resulting in a powerful immune-suppressive effect[19,20]. As exercise is not known to modulate anti-tumor immunity, tumors significantly displaying these traits are unlikely to respond to immunomodulation by exercise on its own. The currently available immunotherapies have been shown to modulate anti-tumor immunity[20], and could therefore possibly increase the efficacy of exercise as an immunomodulatory therapy when used concurrently.

### The direct effects of exercise on the tumor immune microenvironment

A body of evidence has started to develop suggesting exercise itself to suppress tumor growth and improve the prognosis of several types of cancer[7], possibly in part due to the immunomodulating effects of exercise (Figure 1). Animal research shows exercise to enhance the activity of macrophages by increasing their presence in a catecholamine-dependent manner and supporting their effector functions via increased levels of Tumor Necrosis Factor alpha (TNF-α) (Figure 1, *A* and *C*)[21,22]. Indirect measurements of TAM polarization in mice suggest exercise to induce the tumor-suppressive M1 phenotype (Figure 1*A*)[22,23]. Exercise in mice appears to induce catecholamine-dependent recruitment of NK-cell (Figure 1*A*), which are activated and homed towards the tumor by IL-6 dependent pathways (Figure 1*C*)[24]. This particular paper found the exercise-induced increase in NK-cell activity to decrease tumor growth by 60%[24]. In mouse models, exercise-induced increases in catecholamines also upregulate the CTL mobilization (Figure 1*A*)[24]. The same study displayed increased tumor growth in athymic mice, marking the importance of CTLs as tumor-suppressors. Mouse models also display exercise-induced attenuation in T-reg levels, accompanied by decreased tumor growth (Figure 1*B*)[23]. The exercise-induced tumor-suppressive effects appeared to be dose-dependent[23].

Besides increases in circulating CTL numbers, the cytotoxic capabilities of CTLs were also suggested to be upregulated, marked by the increased levels of IL-1, and IL-2 in exercised mice (Figure 1*C*)[25]. The effects of exercise on IL-1 and IL-2 production appeared dose-dependent, as the group of mice performing the most exercise displayed the greatest effects. Exercise has been shown to upregulate lactate transporter genes in humans, to counteract the exercise-induced lactate production[26]. These effects possibly attenuated the tumor-induced lactate concentrations, as CTLs activity was completely diminished *in vitro* when exposed to tumoral lactic acid concentrations (Figure 1*B*)[27]. In summary, exercise appears to induce physiological adaptations which could benefit the TIME.

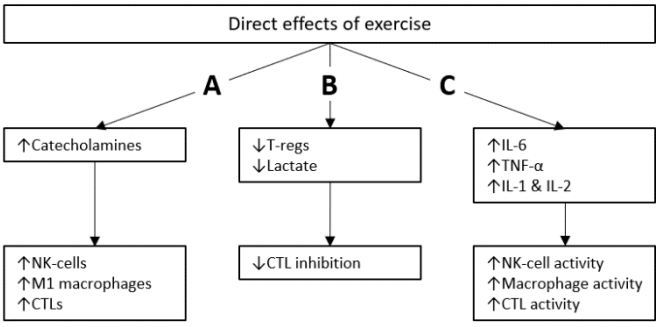


**Figure 1. Schematic overview of the direct effects of exercise on the Tumor Immune Microenvironment.**

### The indirect effects of exercise on the tumor immune microenvironment

Besides from exercise directly affecting the activity of the immune system, exercise is known to induce physiological adaptations which could support the immunomodulating effects (Figure 2). Upon performing exercise, cardiac output is increased and the blood is redistributed to facilitate the exercise-induced changes in the need for substrates by different organs (Figure 2*A*). Surprisingly, a single bout of exercise appears to increase the intratumoral blood flow by 200% in mouse-prostate tumors, whilst the surrounding tissues do not experience an increase in blood flow (Figure 2*A*)[28]. Alterations in the tumor blood-flow might have an impact on tumor development, by changing the quantity of perfused oxygen, immune cells, and therapeutic substances.

Apart from the increase in blood flow, the increase in mean arterial pressure by exercise may enhance the tumor blood perfusion (Figure 2*B*)[29]. In contrast to a normal blood vessel, tumor vasculature is both heterogeneous and tortuous[30]. Normalizing the tumor vasculature structure and functionality could possibly increase the infiltration of oxygen, drugs, and immune cells into a tumor[30]. Tumors of exercised mice display a 2,5-fold increase in blood perfused area[31], suggesting exercise to normalize the tumor vasculature (Figure 2*B*). The actual effect of improved perfusion was tested by assigning chemotherapy to some of the mice, which found increased efficacy of the chemotherapy when combined with exercise[31]. This experiment led to some additional findings, as exercise-only and chemotherapy-only groups experienced the same tumor growth inhibition, confirming exercise has a growth-inhibiting effect on its own[31]. Physical activity in itself is able to increase the core body temperature, which is able to support immune cell infiltration via high endothelial venules (HEV) (Figure 2*C*), possibly attenuating tumor growth[32,33]. In summary, exercise appears to indirectly support the tumor-suppressive effects of the TIME. (*Figure 2.)*.

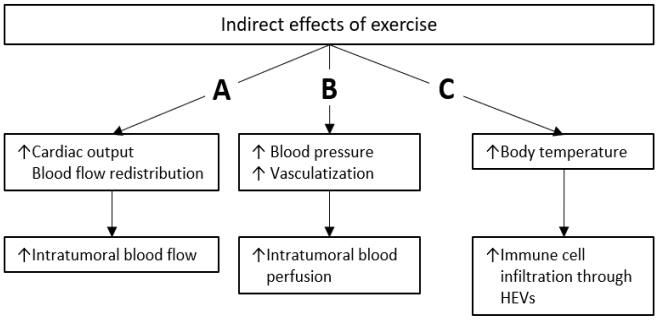


**Figure 2. Schematic overview of the indirect effects of exercise on the Tumor Immune Microenvironment.**

## DISCUSSION

A important effect of exercise on the TIME appears to be catecholamine-dependent, as exercise-induced elevations in catecholamines increase tumor-suppressive immune activity. However, exercise-independent elevations in catecholamines do not appear to fully replicate the tumor-suppressive effects of exercise, indicating additional mechanisms to be involved. In case of NK-cells, these discrepancies appear to be caused by the exercise-induced release of IL-6, which provides a means of activating the catecholamine-mobilized NK-cells. Pedersen and colleagues (2016) attributed the tumor-suppressive effects of exercise to elevated NK-cell activity, as athymic mice displayed similar tumor-suppression. Based on the current understanding of the TIME, this attribution is reasonable, as intratumoral NK-cell abundance experiences the largest fold increase of all immune cells upon performing exercise. The importance of the indirect effects of exercise on the TIME requires further elucidation, although these physiological adaptations are likely to increase the efficacy of conventional cancer treatments. The significance of exercise as an immunomodulating therapy is likely to be affected by anti-tumor immunity, marking the importance of the TIME characterization. Tumors displaying high activity of anti-tumor immunity pathways are likely to have an IE-TIME, whilst low activity suggests an II-TIME. Given the specific immunomodulating effects of exercise, these are likely to be most effective in II-TIMEs.

Most of the studies showing a tumor-suppressive effect of exercise have utilized mouse models in which the tumor cells were introduced, which may not be fully representative of a human cancer situation. Cancer often develops as a co-morbidity in people, suggesting decreased metabolic health. Metabolic dysregulation may affect the effects of exercise on the TIME (e.g. due to low-grade inflammation).

In addition, in a clinical setting most cancer patients would present with a long-established tumor, and are more likely to have developed a form of anti-tumor immunity. These discrepancies between mouse experiments and with a clinical case of cancer, suggest the need for a more representative models. The current indications of a dose-dependent effect of exercise as therapeutic treatment requires future studies to elucidate the variables in exercise efficacy as current studies mainly implemented voluntary wheel-running. These variables would include the effects of exercise intensity, frequency, timing, and duration. Refining the research model and exercise parameters would increase the understanding of exercise as a therapeutic strategy.

## CONCLUSION

Current research suggests exercise to enhance the tumor-suppressive capabilities of the TIME (*Figure 3.*). These effects are mainly attributed to a catecholamine-dependent immune cell mobilization, combined with cytokine-dependent enhanced immune cell activity. In addition, several exercise-induced adaptations have been identified to support the tumor-suppressive capabilities of the TIME. Anti-tumor immunity pathways are likely to attenuate the tumor-suppressive effects of exercise. Therefore, exercise might be a viable therapeutic strategy in II-TIMEs, while concurrently receiving conventional immunomodulating therapy.

## ROLE OF THE STUDENT

Ricky Siebeler was an undergraduate student working under the supervision of Dr. VCJ de Boer at the Human and Animal Physiology department of Wageningen University and Research Centre when the research in this report was performed. All elements of this review were carried out by the student, including the topic proposition.

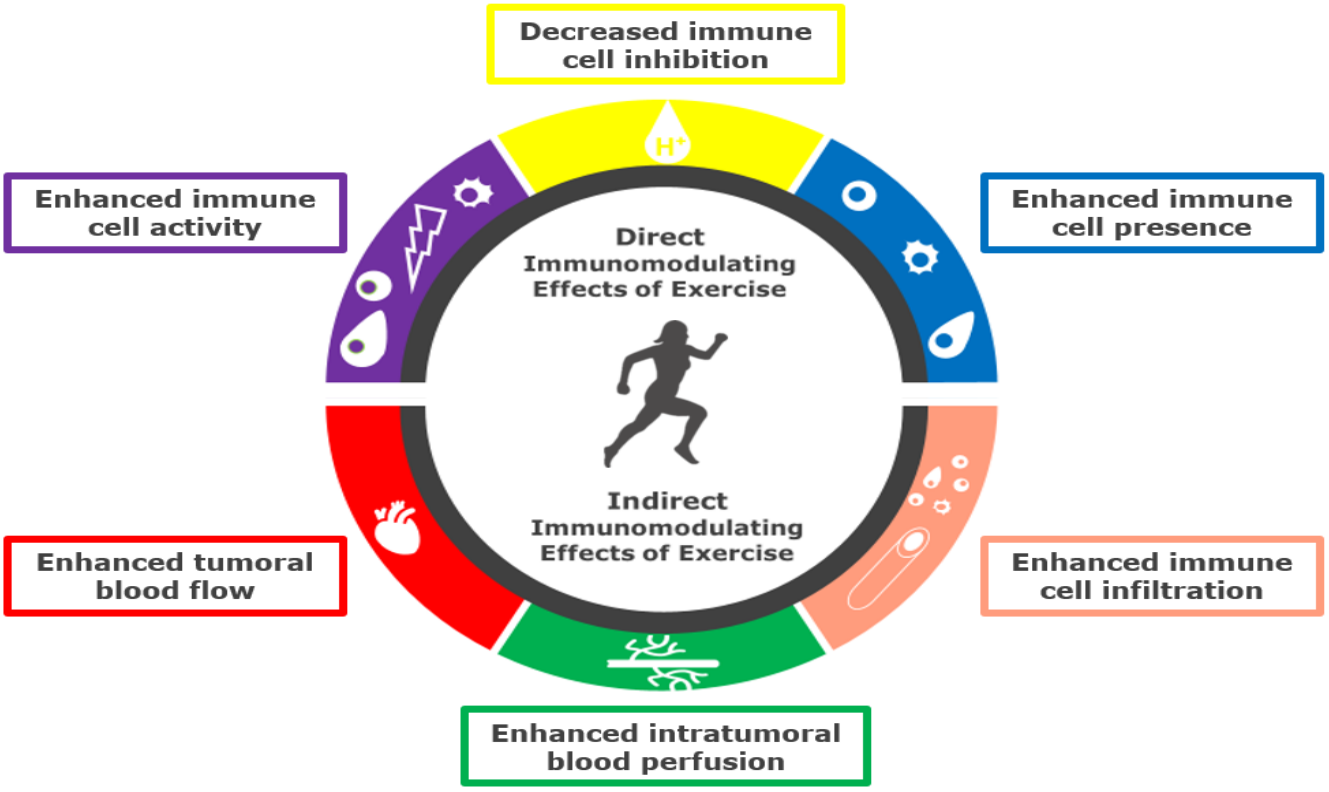


**Figure 2. The Exercise-Induced Effects on the Tumor Immune Microenvironment.** This illustration encompasses the currently identified immunomodulating effects of exercise on the tumor immune microenvironment.

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