Role of Regular Physical Exercise in Tumor Vasculature: Favorable Modulator of Tumor Milieu

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ABSTRACT

The tumor vessel network has been investigated as a precursor of an inhospitable tumor microenvironment, including its repercussions in tumor perfusion, oxygenation, interstitial fluid pressure, pH, and immune response. Dysfunctional tumor vasculature leads to the extravasation of blood to the interstitial space, hindering proper perfusion and causing interstitial hypertension. Consequently, the inadequate delivery of oxygen and clearance of by-products of metabolism promote the development of intratumoral hypoxia and acidification, hampering the action of immune cells and resulting in more aggressive tumors. Thus, pharmacological strategies targeting tumor vasculature were developed, but the overall outcome was not satisfactory due to its transient nature and the higher risk of hypoxia and metastasis. Therefore, physical exercise emerged as a potential favorable modulator of tumor vasculature, improving intratumoral vascularization and perfusion. Indeed, it seems that regular exercise practice is associated with lasting tumor vascular maturity, reduced vascular resistance, and increased vascular conductance. Higher vascular conductance reduces intratumoral hypoxia and increases the accessibility of circulating immune cells to the tumor milieu, inhibiting tumor development and improving cancer treatment. The present paper describes the implications of abnormal vasculature on the tumor microenvironment and the underlying mechanisms promoted by regular physical exercise for the re-establishment of more physiological tumor vasculature.

Introduction

The vascular feature of solid tumors was first described in the 19th century with the discovery of blood vessels present in different tumor types (for references, see [1]). Later, tumors were categorized into four regions based on tumor vasculature: (1) avascular necrotic region; (2) seminecrotic region with capillaries, pre-capillaries, and post-capillaries disposed along the avascular necrotic region; (3) stabilized microcirculation region characterized by many venular and venous drainage vessels with few arteriolar vessels; and (4) tumor advance front region with blood flow similar to the host tissue [2]. Generally, peripheral regions show higher blood vessel density than central regions and the ratio of avascular and seminecrotic regions to well-perfused regions is a function of tumor size, with larger avascular regions present in bigger tumors [3, 4].

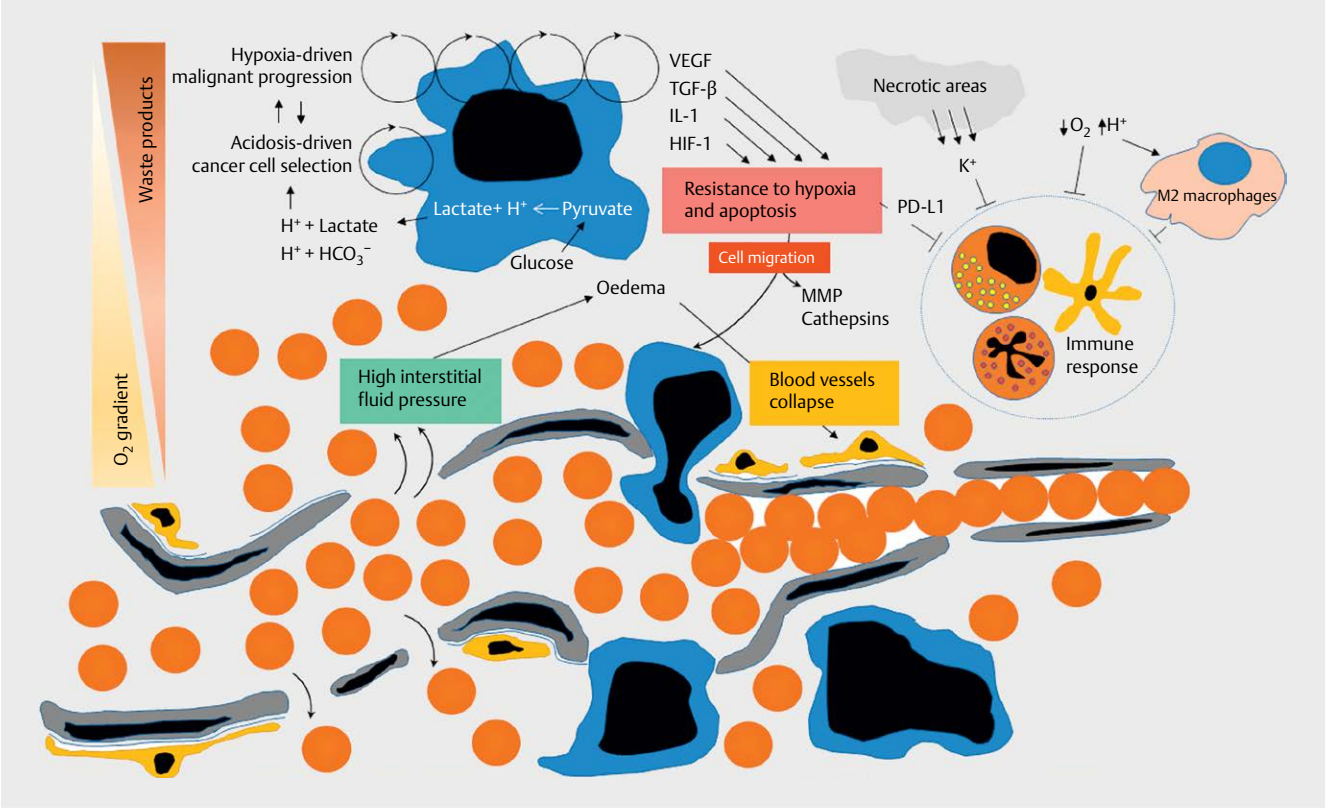
Today, the defective tumor blood vessel network is recognized as a critical factor impacting variations in tumor microenvironment (TME) and supporting tumor evasion [5]. Indeed, non-functional tumor vessels increase vascular permeability leading to the extravasation of blood to the interstitial space, which precludes effective tumor perfusion [6]. As a result, there is insufficient oxygen (O_2) supply and waste product removal, which promote the elevation of the interstitial fluid pressure (IFP) and the development of hypoxic and acidic regions [7]. Consequently, the perfusion and action of immune cells progressively become more inefficient and tumor continues to grow, assuming more aggressive phenotypes [7]. Therefore, various modalities of vascular targeting therapies have been explored in order to delay tumor growth [8, 9]. However, since all drugs present side effects and the outcomes regarding vascular therapies have been largely disappointing, non-pharmacological approaches for tumor vascular remodeling have emerged as an important therapeutic field [10]. In this way, the assumption that physical exercise can prevent cancer initiation was suggested in the 20th century and, since then, many investigations have reported that the rate of cancer mortality is inversely related to the levels of physical exercise accomplished [11, 12]. However, although exercise training has the capacity to modulate multiple biological effects, including metabolism, vascular function, and immunity, little is known about the effects on TME [10]. Therefore, understanding how physical exercise impacts vascular density and tumor perfusion, can create better conditions to improve therapeutic outcomes and potentiate patient care [13]. Thus, the focus of the present review is to describe the implications of abnormal tumor vasculature on TME and to report the candidate mechanisms that may account for the importance and effectiveness of exercise training as a valid therapeutic modality for the reestablishment of more physiological tumor vasculature.

Morphology of Tumor Vessels

Contrary to physiological angiogenesis, in which new vessels rapidly mature and become stable, tumor blood vessels do not become quiescent, allowing the continuous growth of new blood vessels [14]. As a result, tumor vasculature develops a large series of severe structural and functional abnormalities that are quite distinct from the normal blood vessel network [15]. Indeed, whereas normal vessels are organized in a hierarchical fashion with arterioles, capillaries, and venules that are easily differentiated, tumor vessels lack this orderly branching hierarchy that feed a regularly spaced capillary bed [16]. Instead, tumor vessels are often dilated and tortuous, ranging from capillaries to glomeruloid vessel outgrowths and vascular malformations [17]. As such, the concept of specifically targeting tumor vasculature was proposed and the use of vascular targeting agents (VTAs) was established as a potential therapeutic strategy [18, 19]. First, vascular disrupting agents (VDAs) were developed to compromise the function of the already established tumor blood vessels [20]. Indeed, VDAs induce direct damage to the endothelium by disrupting its cytoskeleton and adhesion to the matrix and activating local coagulation [21]. The destruction of the endothelium would result in the occlusion of blood vessels and capillary sprouts causing widespread necrosis and secondary ischemic cell death [22]. VDAs are mostly effective against vessels in the central region of the tumor, possibly because the higher IFP in these regions contributes to vascular collapse [23]. However, although the characteristic pattern of central necrosis produced by VDAs can extend up to 95 % of the tumor, a thin viable rim of tumor cells survives at the periphery, which later regrows [24]. Because at the tumor periphery nutritional support is derived from the vasculature of the adjacent normal tissues, these cells can survive VDA treatment, making it an ineffective strategy to eradicate the total tumor mass [25].

Consequently, instead of disrupting the already established tumor blood vessels, the belief that blocking tumor angiogenesis as much as possible would starve tumors to death led to the concept of antiangiogenic therapy [8]. As a sustained growing vasculature is necessary for tumor survival and development, angiogenesis-inhibiting agents (AIAs) seek to inhibit new tumor vessel formation by blocking the angiogenic stimuli through the inhibition of the angiogenic factors and receptor action, thus preventing endothelial cell proliferation, migration, and tube formation [26]. Due to the importance of vascular endothelial growth factor (VEGF) and its receptor VEGFR2 in angiogenesis, there was hope that blocking this pathway would eradicate the tumor vasculature [27]. As such, anti-VEGF antibodies were developed to re-establish the balance between pro- and anti-angiogenic factors and the vascular network of tumors by pruning immature vessels [28–32]. Indeed, some pre-clinical and clinical studies showed a reduction in vascular density and permeability after angiogenesis-inhibiting treatment [33–35]. However, the effects of such therapy in cancer patients during clinical trials have not fulfilled the expected hopes as the improvement in survival by AIAs was modest, with controversy arising from the finding that after antiangiogenic treatment the levels of tumor hypoxia increased [9, 36, 37]. Indeed, other experimental studies have also demonstrated that AIAs decreased tumor perfusion and the overall distribution of large macromolecules, such as antibodies [38–40]. Following these findings, another two pre-clinical studies presented intriguing evidence showing that VEGF-targeted agents inhibited primary tumor growth but shortened the overall survival by promoting tumor invasiveness and metastasis [41, 42]. In addition, the use of AIAs is likely to mean long-term therapy because after treatment conclusion, dormant tumor cells may regain pro-angiogenic activity and proliferate [43, 44]. Therefore, the continuous blockade of the VEGF pathway can lead to vascular collapse and poorly vascularized regions, inducing a more aggressive tumor phenotype [34].

So, modulating the TME by repairing the function of tumor vessels instead of inhibiting it is likely to be a more efficacious strategy to slow tumor progression and enhance cancer treatment [45]. Indeed, the pioneering work of Algire & Chalkley showed that capillaries in quickly growing tumors have about five times the diameter of those in normal tissue and rarely differentiate into arterioles or venules (for references, see [46]). This difference occurs because vessel walls are compressed by tumor or stroma cells, with some vessels being oversized and others being immature smaller vessels, while in other regions vessels are completely absent [47]. Additionally, tumor vessel walls may have fenestrations, discontinuous or absent basement membranes, fewer pericytes, and less perivascular smooth muscle than normal vessels (▶ **Fig. 1**) [17]. Interestingly, it seems that the judicious application of AIAs might revert much



▶ **Fig. 1** Pathological features of tumor microenvironment. The tumor vessel network is chaotic, presenting low pericyte coverage, loose interendothelial cell junctions, and increased leakiness. The resultant high interstitial fluid pressure induces the collapse of blood vessels, leading to the establishment of hypoxic regions. In addition, the glycolytic nature of tumor cells promotes interstitial acidification, which together will impact the immune response, favoring tumor malignant progression. HIF-1, hypoxia inducible factor-1; IL-1, interleukin-1; MMP, metalloproteases; PD-L1, programmed death-ligand 1; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

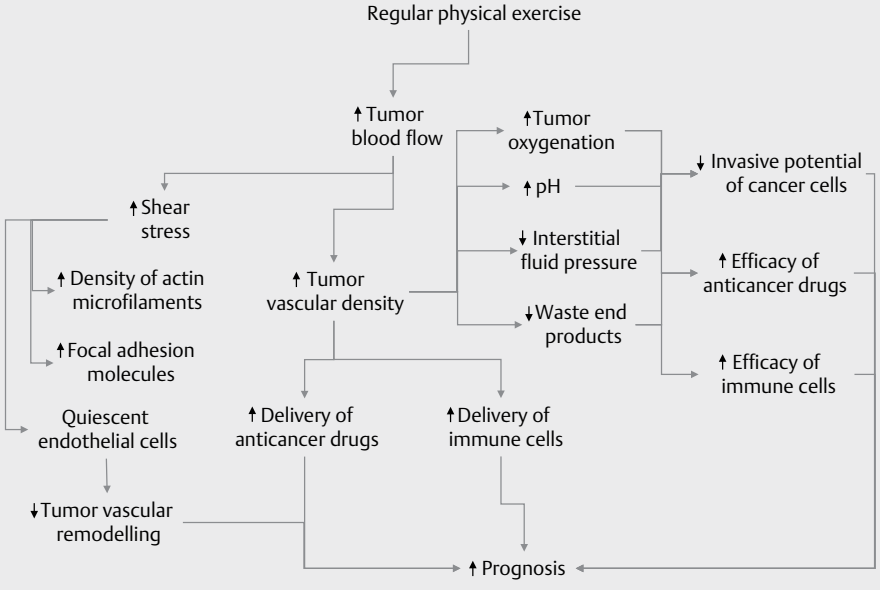
of the abnormal structure and function of the tumor vasculature down to a level where the tumor vasculature might acquire features similar to the functional and quiescent blood vessels of the normal tissues [48]. Indeed, the presence of a temporary window during anti-angiogenic treatment was already demonstrated, wherein a rebalancing of pro- and antiangiogenic signals occurs to the point that vessels become more functional, improving blood flow and oxygenation in tumor regions that were previously poorly perfused [49]. Given the importance of a good vascularization to allow O_2 delivery and the penetration of immune cells into tumor tissue, this strategy aims to turn the abnormal tumor blood vessels into a more functional phenotype by increasing pericyte coverage and basement membrane [50]. Consequently, during the restoring window, tumor vessels become more stable and uniform, reducing the potential for metastasis [51–53]. Pre-clinical and clinical studies already identified this window, typically occurring within 1–2 days after the onset of therapy, followed by a closure coinciding with the loss of functional features (about 6 days) [54]. The window's closure may be related either to the excessively high or prolonged dosing of AIAs or due to the resistance promoted by the activation of alternative pro-angiogenic pathways [54, 55]. Therefore, the transient nature of such therapy means that this approach may be difficult to predict and apply in the clinical setting, thus better strategies to modulate tumor vasculature are still needed [56].

Thus emerging data suggests that the regular practice of physical exercise has a positive impact on vascular remodeling, thus representing a potential non-pharmacological modality to repair tumor vasculature [57–60]. Physical exercise modifies the morphology of vessels along the arterial tree in the skeletal muscle and in the myocardium, increasing its number (angiogenesis) and its diameter (arteriogenesis) [61–63]. The cellular sources of vasodilator compounds during physical exercise include endothelial cells (ECs), erythrocytes, and skeletal muscle. The endothelium releases nitric oxide (·NO), prostacyclin (PGI_2), and endothelium-derived hyperpolarizing factor (EDHF); skeletal muscles release ·NO, ATP, and adenosine; and red blood cells release ATP and ·NO [64]. Similarly, regular physical exercise may increase the number of visible tumor vessel lumens and decrease the average sprout length [10]. In a murine model of breast cancer, voluntary running significantly increased the density and maturity of tumor blood vessels, as assessed by $CD31^+$ vessels and desmin-positive pericyte coverage of capillaries, respectively, resulting in decreased tumor growth [58]. Additional studies have corroborated these findings in mouse models of breast and prostate cancer [60, 65].

In addition to growth factor signaling, blood vessels are regulated by mechanical cues produced by changes in blood flow, velocity, and pressure [66]. Physical exercise can impact the physical forces acting on blood vessels including shear stress, transmural

pressure, and cyclic stretch [67]. Specifically, in skeletal muscle, each bout of physical exercise transiently increases shear stress due to higher blood flow, transmural pressure due to a higher blood pressure, and cyclic stretch of blood vessels due to the increased heart rate (HR) and the pulsatile nature of blood flow [68]. Of these, shear stress plays an essential role driving vascular adaptations in contracting muscles. Shear stress, the mechanical force on the endothelium that is critical for the establishment of mature and functional vasculature, is enhanced when mechanosensors recognize higher muscle perfusion and mediates arterial enlargement leading to an acute increase in vascular conductance [10, 69]. In response to chronic shear stress, ECs hypertrophy, the density of actin microfilaments and focal adhesions increases, and the number of focal adhesion-associated proteins is higher than in cells not exposed to shear stress [70]. Indeed, one of the many effects of aerobic exercise is a systemic increase in blood flow that stimulates the mechanical force on ECs in proportion to exercise intensity (▶ **Fig. 2**) [71]. Accordingly, Schadler and co-workers observed a significant increase in blood flow due to aerobic exercise in mice with melanoma and pancreatic tumors that triggered the remodeling of tumor vessels to a more functional state, inhibiting tumor growth [10]. The authors identified a previously unknown shear stress-responsive pathway in ECs, calcineurin-nuclear factor of activated T cells (NFAT)-thrombospondin 1 (TSP-1) signaling, and demonstrated that TSP-1 expression is critical for exercise-induced tumor vascular repair. During increased shear, the activation of calcineurin-NFAT signaling in ECs upregulates the anti-angiogenic protein TSP-1, which promotes the cross-talk between ECs under shear stress and ECs in areas absent of shear, thus inhibiting the proliferation of naive ECs and promoting vascular remodeling [10]. Moreover, due to their narrowness and low blood rate, tumor vessels have been reported to have cancer cells integrated into their walls [72]. As physical exercise increases blood flow, it could potentially prevent the infiltration of tumor cells in vessel walls and their dissemination to surrounding tissues, thus preventing the development of pre-metastatic niches (▶ **Fig. 2**) [73].

In tumors, there is also significant arterial-venous shunt perfusion and chaotic vascular organization without any regulation matched to the metabolic demands or functional status of the tissue [74]. Indeed, about 50 % of tumor vessels are non-functional, with vessel walls presenting wide interendothelial junctions and transendothelial channels formed by vesicles and pores more than 100 times the size of those in healthy vessels [75, 76]. Some studies already showed that the pore size of tumor microvessels varies from 100 nm to 780 nm in diameter, while microvessels in normal tissues are less leaky, with tight junctions between ECs < 2 nm, whereas the pore size in postcapillary venules is larger at up to 6 nm [77]. In contrast to quiescent ECs, which adhere to the vessel wall, tumor ECs undergo endothelial-to-mesenchymal transition (EMT) and move away from their resident site, leaving behind empty sleeves of endothelial cell-devoid matrix channels, hindering blood flow [78]. Thus, whereas normal vessels are lined with a quiescent monolayer of interconnected adherent ECs that are disposed in the direction of blood flow for optimal perfusion, tumor ECs lose their polarity, detach from the basement membrane and stack upon each other [79, 80]. Other tumor ECs can die or slough off, establishing gateways for cancer cells that become exposed to the blood [81]. The phenomenon of vessel hyperpermeability is influenced by the activation of the sphingosine-1-phosphate receptors 1 and 2 (S1PR1 and S1PR2) on the surface of ECs, which act as shear stress responsive mechanoreceptors that regulate vessel integrity through their signaling pathways [82, 83]. Specifically, S1PR1 signaling promotes tight intercellular junction assembly to properly modulate vascular permeability and induce vessel matu-



▶ **Fig. 2** Mechanisms linking regular physical exercise with improved cancer prognosis through vascular network changes.

rity, whereas S1PR2 expression is associated with pathologic endothelium and higher vascular permeability and is upregulated by the disturbed tumor blood flow [84, 85]. The elegant study by Morrel and colleagues showed that two weeks of treadmill running increased S1PR1 and decreased S1PR2 signaling in tumor-bearing mice, reducing tumor vascular permeability and improving tumor oxygenation [57]. These important studies clearly demonstrated that exercise training may have a unique role in tumor vascular repair, eliminating shunts that leave certain tumor regions deprived of blood supply (▶ **Fig. 2**).

However, growing tumors continuously demand O_2, and because of this high metabolic demand, oncogene activation and exposure to a disturbed microenvironment, tumor cells produce excessive pro-angiogenic factors that render vessels even more abnormal [86, 87]. Compared to normal tissues, tumors show elevated levels of growth factors like VEGF and vasoactive factors like bradykinin and·NO, which increase vascular permeability even more [88, 89]. The resultant TME is characterized by heterogeneous hypoperfusion, high IFP, hypoxia, and acidity that favor the shedding of cancer cells into circulation (▶ **Fig. 1**) [90].

Abnormal Vasculature and Tumor Microenvironment: The Role of Exercise

Hypoperfusion

In vessels, blood flow is directly proportional to the pressure's difference between arteries and veins and inversely proportional to the viscous and geometric resistance [91]. However, due to their continuous remodeling, tumor vessels are leaky and result in higher IFP. Consequently there is an increase in vascular resistance, rendering blood flow not only chaotic but also stagnant in some places, hampering tumor perfusion [92]. Indeed, compared to normal tissues, tumors show greater blood viscosity due to the presence of tumor cells and large molecules like proteins and collagen drained from the extravascular space, and a larger vessel diameter with thin and ragged walls that culminates in increased blood flow resistance [93, 94]. Furthermore, in a given vessel, blood may travel in one direction and then in the opposite way. These flow patterns, together with the abnormal pressure gradients, hinder the uniform delivery of nutrients, O_2, and anticancer drugs [13, 95, 96]. Although disturbances of tumor microcirculation are apparent at early growth stages, blood flow rate tends to decrease with tumor growth [3, 4]. The pathogenic mechanisms directly responsible for this weight-adjusted flow decline, involve a progressive rarefaction of the vascular bed (decrease in the number of patent vessels/g of tumor), an escalation of the structural and functional abnormalities of the tumor vessel network, and the development of necrosis [3, 97]. Indeed, most of the blood vessels in the internal region of tumors are veins or venules, whereas peripheral regions have a reduced number of arteries and arterioles [98, 99]. Therefore, the arteriole-venule pressure difference as a driving force for blood flow is negligible in the central region of tumors and greater in the periphery and, consequently, blood flow is lower at the centre and higher at tumor periphery [100]. As a result, the average blood flow in tumors is lower than in normal tissues, with reduced delivery of O_2 and nutrients and decreased clearance of by-products of metabolism, which leads to hypoxic and acidic regions, mainly in the central part of the tumor (▶ **Fig. 1**) [101, 102].

Endurance exercise represents the most potent physiological stimulus for blood vessel remodeling in skeletal muscle [103]. Indeed, vasoactive factors in the muscle interstitium may have a direct effect on ECs and smooth muscle cells in capillaries, inducing conducted vasodilation [104]. Conducted vasodilation is a mechanism to redirect blood flow to the contracting muscles in which the signal for vasodilation travels along the vascular wall, up and downstream, through gap junctions [105]. This mechanism is critical to accurately modulate blood flow as it allows the occurrence of vasodilation in the distant larger vessels that do not necessarily experience the chemical or mechanical stimuli that is present in the working muscle fibers [106]. These adaptations in the blood vessel network elicit the improvement in the regional distribution of blood to assure proper flow in areas of muscle bed vasodilation [71]. Several studies have shown that regular exercise practice is associated with increased vascularization in tumors as well, which is correlated with enhanced blood perfusion and reduced tumor hypoxia (▶ **Fig. 2**) [58–60, 107]. Recently, McCullough and colleagues demonstrated that an acute bout of treadmill running increased the prostate tumor blood flow in rats up to 200 %, owing in part to the inability of the tumor vasculature to vasoconstrict; importantly, the increase in tumor blood flow resulted in a significant increase in O_2 delivery and a 50 % reduction in tumor hypoxic area [60]. During physical exercise, there is a redistribution of cardiac output, with a shunting of blood flow from non-active tissues to the contracting muscles [108]. In part, this shunting is due to the enhancement of sympathetic system activity and the release of norepinephrine that binds to α-adrenergic receptors on the vascular smooth muscle, inducing vasoconstriction [109]. Indeed, following physical exercise onset there is an increase in HR driven by the vagal withdrawal and the β-adrenergic stimulation [110, 111]. Exercise hyperemia is a highly complex and well structured process that involves sympathetic vasoconstriction and the integration of many vasodilator signals. During physical exercise as the higher sympathetic activity promotes arteriolar constriction, an efficient amount of vasodilators needs to be activated in contracting muscles to promote accurate blood perfusion [112]. This reduced vasoconstriction during contraction (functional sympatholysis) allows adequate O_2 delivery to the active fibers. As a result, there is a decrease in α-adrenergic responsiveness on the smooth muscle cells, promoting a physical exercise-induced sympatholysis [113]. Accordingly, Heinonen and colleagues found that the inhibition of α-adrenergic tone disturbed the perfusion of blood flow to contracting muscles by directing it to the inactive muscle fibers as well [114]. Therefore, the diminished α-adrenergic vasoconstriction and the loss of myogenic tone at higher intraluminal pressures of tumor arterioles may inhibit the action of the sympathetic nervous system in tumor vessels, resulting in the enhancement of tumor blood flow during physical exercise [60]. Clinically, this suggests that physical exercise has the potential to improve tumor oxygenation and thus to be able to mitigate the hypoxic microenvironments that are associated with more aggressive tumor phenotypes (▶ **Fig. 2**) [57, 58, 60].

There are several benefits to improved intratumoral vascularization and blood perfusion: first, there is an increase in tumor oxygenation, preventing the development of intra-tumoral hypoxia;

second, the accessibility of circulating immune cells is greater; and third, the delivery of anti-neoplastic medication to tumors is facilitated [115–117]. Indeed, tumor blood supply plays an important role in the delivery of therapeutic agents to solid tumors [118]. As tumor cells proliferate more quickly than capillary ECs, these cells force tumor vessels apart creating an unfavorable vascular network for drug delivery, which means that most anticancer drugs show modest effects, in part due to limited penetration into tumor cells [91]. Nacev and co-workers observed that tumor cells are often located 100 µm away from the nearby vessels, whereas in normal tissues, cells are closer to capillaries (50–100 µm) [119]. As drug molecules need to travel a longer distance and the commonly used cytotoxic agents like doxorubicin (DOX) are unable to penetrate more than 40–50 µm from blood vessels, there is an insufficient drug penetration rate to kill cancer cells [120].

Indeed, it has been shown that exercise training may also improve the penetration of chemotherapeutic agents into tumors (▶ **Fig. 2**). The study of Schadler and collaborators demonstrated that exercised mice with pancreatic adenocarcinoma presented a 24 % increase in functional vessels and improved the delivery of gemcitabine to tumors [10]. Further, to investigate the delivery of DOX to tumors, Morrel et al. submitted mice with Ewing's sarcoma to a moderate-intensity exercise training protocol and concluded that tumors from exercised mice had significantly higher DOX levels than tumors from sedentary mice [57]. As such, these studies additionally reinforce the importance of functional tumor vasculature to access TME, and physical exercise seems to be a viable option to achieve it.

High Interstitial Fluid Pressure

The interstitial space mediates the exchange of O_2, nutrients, and waste products between the vascular system and cells**,** and the movement of fluid across the vessel wall is governed by the difference in hydrostatic and oncotic pressures (Starling's forces) [121]. In human capillaries, the oncotic pressure is about 28 mmHg, which tends to keep fluid in the capillaries [122]. Contrarily, the capillary hydrostatic pressure (20 mmHg), the interstitial-fluid osmotic pressure (8 mmHg), and the interstitial-fluid hydrostatic pressure (–1 to –3 mmHg) tend to move fluid out from the capillaries [123]. As such, normally there is a net outward filtration pressure from the capillaries into surrounding tissues of 1–3 mmHg [122]. This outward pressure guarantees a flow of fluid out from the vessels and through the interstitium, contributing to the transport of molecules to and from cells [123]. However, in tumors, the incomplete or even missing endothelial lining and discontinuous basement membranes increase vascular permeability with extravasation of blood to the interstitial space (▶ **Fig. 1**) [75, 124]. Indeed, it was already shown in normal tissues that the physiological influx of water into the interstitial compartment varies between 0.5 and 1.0 % of plasma flow, but in tumors this value reaches more than 15 % [125]. Consequently, tumors are characterized by higher geometric and viscous resistance to blood flow, increased microvascular hydrostatic pressure, high resistance to interstitial fluid flow, and impaired lymphatic drainage, resulting in the drastic elevation of the IFP [126–129]. In normal tissues IFP is just above or below atmospheric values (–3 to + 3 mmHg), but in tumors it is generally high at the center, reaching values of 50–100 mmHg and drops steeply at the tumor periphery [130]. This interstitial hypertension causes edema, leading to sluggish blood flow due to the clogging of red blood cells and to the collapse of blood vessels, particularly at the centre of the tumor, triggering the proliferation of cancer cells (▶ **Fig. 1**) [131]. Therefore, functional vessels are present mainly in the tumor periphery, where there is a drop of the IFP to a more physiological level [132, 133].

In many tumors the supportive stroma also contributes to the increase of IFP, through the release of cytokines, growth, and angiogenic factors, which in turn can compress intratumoral vessels, impairing their function [134]. The resultant edema associated with the tumor's high osmotic pressure forms a barrier to adequate infiltration of immune cells and delivery of anticancer drugs [135]. Since IFP was identified to be significantly higher in tumors compared to normal tissues, an enhanced IFP has been observed in several solid tumors and it has been considered a critical prognostic factor [136, 137]. Indeed, in the study of van der Voort van Zyp et al., an increased extracellular pressure of just 15 mmHg was enough to stimulate colon cancer cell adhesion to surgical wounds, leading to tumor recurrence [138]. Based on these data, it has been suggested that tumor IFP forms a link between tumor angiogenesis, tumor hypoxia, and metastasis in which dysfunctional angiogenesis led to the development of a vascular network with serious architectural abnormalities [139]. The result is a TME characterized by elevated IFP and hypoxic regions that promotes the upregulation of pro-angiogenic factors, forcing the interstitial fluid to flow from the center to the tumor periphery where stimulates tumor hemangiogenesis, peritumoral lymphangiogenesis, and consequently lymph node metastasis [139].

Therefore, strategies capable of lowering fluid accumulation in tumors by decreasing the leakiness of tumor vessels or by draining the interstitial fluid should lower the levels of tumor IFP [140]. In this way, by improving vascular maturity, physical exercise may lead to a decrease of non-functional sprouts and an increased hierarchical vasculature with reduced leakiness that may attenuate IFP [55]. Decreasing the level of IFP could potentiate macromolecular and nanoparticle drug transport (> 1000 MW), because the transport of these drugs is governed by the pressure gradient across the vessel wall [120]. Indeed, Betof and co-workers studied the effect of exercise training in mice with breast cancer under chemotherapy treatment and observed an increase in the amount of viable tumor area containing pericyte-covered vessels ($p = 0.006$), an increased vessel area covered by pericytes ($p = 0.024$), and a 3- to 4-fold higher rate of mature vessels when compared to sedentary animals; as a result, the rate of tumor growth was significantly lower [58]. Similarly, in the study of Morrel and collaborators, two weeks of treadmill running promoted the remodeling of tumor vasculature, significantly reducing vessel permeability; however the authors did not observe any impact on tumor growth [57].

In contractile muscles, fluid filtration from the blood to the interstitium markedly increases during acute physical exercise. Indeed, because the movement of fluid initially exceeds the capacity of the lymphatic system, interstitial fluid volume significantly increases at the onset of physical exercise [141]. The transient enhancement of IFP occurs because capillary hydrostatic pressure is higher due to the arteriolar vasodilation, the increased microvascular surface area, the increased muscle vessel density, and the high-

er osmotic concentration that results from the release of metabolites during skeletal muscle contraction [142]. However, with the continuation of physical exercise, transcapillary fluid movement slows to the point that lymphatic drainage and net filtration are in balance, blocking the accumulation of fluid [141]. As physical exercise-induced hypervolemia is associated with higher plasma albumin content, there is a reduced transcapillary escape rate (TER) of albumin and a redistribution from the interstitial to the intravascular compartment [143–145]. Accordingly, Mack and collaborators verified that in contracting muscles the decrease in hydrostatic pressure and increased oncotic pressure promoted a higher lymphatic return of fluid and protein to the vascular compartment [144].

Thus, by enhancing draining volume flow, the skeletal muscle contraction acts as an edema safety agent to limit the increase in IFP [146]. Indeed, the removal of tissue proteins produces a filtrate of plasma that becomes progressively protein-poor in concentration, which decreases the colloid osmotic pressure of interstitial fluid. Consequently, the transcapillary oncotic pressure increases, reducing fluid accumulation in tissues [147]. Physical exercise can prevent the elevation of IFP by different mechanisms. First, the contraction of muscle fibers acts on lymphatics by pumping lymph into the collecting vessels [146]. Second, physical exercise also boosts blood from contracting skeletal muscle by the action of muscle pump, which mitigates the higher capillary pressure induced by arteriolar vasodilation [71]. Finally, the decreased postcapillary resistance induced by muscle contraction also limits the accumulation of interstitial fluid during physical exercise [141].

Collectively, these data suggest that physical exercise could be a potential strategy to prevent high tumor IFP, but further research is still needed.

Oxygen Deprivation

Normally, tumor cells proliferate faster than ECs, reducing vascular density particularly at the center of the tumor, turning it very distant from the blood supply (> 100 µm) [148]. Due to the poorly organized vascular architecture, irregular blood flow, and the compression of blood and lymphatic vessels, the O_2 consumption rate of neoplastic cells may outweigh an insufficient O_2 supply, resulting in the development of areas of very low oxygenation [149].

Because TME also depends on the cellular consumption of O_2 and essential nutrients, tumor cells closer to the vascular supply consume what they need for growth and survival, with less being available for those cells further away. Consequently, radial O_2, nutrients, and pH gradients are established (▶ **Fig. 1**) [97]. Indeed, it has been reported that the O_2 partial pressure (pO_2) of cells next to capillaries can be as low as 15 mmHg, which will reduce the O_2 diffusion distance [150]. All these factors will result in the development of regions of necrosis, which are commonly observed in advanced solid tumors, reflecting the consequences of prolonged periods at O_2 levels that are insufficient to maintain cell viability (▶ **Fig. 1**) [151].

Primarily, hypoxia leads to the loss of proliferative capacity and finally to death of normal and most cancer cells [102]. On the other hand, some tumor cells can survive hypoxia-induced cell death by triggering alterations in the proteome and/or genome, favoring tumor development. This phenomenon is called the "Janus face of hypoxia" [152]. Indeed, the critical pO_2 in tumors below which the harmful changes related to decreased O_2 consumption have been observed is 8–10 mmHg [153]. Specifically, the pioneering work of Kolstad shows that whereas pO_2 is about 36 mmHg in normal cervical mucosa, in cervical cancer it progressively drops to 5 mmHg with the development of the disease [154]. These data are indicative of inadequate tissue oxygenation, most probably due to a restriction of the microcirculation and thus a restriction of O_2 availability to cancer cells in vivo. This phenomenon gets significantly worse with tumor growth [3]. Evidence shows that 50–60 % of locally advanced solid tumors may present hypoxic and/or anoxic regions that are heterogeneously distributed within the tumor mass [155]. Tissue hypoxia results in the stabilization of the hypoxia-inducible factor (HIF) because in normoxic conditions the HIF-α units are unstable and quickly degraded by the proteasome pathway through the ubiquitin E3 ligase complex, the recognition component of which is the von Hippel Lindau (VHL) [156]. However, since very low O_2 levels are available for hydroxylation under hypoxic conditions, the HIF-1α subunit is stabilized, forming a heterodimer with HIF-1β to functionally mediate an array of genes involved in angiogenesis, metabolism, tumor cell survival and proliferation, drug and radiation resistance, and immune evasion [157, 158]. As a result, during hypoxia-driven malignant progression, the capacity for local invasive growth and perifocal tumor cell spreading and dissemination is higher [159, 160]. Indeed, hypoxia enhances the invasive potential of tumors through the activation of pro-migratory proteins and pro-invasive extracellular matrix (ECM) molecules [161]. The first clinical study demonstrating a clear association between tumor hypoxia and the likelihood of distant metastasis was reported by Brizel and co-workers, who observed that the pO_2 of metastasizing tumors (7.5 mmHg) was significantly lower than the non-metastasizing tumors (20 mmHg) [162]. Additionally, hypoxia-induced inhibition of gene expression was observed for cell-surface integrins favoring tumor cell migration [163]. Indeed, the first study involving the exposure of murine fibrosarcoma cells to different O_2 concentrations showed that the more hypoxic the exposure, the greater number of metastases developed [164]. At the same time, recent evidence suggested that hypoxic cells are resistant to radiation therapy and can repopulate the tumor due to the presence of cancer stem cells in hypoxic regions [165, 166]. Finally, in the presence of O_2, most anticancer drugs produce free radicals that damage DNA [167]. These drugs accept electrons from biological sources and then transfer them to O_2 [168]. However, at low O_2 concentrations the cytotoxicity of these drugs, whose activity is mediated by free radicals, is decreased and the elimination of the tumor is ineffective [169].

Collectively, these observations may explain why intratumoral hypoxia favors tumor growth and dissemination, correlating it with a poor prognosis in many human cancers [170]. Unfortunately, today there is no accepted standard of care for reducing tumor hypoxia. Nevertheless, to maintain homeostasis, O_2 supply and demand in skeletal muscle occurs in a dynamic balance and may be modified by changes in blood flow, O_2 tension and by the number of capillaries participating in gas exchange [171]. Indeed, α-adrenergic response to physical exercise causes vasoconstriction of inactive regions, redirecting blood flow to the working muscles to match the increased demand for O_2 [103]. To this end, the splanchnic circulatory system that accounts for about 25 % of car-

diac output at rest, markedly decreases during physical exercise [172]. Similarly, renal flow also decreases proportionally with increasing exercise intensity. Endo and colleagues (2008) noted that even cycling ergometer exercise for 4 min at 40 W decreased blood flow to the kidneys by 20 % [173]. Inversely, physical exercise-induced hyperemia increases the recruitment of non-perfused capillaries in contracting muscles, which not only improves the surface area available for gas exchange but also decreases diffusion distance for O_2 flux [174]. Indeed, the flux of O_2 in skeletal muscles during physical exercise can increase 100-fold over resting values [175]. At rest and during physical exercise, skeletal muscle oxygenation depends on the fine-tuning between O_2 delivery through the microcirculation and O_2 consumption by the skeletal myocytes [176]. The transport of O_2 through the microcirculation is accomplished by convection and diffusion [177]. Convection is an efficient way to move O_2 in blood over large distances, mostly in the larger arterial and venous vessels. In peripheral tissues O_2 moves short distances by diffusion from the terminal vascular sites to nearby parenchymal cells, where it is utilized by the mitochondria [178]. In this way, in contracting muscles, due to increased capillarization and a bigger exchange surface area, there is higher arterio-venous O_2 extraction, which improves O_2 diffusion to the cells [179]. Indeed, it was shown that during physical exercise, O_2 consumption can increase up to a point that 70–80 % of the O_2 delivered to the active muscles may be extracted [180].

Also, the chronic adaptations of skeletal muscle to exercise training leads to better aerobic performance at higher intensity through an improvement in metabolic capacity and O_2 supply [181]. Supporting this notion, it was observed that after exercise training there is an increased mitochondrial enzymatic content, which is associated with larger diffusional O_2 conductance and increased O_2 extraction [182, 183]. In addition, two-legged acute exercise after 4 weeks of unilateral knee-extensor training, resulted in higher HIF-1α concentration only in the untrained leg [184]. Similarly, 6 weeks of endurance training showed increased expression of HIF-1α inhibitors that led to an attenuated PDK-1 expression, thus increasing the muscle capacity to utilize O_2[185]. Therefore, it seems that exercise training can improve O_2 delivery and extraction, attenuating the acute HIF-1α response and enhancing oxidative metabolism [181].

Accordingly, the physiological effects of physical exercise as an inhibitor of tumor hypoxia have already been shown (▶ **Fig. 2**) [58–60]. Betof and colleagues reported that voluntary running throughout tumor development decreased the hypoxic fraction by 50 % [58]. McCullough and collaborators also verified that the practice of chronic exercise significantly improved microvascular pO_2 and decreased the hypoxic fraction within the prostate tumors of rats compared with their sedentary counterparts [59]. Additionally, the same author studied the acute effects of exercise training on tumor hypoxia and verified that a single bout of treadmill running reduced the tumor hypoxic fraction by 15 % [60]. This means that exercise training immediately promotes adaptations on TME that can be exploited to mitigate hypoxia and cancer progression.

Acidic pH

In tumors, the development of hypoxic regions promotes the activation of genes involved in the regulation of glycolysis, increasing glucose consumption and leading to the extrusion of lactic and carbonic acid outside the cell [186]. The result is ineffective clearance of by-products of metabolism that lowers the interstitial pH, leading to tumor acidosis (▶ **Fig. 1**) [187]. Indeed, at perfusion rates <0.2 ml/g/min tumor venous blood become acidic and pH falls below 7.0, which means that tumor tissue acidosis mainly develops because of inadequate drainage [188]. This was true for several tissue samples from cancer patients that were shown to be acidic, with an extracellular pH (pHe) of 5.6 to 6.8, whereas the pHe of normal tissues is significantly more alkaline, at 7.2–7.5 [189, 190]. In contrast, the cytosolic pH of tumor cells is commonly preserved at a slightly more alkaline level (7.2–7.5), acting as a pre-requisite for effective protein and DNA synthesis and cell survival [191]. In order to ensure this pattern, tumor cells secrete the excessive produced acids and protons to the extracellular space [192]. However, as quickly growing tumor cells exhibit high glycolytic rates and high lactate production together with insufficient drainage, there is an accumulation of H^+ in the respective tissue [193]. The result is an acid-outside pH gradient typically in opposition to that observed in normal tissues in which intracellular pH (pHi) is lower than pHe [194].

In addition to non-optimal vascularization and drainage, the development of tumor acidosis can also occur through the availability of glucose to hypoxic cancer cells, which usually occurs because the diffusion distance for glucose is larger than for O_2 [97]. This was first noted by Kallinowski et al., when the authors observed that the hypoxic tumor cells distant from the supplying vessel could still cleave glucose to lactic acid [195]. Therefore, it is not unusual to observe an inverse correlation between the lactic acid content and the interstitial pH in many tumors [196]. Although lactate was initially thought to be just a glycolytic waste product, it is now established that it can be consumed by aerobic tumor cells, thus reserving glucose for distant hypoxic tumor cells [197]. So, sharing of energy substrates between aerobic and hypoxic tumor cells is a key mechanism for the survival of hypoxic tumor cells [198]. Indeed, acidosis causes additional stress on cancer cells, leading to the selection of cells that are best prepared to withstand harsh conditions, likely owing to the acquisition of specific mutations, including the activation of VEGF, transforming growth factor (TGF)-β, interleukin (IL)-1 and HIF-1 [199, 200]. Together, these mutations turn tumor cells in the acidic regions more resistant to cell death than in normally perfused regions [192]. These observations led to the development of the "acid-mediated invasion hypothesis" in which tumor acidification favors tumor cell migration by enhancing tumor cell resistance and ECM degradation through the activity of matrix metalloproteases (MMP) and cathepsins, thus creating the pre-condition for tumor dissemination (▶ **Fig. 1**) [186].

Low pH levels have also been shown to decrease the radiosensitivity of cells and to modulate the cytotoxicity of certain anticancer drugs [201]. Indeed, as in tumors pHe is low and the pHi is alkaline, weakly basic drugs with an acid dissociation constant of 7.5–9.5, such as DOX and mitoxantrone, are protonated, displaying decreased cellular uptake [202]. Interestingly, the acidic TME has also been shown to be partially responsible for unsuccessful anti-angiogenic therapies. Faes and collaborators showed that exposure

to an acidic milieu of pH 6.4 decreased the expression of VEGFR-2 in ECs, making AIAs inefficient [203]. Taken together, it seems that tumor cells have the ability to adapt to a low pHe, activating mechanisms for cancer survival and proliferation [193]. Because this acidic milieu is so favorable for tumor migration, strategies to rebalance the pH levels of cancer cells are a viable option in complex anticancer treatment [204].

In resting skeletal muscles, the regulation of pHi depends on passive membrane fluxes of hydrogen ions (H^+) and bicarbonate, and membrane transport systems mediating a secondary active transport, thus balancing the acidic load [207]. However, muscular contraction induces several chemical, physical, and physiological challenges within and outside the cells. Therefore, as a consequence of intense physical exercise, the formation of lactate, carbon dioxide (CO_2), and H^+ induces intracellular acidosis [208]. The physiological adaptation to these insults involves a quick and intense increase in ventilation to match the higher O_2 demand and to remove CO_2, and the increase of lactate- dependent and lactate-independent H^+ transport [209, 210]. At low-intensity physical exercise, as lactate formation is low, H^+ removal is managed mainly by the sodium (Na^+)-dependent transport system and involves Na^+/H^+ exchange and Na^+/bicarbonate co-transport, whereas lactate-dependent H^+ removal plays a minor role [207]. Nevertheless, because after high-intensity physical exercise the lactate concentration may reach 40 mM with extensive H^+ release from the contracting cells, the pHi of skeletal muscle may decrease to 6.5 [211]. Therefore, the lactate/H^+ and Na^+/H^+ carriers increase to mediate lactate and H^+ efflux. Indeed, during high-intensity physical exercise both systems increase, but lactate-independent H^+ removal quickly reaches its maximal capacity, whereas lactate-dependent H^+ removal can increase by at least five times. Therefore, the lactate/H^+ co-transporters seem to be the most important systems to remove H^+ during high-intensity physical exercise [207].

Importantly, the regulation of pH in blood and skeletal muscle can adapt in response to exercise training and the beneficial effect of training has been described at the protein and functional level [207]. Indeed, exercise training can increase the density of the lactate/H^+ co-transporter proteins MCT1 and MCT4, and the capacity to transport lactate and H^+ 212, 213]. Also, the amount of the Na^+/H^+ exchanger protein NHE1 increased in humans after 8 weeks of submaximal exercise training [212]. Similarly, soleus Na^+/bicarbonate transporters of Wistar rats were shown to increase after 5 weeks of high-intensity training [214]. On the other hand, the improved blood flow induced by physical exercise probably contributes to the increased release of H^+ and lactate with training. Indeed, the involvement of increased blood flow is consistent with the finding that a better washout of lactate and H^+ can occur with smaller muscle-to-arterial concentration gradients after exercise training [207]. Na^+/potassium (K^+) homeostasis also improved in trained subjects, representing another mechanism through which exercise training potentiates pH regulation in skeletal muscle [215].

Therefore, given that exercise training can decrease lactate and H^+ levels, it is possible that acidic TME could also be impacted (▶ **Fig. 2**). Currently, there are no reports on how physical exercise affects tumor pH. However, treadmill running in mice with mammary carcinomas reduced tumor and circulating lactate concentrations by approximately 17 % compared with sedentary counterparts [205]. Accordingly, Bacurau et al. also reported that a moderate-intensity treadmill running protocol significantly decreased glucose consumption and lactate production in rats with Walker-256 tumors [206]. Nonetheless, as evidence is lacking, future studies are required.

Immunosuppression

The impaired vascular supply of tumors and the consequent hostile TME characterized by hypoxia and acidosis hampers T-cell infiltration, function, and survival [216]. Physiologically, immune cells permanently patrol tissues to signal and remove pathogens, foreign antigens, and abnormal cells [217]. However, under hypoxic and acidic conditions there is an upregulation of growth factors and cytokines that inhibit the activity of T-cells and the ability of dendritic cells (DCs) to process and present tumor antigens (▶ **Fig. 1**) [218–220]. Although poor lymphocyte infiltration due to an abnormal tumor vasculature represents the main reason for the immune failure in the elimination of cancer cells, the presence of immune suppressive agents in the TME is also important because it leads to T-cell dysfunction in the context of anergy, senescence, and exhaustion [221]. Consequently, the immune cells that successfully infiltrate in the TME are not fully effective [222].

A critical player of the metabolic reprogramming in the TME is hypoxia, and cells of both innate and adaptive immunity are very sensitive to these conditions, because it was shown that hypoxia can regulate aggregation, invasion, and motility of macrophages and neutrophils, favoring local inflammation and immunosuppression [223, 224]. Low O_2 levels can also impact T-cell differentiation by changing the balance toward a T helper (Th) 17/T regulatory (Treg) phenotype and impairing the cytotoxic properties of natural killer (NK) cells [225]. Additionally, hypoxia can inhibit T-cell function by exacerbating glucose deprivation, reducing cytosolic levels of calcium (Ca^{2+}), which is essential for cytokine production and promoting excessive formation of reactive oxygen species (ROS) [226]. Indeed, it was proved that hypoxia can upregulate programmed death-ligand 1 (PD-L1) on tumor cells, which in turn dampens T-cell function by interacting with the inhibitory receptor programmed cell death protein 1 (PD-1) on the T-cell surface (▶ **Fig. 1**) [227]. Hypoxia also upregulates indoleamine 2,3-dioxygenase (IDO) expression in DCs, which promotes Treg survival and function, inhibiting the generation of effector $CD4^+$ and $CD8^+$ T cells [228]. In addition, IDO leads to the upregulation of several cytokines like IL-6, IL-10, and TGF-β, further accentuating the immunosuppressive state [229].

Inefficient tumor vasculature and subsequent hypoxia lead to the development of necrotic foci, a very common feature of solid tumors [230]. Necrosis within TME results in increased concentrations of K^+, which suppresses T-cell function (▶ **Fig. 1**) [231]. Indeed, K^+ released by necrotic cells, can be internalized by infiltrating T cells, inhibiting their effector functions due to the downregulation the Akt/mTOR signaling [232]. Besides, abnormal tumor vasculature not only deprives TME of O_2 and nutrients, but it also fills it with byproducts of metabolism, some of which display immune suppressive activities [233]. Indeed, the degradation of glucose into lactate results in the acidification of the TME that further suppresses T-effector functions [220, 234]. At reduced pH, poly-

morphonuclear leukocytes (PMNs) display reduced chemotaxis and respiratory and bactericidal capacity, and lymphocyte cytotoxicity is also inhibited [235]. Further, low pH levels increase the suppressive activity of tumor-infiltrating myeloid derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs), reducing the proliferation of cytotoxic T-lymphocytes (CTLs) in the TME (▶ **Fig. 1**) [236]. The inhibitory effects of acidic pH on effector T-cell response in the TME is associated with generalized T-cell anergy, impaired cytokine secretion, and decreased perforin degranulation [237]. In addition, Soriano and colleagues observed that tumors also escape $CD8^+$ T-cell-induced cytotoxicity by overexpressing the inhibitors of perforin/granzyme pathway. In their study, the authors found that tumors showed an increased expression of protease inhibitor-9, a granzyme-B inhibitor [238]. Consequently, the capability of CTLs to kill tumor cells is reduced by one half [239]. Thus, similar to hypoxia, tumor acidity negatively regulates tumor-specific effector T cells, contributing to the dysfunction of antitumor immunity [240]. Therefore, alternative strategies to increase T-cell activation, infiltration, and cytotoxicity remain one of the main challenges today [241].

Immune recognition and elimination are important intrinsic mechanisms against tumors and their immunological profile is strongly associated with cancer prognosis [242]. A general model of exercise-driven modulation of immune cell distribution in tissues was proposed, describing the way that NK cells, T cells and B cells are mobilized to the blood [243]. This action seems to represent the recruitment of stored immune cells and not the formation of new ones [244]. Indeed, both local and systemic effects of physical exercise may potentiate T-cell incursion into tumors [245]. First, it increases circulating levels of IL-6, which can upregulate the adhesion molecules on tumor vascular endothelium, thus enhancing T-cell trafficking [246]. Second, exercise training causes redistribution of NK and $CD8^+$ T cells that have cytotoxic activity against cancer cells, increasing their concentrations approximately 10-fold and 2.5-fold, respectively [247]. Physical exercise can also influence the immune system by regulating Th1 and Th2 responses. The increase in Th1-type cytokine (IL-12 and interferon gamma (IFN-γ)) production and T-box transcription factor (T-bet) expression after exercise training may contribute to the increased immune response against tumors [248]. T-bet is the main transcription factor involved in the differentiation of $CD4^+$ T cells in Th1 cells that are able to inhibit tumor growth and metastasis [248]. However, several studies have shown that tumor cells produce molecules that inhibit DC maturation such as IL-10, prostaglandin E2 (PGE2), and TGF-β [249–251]. Nevertheless, it was shown that exercise training potentiates the synthesis of IFN-γ, tumor necrosis factor (TNF)-α and IL-12, inducing an increase and maturation of DCs [248]. Additionally, recent evidence indicates that the practice of regular physical exercise also tends to increase the infiltration of CTLs in murine tumors [252]. Indeed, exercise training may represent an effective strategy to improve immune response. A study comparing healthy and tumor-bearing animals concluded that physical exercise had a positive impact on macrophage function, which induced a reduction in metastasis [253]. On the contrary, sedentary tumor-bearing animals showed an increase in Th2 and Treg profile, resulting in a lower antitumor immune response and, consequently, facilitating the development of external tumor masses [254]. Furthermore, the typically conversion of type 1 macrophages (M1) into type 2 (M2) seen in tumors produces higher levels of IL-10 and TGF-β, changing the differentiation of T cells away from a cytotoxic Th1 response [255, 256]. IL-10 downregulates the adaptive immune response, inhibiting the activation of pro-inflammatory cytokines, further compromising the ability of effector T cells to maintain the inflammatory response [257]. Indeed, tumor-bearing animals exposed to long-term physical exercise developed less infiltrative and more benign histological lesions compared to sedentary tumor-bearing rats [258, 259]. Exercise training may hinder the progression from non-invasive to invasive lesions by inhibiting uncontrolled cell proliferation and by increasing cell death, which partially explains the significant decrease in the total amount of malignant cells in exercised animals [259].

Similar to the remaining tissues, skeletal muscle contains resident immune cells to maintain homeostasis [260]. However, as pathological and physiological conditions like muscle contraction can induce chemical and mechanical stress threatening this condition, there is an additional infiltration of immune cells in skeletal muscles following physical exercise [261]. For immune cells to infiltrate skeletal muscle, the production of factors with attracting and activating properties is necessary [260]. Experimental evidence showed exercise-induced muscle production of several cytokines, including IL-6, IL-8, IL-10, IL-15, CC-chemokine ligand (CCL) 2, IL-1 receptor antagonist, and VEGF [262]. An important function of these cytokines in contracting muscles is to attract immune cells to control inflammatory processes and to support muscle regeneration following physical exercise [263]. Accordingly, Malm and colleagues observed that single bouts of eccentric exercise increased immune cell infiltration and inflammatory markers (CD11b, CD3 and HIF-1β) in muscle epimysium [264]. Indeed, supporting the role of inflammatory response in muscles recovering from physical exercise, cDNA array analysis identified changes in gene products regulated by the NF-κB pathway such as CCL2, IL-18, C-X-C motif chemokine ligand 1 (CXCL1), leukemia inhibitory factor (LIF), and TGF-β1 [265]. Of these, CCL2 regulates migration and infiltration of monocytes and macrophages in skeletal muscle, which are indispensible for tissue repair [260]. The macrophages that infiltrate the tissue earlier after injury are activated M1. They generate inflammatory cytokines and sustain the activation and the proliferation of muscle stem cells [266]. Alternatively, activated M2 predominates during the resolution phase, regulating the ending of the inflammatory response [267]. Monocyte-derived macrophages undergo dynamic transitions between M1 and M2 and this timely transition is increasingly felt to be the key to muscle homeostasis [268]. Indeed, although PMNs, including neutrophils and eosinophils, are the first leukocytes to be recruited into the tissue, macrophages accumulate shortly thereafter and subsequently become the dominant leukocyte population [269]. In contrast, the accumulation of $CD4^+$ or $CD8^+$ T lymphocytes reflects a persistent inflammatory or immune-mediated injury, such as that taking place as a consequence of muscular dystrophy or inflammatory myopathies [270]. The importance of these cellular adaptations in the health-promoting effects of physical exercise is further emphasized by the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit the acute rise in skeletal muscle protein synthesis and the activation of satellite cells [271]. Therefore, these

data support the role of physical exercise-induced immune response as a beneficial mechanism to a stress-inducing condition.

Taken together, these observations allow us to conclude that by contributing to the repair of tumor vasculature, physical exercise creates better conditions to improve antitumor immune response, systemically, by increasing Tbet gene and Th1 cytokines expression and, locally, by providing superior access and function of immune cells (▶ **Fig. 2**).

Conclusion

The spatial and temporal heterogeneities in blood supply and vessel permeability associated with inefficient lymphatic drainage exacerbate the dysfunctional microenvironment that impairs a uniform distribution of O_2 and therapeutic agents in tumors [50, 90, 272]. In addition, pharmacological approaches to restore tumor vasculature present transient effects and, in some cases, may increase tumor hypoxia, which is a strong stimulus for tumor cells to metastasize [273]. Since tumor vascular repair in response to physical exercise has been described, new hopes were raised to mitigate tumor aggressiveness that is intimately associated with hypoxic microenvironments. Taken together, these data suggest that exercise training has direct antioncogenic effects [252, 259, 274]. The mechanistic insight into the immunological role of physical exercise indicates that it may be able to mediate intratumoral adaptations, by triggering alterations in the TME that lead to vascular repair, enhancing tumor perfusion, oxygenation, and infiltration of immune cells [275]. Thus, the practice of regular physical exercise as a non-pharmacologic therapy for remodeling tumor vasculature may overcome the limitations associated with AIAs [10, 57]. In addition to the associated adverse side effects, pharmacologic AIAs have a small therapeutic window with lower doses being ineffective and higher doses depleting too many vessels [45]. In contrast, it is unlikely that exercise training will over-prune tumor vasculature because capillaries adapt to chronic exercise by maturing and then becoming quiescent [276].

Globally, the available evidence suggests that exercise training may represent a valid therapeutic modality to the remodeling of tumor vasculature, improving TME and inhibiting tumor development. However, as the responses to physical exercise are complex and may be influenced by training parameters and by patients' socio-demographic variables, the results from pre-clinical investigations need to be replicated in the clinical setting, so additional studies are imperative.

Conflict of Interest

The authors declare, beyond the absence of any conflict of interest, that the manuscript complied with IJSM ethical standards [277].

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