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Effects of exercise-induced changes in myokine expression on the tumor microenvironment

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Introduction

The positive influence of exercise on cancer has been shown in multiple contexts. For instance, exercise may prevent the onset of colon cancer and improve overall quality of life in patients with various cancer types while also reducing side effects caused by medication, such as fatigue [1–5]. Additionally, in vivo studies suggest that exercise might inhibit tumor growth itself [6]. However, the underlying mechanisms of these effects, as well as the cause of slowed tumor growth through exercise, remain to be elucidated [7]. One explanatory approach toward this topic is changes within the surroundings of the tumor itself, the so-called tumor microenvironment (TME) [8].

The TME surrounds the tumor and consists of nonmalignant as well as malignant cells. The interactions between these various cell types create the TME [9]. While the cells that make up the

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TME vary between individuals as well as cancer types, the main components are the extracellular matrix, immune cells, the vascular system and stromal cells [10]. The TME is an important contributor to metastasis, tumor formation and therapy response. It plays a role in each step of tumorigenesis, from ensuring cancer cell survival in the early stages to cell evasion in the later stages [11]. The tumor influences the TME to favor vascularization and evade the body's immune response, and depending on the type of immune cells within the TME, they can either inhibit tumor growth or promote inflammation and thereby favor it [7, 11]. Furthermore, the efficiency of therapies depends on the type of immune cells in the TME [12]. As the composition of the TME may determine the outcome and alter the prognosis, it is favorable to find ways in which it can be influenced [13]. In this review, the components of the TME are not described in detail as a review on this topic has been previously published [11].

Changes in the TME are an important factor in tumor regulation and can be caused by exercise [14]. As there are strong indications that exercise can influence tumor growth, changes in the TME may be one important aspect [15]. Four known entities can alter the TME through exercise. These are vascularization, the immune system, cancer cell metabolism and myokines [7, 16]. While recent reviews on the topic have focused on the changes in the TME as a whole, to our knowledge, there are no reviews focusing on cancer-muscle crosstalk concerning the TME. In recent years, there have been a number of studies on cancer-muscle cross talk, which evokes the necessity to summarize these findings to further concentrate on the direct influence of muscle activity on changes in the TME and therefore possibly tumor growth [8].

Myokines are proteins that are released by contracting skeletal muscles and function in a similar way as hormones. Some are also classified as cytokines. They play a role in the prevention of multiple chronic diseases, e.g., breast cancer, type 2 diabetes and cardiovascular diseases. While these are fundamentally different diseases, there appear to be similar underlying mechanisms that can be influenced by myokines [17]. To date, only a few myokines have been identified and connected with a specific function that can be executed in an endocrine, paracrine or autocrine manner [18].

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Myokines are involved in various communication pathways, including muscle-organ cross talk and metabolism as well as vascularization [7]. Involvement in other pathways is very likely. First hints toward the effects that muscle activity has on cancer were presented in a study which showed that patients with higher muscle strength had a lower risk of developing cancer compared to patients with lower muscle strength [19]. Aerobic exercise has been suggested to increase vascularization in previously oxygen-low areas of the tumor, which can enhance the immune and drug response [8]. Myokines influence the transcription factors responsible for vascularization; therefore, exercise can normalize vascularization and metabolism within the TME [7].

While the number of known myokines is within thousands, the most prominent ones, which are likely to influence the TME, will be discussed in this review [18]. The effects of myokines can be local or systemic, thereby affecting cells directly and indirectly [20]. Most myokines show effects within the muscle tissue but the ones that enter the blood stream can have direct as well as indirect effects, depending on the target cell via the bloodstream, myokines can influence immune cells, and have an indirect effect on tumor cells via various immune cells, or they can have a direct effect if they come in contact with the tumor cells [16, 21, 22]. Therefore, one can assume that there are direct and indirect effects on the TME [18]. This distinction will be used as a structure to describe the effects of myokines on the TME.

Material and Methods

A literature search of PubMed and Google Scholar was conducted between January and July 2023. As literature density regarding the topic of this review is low, a narrative approach was chosen to give an overview of the topic[23]. First, the search terms in table 1 were defined. We used a primary search term, the name of the myokine, and added the listed variations to our primary search terms. We included systematic reviews, meta-analysees and original studies on all species. Articles were excluded if they were not in English, grey literature or if the full text version was unavailable to us. Supplementary references were regonized from the articles we found during our first search.

Results

Myokines and their response to exercise

Different types of exercise can have different influences on myokine expression [24]. Effetcs by exercise can be distigushed in acute changes in myokine expression which are present directly after exercise or chronic changes which are only present after a prolonged intervention period [25].

Interleukin-6 (IL-6) levels in men and women decreased after an endurance intervention [26] over the time period of eight months which was observed in combination with a lowered inflammatory status. Contrary to these findings, IL-6 levels remained similar in men who performed either strength, concurrent or endurance training for 16 weeks [27]. In a study on middle-aged women who performed resistance training for 16 weeks, a deacrease in IL-6 levels was observed 48h after a training session [28]. In marathon runners, an increase in IL-6 plasma concentration was observed directly after the race, while values correlated with the instenity of the run [29]. Changes in Oncostatin M (OSM) levels were observed after a 12 week resistance training intervention in postate cancer patients and also after a six month intervention which included endurance and resistance training [30, 31]. The levels of secreted protein acidic and rich in cysteine (SPARC) are not changed through sprints or directly after resistance training in young men [32, 33]. In prostate cancer patients on the other hand, serum and relative SPARC levels increased after a six month intervention phase consisting of endurance and resistance training [31]. Irisin levels in plasma were elevated directly after endurance and resistance training in men and women [34]. It was also recently observed, that the increase in irisin levels in endurance exercise is related to its intensity. High intensity interval training therefore resulted in higher levels compared to high volume training [35]. After a 26 week intervention of combined exercise, no changes in irisn levels were found [36]. Brain-derived neurotropic factor (BDNF) levels in older men were elevated acutely after resitance as well as endurance exercise [37]. After a 26 week endurance intervention in younger men, BDNF levels were

decreased overall [38]. In older women, a 22 week resistance training intervention resulted in no changes of BDNF levels [39].

Figure 1 summarises the acute and chronic changes of myokine concentrations discussed in this review in serum or plasma, devided by resistance and endurance exercise.

Myokines and their influence on the TME

Interleukin-6

The most popular and first discovered myokine is IL-6, which is involved in pathways that regulate muscle hypertrophy as well as cellular oxygen uptake and fat metabolism [18]. In addition to its metabolic function, IL-6 is also a key player in chronic and acute inflammation. In acute inflammatory processes, IL-6 stimulates the production of most proteins whose increase marks the beginning of an acute inflammatory response [40]. Overall, the effect of IL-6 in acute inflammation is preservative, as the amount of anti-inflammatory cytokines remains intact while pro-inflammatory cytokines are repressed. Normally, Il-6 binds to the membrane-bound nonsignaling IL-6 receptor α (IL-6Rα). The resulting complex can then bind to the signal transducing subunit glycoprotein 130 (gp130), which is expressed on most cell types. This process actively limits the IL-6 pathway, as only two cell types, hepatocytes and leukocytes, express IL-6Rα. Apart from the usual pathway, IL-6 can bind to soluble interleukin-6 receptor α (sIL-6Rα) [41]. This receptor is usually membrane bound but can be found in fluids after being shed from neutrophil membranes in highly inflammatory environments. The resulting Il-6/IL-6Rα complex favors chronic inflammation by promoting the shift of neutrophils into monocytes [40]. The soluble complex also binds to gp130, and as the local restriction is forfeited, IL-6 signaling can take place in every cell [41]. In the context of inflammation, IL-6 is therefore a two-sided sword, as it mediates the transition from acute to chronic inflammation by interacting with the sIL-6Rα receptor. While it exhibits anti-inflammatory properties in the acute response, it promotes inflammation in chronic events [42]. In chronic inflammatory diseases, IL-6 is therefore already used as a target for treatment [43].

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In cancer, IL-6 generally has a negative impact, as its signaling is connected to disease progression in humans and mouse models. Among these negative impacts are the avoidance of apoptosis, favoring migration and metastasis as well as angiogenesis. The vasculature of a tumor corresponds with its malignancy, and the process of angiogenesis in tumors diverges from normal angiogenic processes [44, 45]. The vasculature of a tumor is generally more unstable and unorganized than healthy vasculature [45]. Vascular endothelial growth factor-A (VEGF-A), a promotor of early-stage angiogenesis, is highly available in the TME, as it is produced directly by tumor cells [46]. IL-6 has been shown to favor angiogenic processes by upregulating vascular endothelial growth factor (VEGF) via the signal transducer and activator of transcription 3 (STAT3) pathway [47]. In the TME itself, IL-6 favors a tumor-friendly environment, but similar to inflammation, Il-6 can also have a positive effect in cancer [48]. In an indirect manner, IL-6 can influence the response of T cells toward an active immune response. Janus kinases (JAKs) within the TME are activated as part of the IL-6 pathway, which results in STAT3 signaling, which will be discussed in more depth later on. Downstream of this pathway, multiple transcription factors can be activated that navigate the pro-tumorigenic IL-6 response [41].

According to current knowledge, the origin of IL-6 in the TME is tumor cells themselves, CD4^{+} T cells, stromal cells and macrophages [41]. IL-6 levels can also be increased in the serum. The main source here is contracting muscles [49]. For example, an acute endurance exercise intervention led to an increased IL-6 concentration in the serum of men who have lifestyle risks for colon cancer. Colon cancer cells were treated with this serum, and decreased proliferation was observed. The authors suggest that cancer cells show enhanced DNA repair when they are exposed to exercise regularly. A sign or this suggestion is the fact that the effects of IL-6 on colon cancer cells were dependent on the dose they were treated with [50]. Whether IL-6 that is released into the serum has an effect on the TME remains to be explored but appears plausible, as it is likely that sIL-Rα is present as a binding factor [51]. Therefore, chronically increased IL-6 levels in serum may increase tumorigenesis [52].

Direct effects

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IL-6, when located in the TME, can have multiple effects, such as STAT3 signaling activation and other metastasis-promoting effects [53]. STAT3 signaling by IL-6 can influence gene expression in cancer cells. Soluble IL-6 forms a complex with its receptors, which can induce STAT3 signaling via activation of JAK. Activated STAT3 can change the gene expression of the cell, which will lead to anti-inflammatory gene transcription via membrane-bound activation but pro-inflammatory transcription if the activating IL-6 complex is soluble as it is in the TME. Soluble IL-6 in the TME will therefore directly change gene expression in cancer cells to favor an inflammatory environment, which contributes to cancer progression [54]. As previously mentioned, IL-6 in the tumor microenvironment can have multiple sources. In addition to the cell types that were mentioned, carcinoma-associated fibroblasts (CAFs) can be a main source. CAFs that produce IL-6 are suspected to be the main cause of epithelial-mesenchymal transition (EMT) [55]. EMT is a process that is necessary for embryogenesis, wound healing, stem cells and cancer progression and is characterized by cell differentiation [56]. During this differentiation, epithelial cells that are immobile and interact with other cell basement membranes transition into mesenchymal cells that can move freely. This new phenotype enhances the ability of cells to migrate [57]. In cancer, this process favors metastasis and drug resistance [58]. During EMT, cell–cell adhesions are loosened through genes whose transcription factors are induced by different processes [57]. Factors that induce EMT include cytokines and other soluble factors [59]. In breast cancer, an EMT phenotype can be induced, and IL-6 has been identified as a direct inducer of this phenotype in MCF-7 cells. In this context, the MCF-7 cells produced IL-6 themselves, leading to a feedback loop. Additionally, proliferation was increased. E-cadherin, a protein in the cell membrane, is responsible for cell–cell adhesion, and its absence can cause elevated invasiveness in cancer cells. In the presence of autocrine IL-6 in MCF-7 cells, a complete halt of E-cadherin expression was observed [60]. The expression of gene tumor protein 3 (TP53), which encodes tumor suppressor protein p53, is also influenced by IL-6 via the IL-6/JAK/STAT3 pathway. Similar to E-cadherin, p53 expression is attenuated by IL-6 originating from CAFs via ubiquitination. This results in

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chemotherapy resistance against the drug doxorubicin in prostate cancer cells (LNCaP) and possibly against other chemotherapies by resisting cell death [61].

Indirect effects

The indirect effects of IL-6 on the TME mostly revolve around its influence on the immune system [62]. Similar to the IL-6-driven inflammatory response, the influence of IL-6 on the immune system in a cancer context can be just as equivocal [41]. Recently, the positive effects of IL-6 were highlighted. As a part of this response, the effect of IL-6 occurs in the lymph nodes and modulates the immune system [63]. The activated immune cells then travel to the TME and influence it locally. IL-6 can modulate the T-cell response by enhancing the survival and proliferation of leukocytes. Additionally, IL-6 favors the transport of antitumor T cells toward the TME [41]. While the positive properties of IL-6 in a tumor response are still to be discovered, there is recent progress in understanding. It was shown in a mouse model that animals with access to aerobic training exhibited slower tumor growth, which was linked to increased CD8^{+} T-cell metabolism induced by muscle activity. One can therefore assume that exercise can shift the IL-6 response in tumors toward a positive response [64]. In general, infiltration of the TME with T cells favors a good prognosis. CD8^{+} cells can differentiate into interleukin-21 (IL-21)-producing CD8^{+} cells via IL-6-induced STAT3 signaling, which supports B cells in viral responses [65]. In the context of chronic inflammation, Forkhead-Box-Protein P3 (Foxp3[+)]CD8^{+} cells develop in the presence of IL-6 and suppress autoimmune responses [66].

T-cell immunity can also be reduced via IL-6 signaling. IL-6, as a soluble factor, increases the number of myeloid-derived suppressor cells (MDSCs) in vitro. These cells are an immature form of myeloid cells and can inhibit innate and adaptive immune responses. In hepatocellular carcinoma (HCC), the number of MDCs increased through IL-6 signaling and resulted in a reduction in T-cell immunity. This mechanism causes cancer progression. It is important to note that the authors mention a strong hint toward this mechanism but that further experiments are needed to show a direct link [67]. Another example of the negative effects of STAT3 signaling via IL-6 was found in colorectal cancer. STAT3

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phosphorylation by IL-6 in the presence of transforming growth factor β (TGF-β) in colorectal cancer caused the differentiation of CD4^{+} cells into Th17 cells, which can cause disease progression by onco- and angiogenesis [54]. In a study with colorectal cancer patients, a positive correlation was found between STAT3^{+} cells in the TME and patient survival. The auhtors also showed that IL-6^{+} immune cells were found significantly more often in early-stage tumors than in later-stage tumors [68]. Multiple mouse model studies showed that tumor growth is either suppressed or slowed when mice exercised prior to tumor injections. The authors found that the slowed tumor growth rate correlated with natural killer cell (NK cell) infiltration within the tumor. In further studies, they found that this effect is caused by acute IL-6 increases, as NK cells are IL-6 sensitive, and elevated IL-6 levels were shown in serum after acute intervention. Therefore, the authors suggest that the acute rise in IL-6 that causes an acute inflammatory process may inhibit tumor growth, while repeated exercise bouts before the disease can slow or prevent tumor progression by immune system activation [69].

Oncostatin M

OSM belongs to the family of IL-6 cytokines, as it can also bind to gp130 complexes [70]. In addition to gp130 complexes, OSM can bind to OSMRβ chains, which are expressed on a variety of cells [71]. While OSM is produced by multiple cells of the immune system, such as macrophages and dendritic cells, it is also secreted by skeletal muscle, which classifies it as a myokine [70, 72]. It is involved in multiple processes, such as liver development and blood cell production, and has been suggested as a target for treatment in common diseases, as OSM is also involved in the inflammatory response and can prevent neural cell damage [72, 73]. In cancer, OSM can promote cancer progression but was originally regarded as inhibitory [74].

OSM in the TME contributes to cancer progression by recruiting M2 macrophages into the tumor environment and by altering the phenotype of CAFs. In general, elevated OSM levels in serum as well as in the TME have been associated with disease progression in different cancer types [75]. While aerobic exercise increases OSM concentration in muscle tissue, it has been shown that OSM

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concentration also increases in serum after aerobic exercise in mice that were previously injected with breast cancer cells [73, 76]. In cancer cells, the oncostatin M receptor (OSMR) can be overexpressed. This overexpression leads to increased OSM signaling, which will cause angiogenesis, invasiveness and cell migration. OSMR overexpression will therefore favor disease progression. As OSM binds to OSMR, STAT3 signaling is activated, and gene transcription of VEGF-A and transglutaminase 2 (TGM2) is induced. VEGF-A induces angiogenesis, while TGM2 causes cell migration [77]. An in vitro experiment with triple negative breast cancer cells that were cocultured with neutrophils suggests that neutrophils in the TME will increase OSM production, which will then promote metastasis and tumor progression [70]. Similar to IL-6, OSM concentration appears to increase in serum and tumor tissue after exercise in mice [76].

Direct effects

In the TME, OSM has been brought into the context of EMT and was identified as the largest contributor toward the attainment of cancer stem cell characteristics (CSCs). Similar to IL-6, OSM can bind to STAT3. OSM/STAT3 signaling will then lead to an accumulation of mothers against decapentaplegic homolog 3 (SMAD3) in the nucleus [78]. SMADS are intracellular proteins that function as transcription factors that are activated by TGF-β and control the transcription of TGF-β target genes in a cofactor-dependent manner [79]. The altered transcription by OSM/STAT3 signaling favors gene transcription that will enhance EMT as well as CSCs. This increases the invasiveness and drug resistance of the tumor [78].

Indirect effects

Overexpression and promotion of tumor growth by OSM in vitro was observed in a study by 80 [80] in skin cancer. In the same study, the authors showed that tumor size in vitro and the polarization of M2 macrophages are reduced if OSM is absent, which suggests that OSM is an indirect promotor of cancer progression. The authors of a 12-week intervention study on prostate cancer patients analyzed serum myokine levels before and after the intervention and found a significant rise in OSM

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serum concentration, which correlated with lean body mass. The intervention consisted of aerobic and resistance training. In cell culture, the growth rate of cells with the conditioned serum slowed. The authors mention though, that a direct connection between the rise of myokines and slowed cell growth could not be shown [30]. OSM was identified as a promoter of breast cancer and metastasis by directing stromal intracellular crosstalk between cancer cells, immune cells and cancer cell-associated fibroblasts [81]. In the context of this study, the authors took OSM produced by myeloid cells into account and found a feedback loop between these cells and cancer cells with OSM receptors. In summary, the authors state that the role of OSM within the TME remains unclear, while it is also suggested that OSM/STAT3 signaling is a promising target to reduce drug resistance [78].

SPARC

Another myokine that was observed in an intervention study is SPARC [82]. SPARC is a common protein within the extracellular matrix (ECM) that can be found in the TME. SPARC was described as a family of closely related proteins that have multiple functions in adult as well as embryonic tissue [83]. As the authors reported, SPARC can influence the cell cycle in late phases, vascularization, matrix mineralization and cell adhesion. Its role is not clearly understood, but according to the current literature, the role of SPARC within the tumor is dependent on the cell type and the tissue in which the tumor lies [84, 85].

As a protein of the cellular matrix, SPARC regulates the interaction among cells and the communication between cells and the extracellular matrix (ECM). In cancer, SPARC influences cell–cell adhesions and can therefore increase the migratory properties of cancer cells, which may lead to metastasis [86]. Low SPARC levels in a murine melanoma model in vitro and in vivo appear to reduce invasiveness and cell migration, supporting the previous statement [87]. Contrary to this finding, SPARC is suspected to inhibit tumor progression and metastasis in bladder carcinoma, partly by limiting the inflammatory response [88].

Direct effects

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There are no known receptors of SPARC in humans, but there are a few suspicions on how SPARC might directly influence cancer cells [89].

An antibody study with different human tissues was contucted to determine the amount of SPARC within those tissues. The most prominent findings were that SPARC appeared to be binding to the ECM rather than being incorporated in it. Additionally, it was shown that the SPARC concentration is higher in malignant tissues [83]. SPARC can directly bind to collagen and interacts with factors such as VEGF, fibroblast growth factor (FGF) and TGF-β [85].

Indirect effects

In biopsies of colon cancer patients, SPARC expression correlated positively with VEGF, and low SPARC expression was associated with a poor outcome [90]. In renal cell carcinoma, SPARC is a downstream effector of TGF-β, and its expression is increased by TGF-β concentration. In this context, matrix metalloproteinase-2 (MPP2) expression was increased in vitro, which promotes invasion and therefore metastasis [91]. On the other hand, SPARC normalized the TME of ovarian cancer cells in vitro and in vivo via downregulation of VEGF [92]. SPARC is released through acute as well as longitudinal training interventions. An increase in SPARC in the plasma was shown in mice as well as humans, while gene expression after acute and longitudinal training was also elevated [24]. Plasma levels of SPARC appear to return to preexercise levels within 6 hours in mice and humans [3]. In prostate cancer patients specifically, no elevation in serum SPARC levels was observed, but a trend could be seen after a 12-week exercise training intervention [30]. The inhibitory and promoting properties of SPARC may be dependent on the origin or the cell type, which can be malignant or stromal. Therefore, it may be beneficial to involve these factors in further studies [90].

 In summary, the role of SPARC within the TME remains to be elucidated and may be altered by multiple factors, while it is clear that SPARC expression is influenced by exercise and plays a role in cancer progression [82, 85, 90].

IRISIN

Irisin was first described as a hormone that is secreted after exercise in mouse models as well as humans through fibronectin type III domain-containing protein 5 (FNDC5) cleavage [93]. FNDC5 is a transmembrane protein that is located in multiple tissues, one of which is skeletal muscle. Upon physical exercise, the extracellular part of the protein, which is irisin, is cleaved from FNCD5 and will enter the bloodstream, but it is unclear what causes this cleavage [94, 95]. Additionally, FNDC5 expression is upregulated by peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), which is an exercise-induced coactivator. In humans and mice, irisin levels in serum increase after exercise, while the increase is higher in trained humans, while irisin levels decrease with age. Additionally, irisin injections may induce muscle hypertrophy in mice [96, 97]. In an acute setting, resistance exercise provoked the strongest irisin response compared to endurance or combined exercise [98]. In a recent study in which adults performed an acute high-intensity interval training (HIIT) intervention, irisin levels in serum increased compared to moderate exercise and control [97]. Interestingly, a meta-analysis demonstrated that chronic exercise decreases the circulating concentration of irisin [99].

Myokine was first shown to promote brown fat development in vivo via mitochondrial uncoupling protein 1 (UCP1) expression [93]. Soon after, irisin became linked not only to obesity but also to multiple diseases [100]. The link between cancer and irisin has been drawn, as obesity favors an inflammatory environment that increases cancer cell survival and proliferation [96]. Recently,the role of Irisin in breast cancer was examined [94]. examined the role of irisin in breast cancer. The authors found that tumor progression relates to decreased Irisin levels and that high levels respond to an increased survival time. Irisin levels also appear to play a role in renal cancer. FNDC5/irisin levels were tested in the serum of patients and compared to a healthy control group with an enzyme-linked immunosorbent assay (ELISA). The study revealed elevated FNDC5/irisin levels in the patient group compared to the control group [101]. In contrast to this study, most in vitro experiments have shown that irisin has an inhibitory effect on cancer progression [102].

Direct effects

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Irisin was recently brought into context with exercise and the TME. The idea behind that being that irisin has a metabolic effect, which may be transferable to cancer cells, as one hallmark of cancer is altered glucose metabolism. This was tested in vitro with multiple ovarian cancer cell lines. In a time- and dose-dependent manner, irisin suppressed cell proliferation and migration, as well as the clonogenic potential of ovarian cells, in addition to a heightened sensitivity toward chemotherapy treatment [103].

An in vitro experiment with breast cancer cells showed that the activity of caspase-3/7 is increased while nuclear factor 'kappa-light-chain-enhancer' of activated B cells (NF-kB) activity is suppressed after irisin treatment. This leads to a lower count of breast cancer cells and decreased cell migration [104]. Caspase-3/7 are both proteases that can directly induce apoptosis and are therefore important markers, e.g., in cancer drug efficiency [105]. NF-kB summarizes a group of transcription factors that regulate inflammation as well as cell migration and other mechanisms that are important in cancer development [106]. Irisin treatment of OC cells decreased hypoxia-inducible factor-1-alpha (HIF-1α) and VEGF expression, possibly favoring tumorigenesis. Aside from these observations, an induction of apoptosis was also observed [103]. In another in vitro study on pancreatic cancer, ferroptosis, an iron-dependent type of apoptosis in which reactive oxygen species accumulate, was enhanced when cells were treated with irisin. These findings suggest that irisin may have a direct effect on cell death and therefore is an interesting therapeutic target [107].

Indirect effects

Serum irisin levels decrease in humans with age, while they are increased after acute exercise interventions but remain unaffected by chronic exercise [108]. In regard to aerobic metabolism genes, irisin had an inhibitory effect on VEGF expression, while the expression of other observed genes varied among cell lines. The effects on metalloproteases are still inconclusive and will need further studies, which involve the effect of different exercise interventions on myokines and cancer cells [103].

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BDNF

BDNF is a myokine as well as a neurotropin that is known to influence multiple mental disorders [109]. Another important aspect of BDNF is its metabolic effects. BDNF binds to tropomyosin receptor kinase B T1 (TrkB. T1) in pancreatic cells and thereby increases insulin secretion in a murine model. These findings support the notion that BDNF is regulated not only by hippocampal activity but also by muscle activity and has a peripheral effect [110]. These findings are supported by the discovery of increased BDNF serum levels in obese patients after an eight-week moderate- or high-intensity training intervention [111]. In contrast, in other studies, increasing levels of BDNF were detected within the muscle but not the periphery, leading to the conclusion that BDNF exhibits its function in an autocrine and paracrine manner while it may have an effect on peripheral metabolic activity. While the amount and mRNA expression of BDNF is increased in muscle through exercise, the effects appear to be local without release into the bloodstream, which makes an influence on the TME unlikely [25, 112]. Despite this, there is evidence that BDNF contributes to cancer progression by increasing metastasis-promoting cell properties, angiogenesis and chemotherapy resistance [113]. As there appears to be no consensus on the effects of BDNF and it is unclear whether central nervous system or muscle activity causes increased serum BDNF levels, it remains elusive whether BDNF can have an effect on the TME.

Discussion

Exercise is an important factor in cancer prevention, treatment and rehabilitation due to its multiple positive effects on patients. The question that remains unanswered is which molecular mechanisms contribute to these findings. A summary of the currently known effects of the myokines presented above is presented in Figure 2. The current literature shows that myokines are a promising aspect for answering these questions. All myokines that we described above may contribute to cancer development in different manners, but all of them need further exploration. Further studies also

need to be conducted to understand which exercise has the greatest impact on the different myokines to determine which exercise mode is most helpful as supportive cancer treatment and rehabilitation. As pictured in Figure 1, the serum and plasma levels of myokines are influenced by different types of exercise. While the majority appears to be more affected by acute exercise, it is unkown if the alterations in serum or plasma concentration by acute exercise remain persistant in regularly trained individuals or if adaptions can be observed. This would entail that repeated training sessions are required to have a direct effect on the TME, while long-term adaptations may lead to enhanced perfusion through angiogenesis and therefore a better response towards treatment [8]. This is supposedly caused by chronic changes in myokine concentration in serum, which can be either elevated or depleated [17, 21, 26, 108] . Overall, the intensity of exercise may be related to the levels found in serum, therefore one could assume that overall high intensities in exercise are favorable in the context of cancer prevention and rehabilitation [29]. Currently, the acute effects of myokines appear to be of higher importance.

An important question that remains to be answered is whether myokines from the periphery have a direct influence on signaling pathways within the TME. As a part of cancer research, the discovery of new approaches in cancer treatment is imminent. This includes research directed toward drug resistance as well as the discovery of new target pathways. One approach toward this goal is to understand the molecular aspects of the TME and how modulations influence tumor growth. Tumor growth has been shown to be slowed or inhibited by different modes of exercise in animal studies and in vitro. As there is no consensus about the exact molecular mechanisms of exercise on the TME, we propose the approach of investigating the role of myokines in the TME [74]. In this review, we presented the most commonly known myokines and their influences on the TME and consequently tumor growth and progression. It was shown that myokines can have tumor progression as well as inhibitory effects. These appear to depend on multiple aspects. For instance, dose dependent effects. Additionally, the interactions between myokines themselves and between myokines and cytokines may contribute to the effects on the TME.

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In summary, the findings of this review show tumor progression as well as inhibitory properties for all myokines discussed. These effects may be dose dependent, and exercise can therefore have negative as well as positive effects on tumors. Another important aspect is the differentiation between acute and chronic myokine effects in addition to interactions between myokines and between myokines and other cytokines, as this can also alter the effects on the TME. Exercise is a promising contributor to altering the TME, and the inhibitory effects of exercise on cancer have been demonstrated by in vivo and in vitro studies. Myokines likely contribute to these effects, which makes them an interesting target to further elucidate the effect of exercise on cancer disease.

Conclusion

The objective that this narrative review aimed to answer is the question, whether the influence of myokines on the TME may be one of the reasons, why positive effects of exercise in cancer are observed as the underlying molecular mechanisms are still unkown. In doing so, six common myokines were first described and then brought into the context of TME based on a literature review. While it cannot be clearly stated which type of exercise enhanced the expression of which myokines, there are clearly parts within the TME that respond to myokine regulation. Similar to inflammatory processes, it appears that all myokines discussed exhibit progressive as well as inhibitory properties within the TME and in cancer disease in general. To gain further understanding, future studies may focus on the currently known myokines and which type of exercise promotes their expression. There are no studies with similar cohorts investigating the changes of myokine expression in different types of exercise. It therefore remains questionable if one can reliably state which myokine is influenced by which exercise. In further human studies this should be compared to cancer patients, also in regard to their treatment. Furthermore, cell culture studies with contidioned serum may show if myokines that can be found in the serum have direct interactions with the TME. These findings can enhance existing exercise recommendations for cancer patients as they add to an

in-depth understanding of the positive effects that different traing modalities have on cancer patients.

One limitation of this review is that it is narrative. Therefore, there is no quantitative support of our observations. Moreover, existing literature was used to create a more concice picture of a topic within sports medicine that may be worth exploring. This review therefore lacks the clearity a systematic review may offer. Due to a lack of literature concerning the direct and indirect effects of myokines on the TME, this was not possible but should be reconsidered in the future. There may also be more possible interactions of myokines discussed within the TME, which may not have been included if they did not match the search terms.

Despite these limitations there are clearly molecular mechanisms which were pointed out in this review and may explain the positive influence of exercise on cancer and are therefore worth further investigations.

List of abbreviations

Tumor microenvironment = TME

Interleukin-6 = IL-6

Nonsignaling interleukin-6 receptor α = IL-6Rα

Glycoprotein 130 = gp130

Soluble interleukin-6 receptor α = sIL-6Rα

Vascular Endothelial Growth Factor = VEGF

Vascular Endothelial Growth Factor-A = VEGF-A

Signal transducer and activator of transcription 3 = STAT3

Janus Kinase = JAK

Carcinoma-associated fibroblast = CAF

Epithelial-mesenchymal-transition = EMT

Tumor protein 3 = TP53/p53

Interleukin-21 = IL-21

Forkhead-Box-Protein P3 = Foxp3^{+}

Myeloid-derived suppressor cell = MDSC

Transforming growth factor β = TGF-β

Natural killer cell = NK cell

Oncostatin M = OSM

Oncostatin M receptor = OSMR

Transglutaminase 2 = TGM2

Cancer stem cell = CSC

Mothers against decapentaplegic homolog 3 = SMAD3

Mothers against decapentaplegic = SMAD

Secreted Protein Acidic and Rich in Cysteine = SPARC

Extracellular matrix = ECM

Fibroblast growth factor = FGF

Matrix metalloproteinase-2 = MPP2

Fibronectin type III domain-containing protein 5 = FNDC5

Peroxisome proliferator-activated receptor γ coactivator 1α = PGC-1α

Mitochondrial uncoupling protein 1 = UCP1

Enzyme-linked immunosorbent assay (ELISA)

Nuclear factor 'kappa-light-chain-enhancer' of activated B cells = NF-kB

Hypoxia-inducible factor-1-alpha = HIF-1α

Brain-derived neurotropic factor = BDNF

tropomyosin receptor kinase B T1 = TrkB. T1

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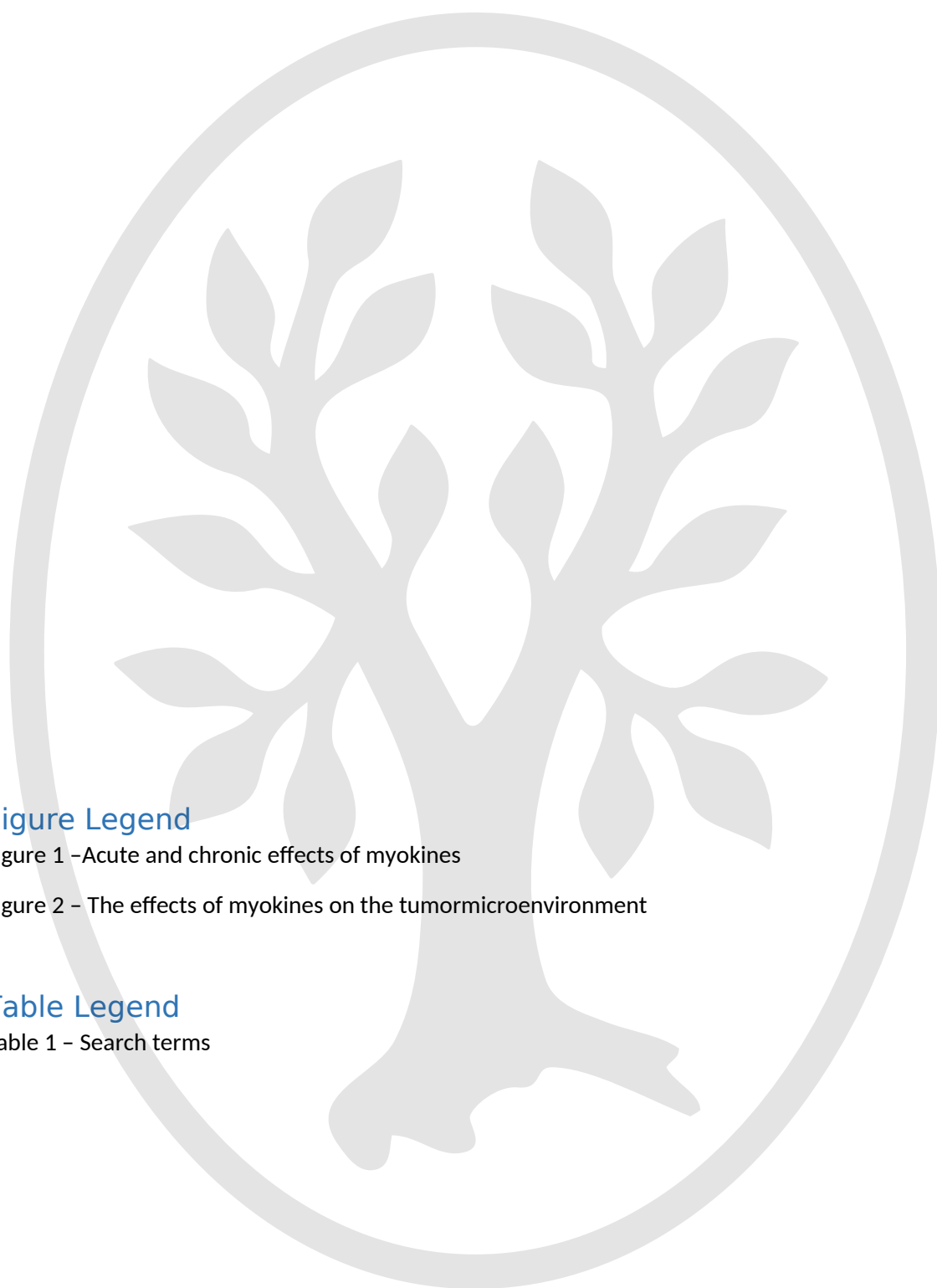
Figure Legend

Figure 1 –Acute and chronic effects of myokines

Figure 2 – The effects of myokines on the tumormicroenvironment

Table Legend

Table 1 – Search terms

Table 1: Search terms

Primary search term	Variations added to the primary search term						
Interleukin-6	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND cancer	AND exercise AND tumor microenvironment
IL-6	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND cancer	AND exercise AND tumor microenvironment
Oncostatin M	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND cancer	AND exercise AND tumor microenvironment
SPARC	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND cancer	AND exercise AND tumor microenvironment
Osteonectin	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND cancer	AND exercise AND tumor microenvironment
Irisin	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND cancer	AND exercise AND tumor microenvironment
BDNF	AND myokine	AND cancer	AND tumor microenvironment	AND exercise	AND cancer AND tumor microenvironment	AND exercise AND	AND exercise AND tumor microenvironment

							cancer	

Myokine	Acute effects		Chronic effects	
IL-6	✔	✔	✔	✖
OSM	?	?	✔	✔
SPARC	✖	✖	✔	✔
Irisin	✔	✔	✖	✖
BDNF	✔	✔	✔	✖