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Invited Mini Review

The role of myokines in cancer: crosstalk between skeletal muscle and tumor

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Loss of skeletal muscle mass is a primary feature of sarcopenia and cancer cachexia. In cancer patients, tumor-derived inflammatory factors promote muscle atrophy via tumor-to-muscle effects, which is closely associated with poor prognosis. During the past decade, skeletal muscle has been considered to function as an autocrine, paracrine, and endocrine organ by releasing numerous myokines. The circulating myokines can modulate pathophysiology in the other organs, as well as in the tumor microenvironment, suggesting myokines function as muscle-to-tumor signaling molecules. Here, we highlight the roles of myokines in tumorigenesis, particularly in terms of crosstalk between skeletal muscle and tumor. Better understanding of tumor-to-muscle and muscle-to-tumor effects will shed light on novel strategies for the diagnosis and treatment of cancer. [BMB Reports 2023; 56(7): 365-373]

INTRODUCTION

Skeletal muscle comprises approximately 40% of the whole body weight, and contains the largest body protein pool (1). The major functions of skeletal muscle are to contract to produce movement, maintain body temperature, store nutrients, and stabilize joints (1). In this regard, skeletal muscle wasting is closely associated with numerous human diseases (2). Sarcopenia is characterized by the decline in skeletal muscle mass and strength, emerging as a major health problem, particularly related to aging (3). Thus, maintaining skeletal muscle mass is crucial for human health and wellness.

During the past decade, skeletal muscle has been recognized as an endocrine organ (4). Skeletal muscle is composed of various types of cells, such as myocytes, fibroblasts, adipocytes, neurons, and connective tissues, which can release bioactive molecules referred to as 'myokines' (5). The myokines are peptides that are synthesized, expressed, and secreted by skeletal muscle fibers, including cytokines, interleukins (ILs), and neurotrophins (5). These myokines can regulate extracellular matrix organization, angiogenesis, and metabolism in both paracrine and endocrine manners (6).

Notably, most of the patients with advanced cancers represent sarcopenia with or without loss of fat mass, distinct from age-related sarcopenia or malnutrition, which is termed 'cachexia' (7). The cancer-associated cachexia is a multi-organ metabolic syndrome, which is not fully recovered by nutritional support, and accounts for 20% of cancer deaths (8). In this regard, skeletal muscle is suggested as a crucial player in carcinogenesis; however, its underlying mechanism is not fully understood. Herein, we focus on how skeletal muscle regulates cancer promotion and progression by affecting the tumor microenvironment (TME), particularly through myokines.

SKELETAL MUSCLE MASS AND CANCER: TUMOR-TO-MUSCLE EFFECTS

Cancer cachexia: tumor-to-muscle effects

Cancer cachexia is a devastating syndrome of remarkable weight loss, muscle wasting, and anorexia, which occurs in about 30% of total cancer patients, and in 70-80% of advanced cancer patients (8). Both cancer cachexia and sarcopenia show loss of skeletal muscle mass, sharing a complex pathophysiology, while cachexia is involved with more inflammatory responses than sarcopenia (9). Cancer has long been considered as a chronic and systemic inflammatory status that creates TME more favorable to tumor promotion and progression, leading to metabolic alterations in multiple organs (10). Among the pro-inflammatory factors released from tumors, IL-6 and tumor necrosis factor α (TNF-α) are well known to trigger skeletal muscle wasting (11, 12). Notably, serum levels of IL-6 and TNF-α were dramatically increased in pancreatic cancer patients with weight loss, compared to those without weight change (13, 14). A prospective cohort study further demonstrated that the plasma IL-6 level was markedly higher

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in cachectic lung cancer patients than in non-cachectic patients (15). Higher IL-6 and TNF-α levels were associated with cachexia, as well as mortality in cancer patients (16, 17). In tumor-bearing murine models, the elevated serum levels of IL-6 and/or TNF-α were also correlated with skeletal muscle loss, further supporting the sarcopenic effects of cancer-derived inflammatory cytokines (18, 19). However, ablation of IL-6 attenuated skeletal muscle wasting in tumor-bearing mice (19, 20). Similarly, administration of an anti-TNF-α antibody improved cachectic conditions in tumor-bearing mice (21). As illustrated in Fig. 1, these data suggest that cancer-derived IL-6 and/or TNF-α promote skeletal muscle wasting via tumor-to-muscle effects.

Skeletal muscle mass as a cancer prognostic marker

Notably, low skeletal muscle mass is correlated with poor prognosis in various types of cancer, including pancreatic and oesophageal cancers (8, 22, 23). In contrast, increased skeletal muscle mass was associated with longer survival in pediatric patients with malignant solid cancers (24). Thus, skeletal muscle mass is considered a putative marker for predicting cancer prognosis.

Moreover, skeletal muscle mass can affect chemotherapy-induced toxicity in cancer patients. Cancer patients with loss of skeletal muscle mass presented susceptibility to chemotherapy-induced toxicity and poor prognosis, compared to patients with lean body mass (25, 26). A meta-analysis including 48 studies has demonstrated that low skeletal muscle mass is associated with dose-limiting toxicities in cancer patients under neoadjuvant/adjuvant chemotherapies or curative radio-chemotherapies (27). In cachectic tumor-bearing mice, 5-fluorouracil chemotherapy exacerbated skeletal muscle wasting (28). Likewise, sarcopenia has been reported as a poor prognostic marker in cancer patients treated with immune checkpoint inhibitors, implying that skeletal muscle mass is crucial for optimizing chemotherapeutic regimens (29, 30). Taken together, skeletal muscle mass can reflect the body status in cancer patients and skeletal muscle might prevent and/or block carcinogenic processes, possibly through its secretome, while tumors induce skeletal muscle atrophy via secretion of IL-6 and TNF-α.

MYOKINES: MUSCLE-TO-TUMOR EFFECTS

Myokines, exercise, and cancer

In addition to tumor-to-muscle effects, skeletal muscle can modulate TME through its secretome. These skeletal muscle-derived molecules, termed myokines, include more than 600 proteins, such as cytokines (IL-8; IL-15) and neurotrophins (brain-derived neurotrophic factor, BDNF) (5). Myokines exert biological functions in autocrine, paracrine, and endocrine fashions (6). In particular, exercise can continuously stimulate skeletal muscle contraction, resulting in the secretion of a large amount of myokines (31). These myokines enhance skeletal muscle hypertrophy in an autocrine manner (31). Once released into the systemic circulation, myokines facilitate communication between muscle and the other organs (6).

It is well established that exercise is inversely correlated to cancer risk (32, 33). Exercise and/or regular physical activities can inhibit tumor promotion and progression in animal models, as well as cancer patients (34-36). The secreted myokines during the physical activities can regulate metabolic pathways,

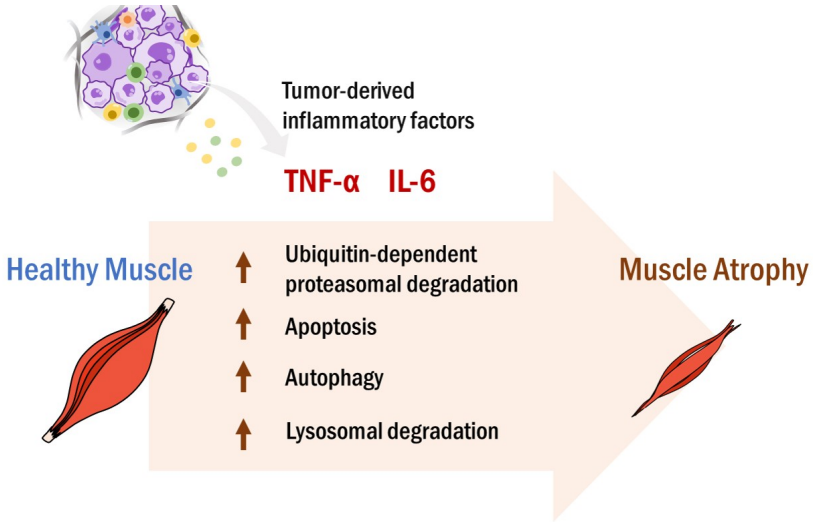

Fig. 1. Tumor-to-muscle effects. Tumor tissues constantly release various types of pro-inflammatory molecules into the bloodstream, maintaining the systemic and chronic inflammatory status. The circulating tumor-derived inflammatory factors, such as IL-6 and TNF-α, promote skeletal muscle atrophy through activating ubiquitin-dependent proteasomal degradation, apoptosis, autophagy, and/or lysosomal degradation. Loss of skeletal muscle is closely associated with poor survival in cancer patients.

immune system, and inflammation in TME (37). Thus, myokines play a key role in muscle-to-tumor effects, which mediates the beneficial effects of exercise in cancer patients. In the following sections, we discuss how skeletal muscle-derived myokines modulate cancer promotion and progression by affecting TME. Among various myokines, we focus on myokines that are known to be released by exercise from skeletal muscle and to function in TME in both direct and/or indirect manners.

Effects of myokines on TME

Irisin: Irisin, a recently discovered myokine, is a cleaved form of fibronectin type III domain-containing 5 (FNDC5) (38). During exercise, muscle contraction can upregulate the plasma levels of FNDC5 and its proteolytic product irisin (38, 39). Notably, it has been reported that the serum level of irisin was significantly reduced in patients with breast and liver cancers, compared to healthy individuals, implying the tumor-suppressive role of irisin (40, 41). In line with this notion, irisin treatment inhibited cell proliferation in breast and lung cancer cell lines (42, 43). Moreover, irisin prevented epithelial-to-mesenchymal transition (EMT), a major driver of cancer metastasis (43, 44). Exposure to irisin or overexpression of FNDC5/irisin diminished migration and invasion in different types of human cancer cell lines (43, 45). In ovarian cancer cell lines, irisin blocked hypoxia-inducible factor 1α signaling pathways responsible for the expression of metastasis markers, supporting its anti-metastatic activities (46). In the xenograft glioblastoma mouse model, administration of irisin dramatically repressed tumor growth (47). Furthermore, bladder cancer patients with lower serum irisin levels showed higher mortality (48). Taken together, these data suggest that irisin is a tumor-suppressive myokine.

Decorin: Decorin (DCN) is a member of the small leucine-rich repeat proteoglycan family that is ubiquitously expressed in connective tissues (49). During exercise, muscle contraction can upregulate DCN expression in human tendon and muscle, and also induce its secretion into the systemic circulation (50, 51). DCN has been reported to act as a soluble inhibitor of pan-receptor tyrosine kinases, such as Met receptor and epidermal growth factor receptor (EGFR), pro-survival signals for tumor cells (52). DCN treatment or overexpression reduced cell proliferation, migration, and EMT marker expression in various types of cancer cells, which can be mediated by the inhibition of Met/EGFR pathways (53-56). In consistent manner, systemic injection or overexpression of DCN suppressed tumor growth through blocking Met/EGFR pathways in the orthotopic xenograft models (54, 57). DCN significantly reduced angiogenesis and pulmonary metastasis in the tumor xenograft models (58, 59). In contrast, DCN ablation showed more and larger tumors in mice subcutaneously injected with murine colon cancer cells (53). Moreover, it has been reported that DCN is downregulated in tumors from patients with invasive breast and gastric cancers, which is associated with poor prognosis (60, 61). Overall, these data suggest that muscle-derived DCN can exert anti-carcinogenic activities in an endocrine manner, particularly in patients with DCN-low tumors.

IL-15: IL-15, a cytokine that belongs to the four α-helix bundle family, is responsible for natural killer (NK) and T cell immunity (62). Besides the immune cells, IL-15 is abundantly expressed in skeletal muscle, acting as a myokine. Exercise increased IL-15 levels in skeletal muscle and circulation in human subjects (63-65). It is noteworthy that exercise-induced IL-15 expression was correlated with better prognosis in pan-cancer cohorts, suggesting IL-15 as an anti-tumorigenic myokine (66). Consistently, the serum IL-15 level was significantly increased by exercise in prostate cancer patients (35). The pooled sera isolated from the exercising patients reduced cell growth in human prostate cancer DU-145 cells (35). Its anti-cancer effects could be attributed to immune modulation in TME. In tumor-bearing mice, IL-15 was co-localized with CD8 T and NK cells in TME (67). Heterodimeric IL-15 injection suppressed metastatic burden through increasing intratumoral CD8 T and NK cells in several different mouse cancer models, implying the involvement of CD8 T and NK cells in immune modulation by IL-15 (68). Likewise, subcutaneous injection of recombinant human IL-15 induced the number of circulating CD8 T and NK cells, while decreasing the number of leukemic cells in the blood of patients with T-cell malignancies (69). Recently, Kurz *et al*. demonstrated that exercise enhanced CD8 T cell immunity via increasing IL-15, which suppressed tumor growth in a pancreatic cancer mouse model (70). Overall, these data support that skeletal muscle-derived IL-15 promotes anti-tumor immunity.

Secreted Protein Acidic and Rich in Cysteine: Secreted Protein Acidic and Rich in Cysteine (SPARC), also known as osteonectin, is a calcium-binding matricellular glycoprotein that is involved in development, wound repair, tissue remodeling, differentiation, and proliferation (71). It has been reported that exercise induced circulating SPARC levels in healthy adult men (72). Exercise increased skeletal muscle expression and serum level of SPARC in both human and mice, which suppressed colon tumorigenesis (34). In wild type (WT) mice, regular exercise significantly reduced the number of aberrant crypts driven by a chemical carcinogen azoxymethane (34). However, SPARC-null mice developed more colon tumors than WT mice, which was not attenuated by exercise (34). In a rat model bearing colon cancers, high-intensity swimming training enhanced serum SPARC levels, finally suppressing tumorigenesis (73). Likewise, exercise significantly stimulated SPARC release from the skeletal muscle in patients with metastatic castrate-resistant prostate cancer (35). The serum isolated from these patients suppressed cell growth in human prostate cancer cell lines (35). These data suggest that exercise-induced SPARC can act as an anti-carcinogenic muscle-to-tumor signaling molecule.

SPARC can suppress multiple stages of carcinogenesis. SPARC inhibited cell proliferation in different types of cancer cell lines (74-76). In consistent manner, SPARC-null mice showed accelerated growth of tumor grafts, compared with WT mice (75, 77). Moreover, overexpression of SPARC hampered the expres-

sion of EMT markers and migratory capability in gastric cancer cells (78). In athymic nude mice subcutaneously implanted with gastric cancer cells, SPARC overexpression diminished tumor growth and angiogenesis (78, 79). Said *et al*. demonstrated that SPACR silencing promoted tumor growth and invasiveness, while reducing stromal collagen in the transgenic prostate cancer mouse model (80). Furthermore, SPARC enhanced chemosensitivity *in vivo* (78, 81). Taken together, these data suggest SPARC as a tumor suppressive myokine.

In contrast, SPARC can act as a tumor promoter as well. SPARC is highly expressed in metastatic tumors, such as glioblastomas and melanoma (82). SPARC increased the expression of EMT markers, enhancing invasion and migration abilities in cancer cells (83, 84). Tumor-derived SPARC induced vascular permeability and lung metastasis in mice inoculated with melanoma cells via tail vein injection (85). Moreover, SPARC overexpression promoted cell proliferation in liver and pancreatic cancer cells, further supporting tumor-derived SPARC as a tumor promoter (86, 87). It has been reported that certain types of cancers display contradictory compartmentalized expression of SPARC in TME, which contributes to the complex functions of SPARC in tumorigenesis (88). In the case of pancreatic cancer, stromal expression of SPARC was associated with poor prognosis, while its tumoral expression showed no significance (89). Furthermore, Pan *et al*. suggested that the oncogenic roles of SPARC might be due to its autocrine secretion into TME (87). Therefore, the roles of SPARC on TME can vary depending on the site of secretion, either TME or skeletal muscle, as well as its localization in TME.

Oncostatin M: Oncostatin M (OSM) is a member of the IL-6 family cytokines that exerts biological functions through binding to its heterodimeric receptor complex comprising OSM receptor β (OSMRβ) and gp130 (90). Interestingly, exercise remarkably increased the serum level of OSM in healthy individuals and cancer patients (35, 91). OSM has been reported to suppress cell growth in breast cancer, lung adenocarcinoma, and glioblastoma cells, implying OSM as an anti-tumorigenic myokine (92-94). In the orthotopic mouse cancer model, OSM-expressing glioma cells were unable to generate tumor mass (95). In prostate cancer patients undertaking androgen deprivation therapy, the exercise program significantly enhanced the serum level of OSM, while the expression levels of the other myokines were not altered (96). Human prostate cancer DU145 cells exposed to the sera from these patients showed retarded cell growth, further supporting the anti-cancer effect of exercise-induced OSM (96). Similarly, the sera pooled from exercising mice contained abundant OSM levels, which inhibited the proliferation of human breast cancer MCF-7 cells (97). OSM-containing conditioned media reduced EMT phenotypes and cancer stemness in lung adenocarcinoma cells (98). Moreover, treatment with OSM suppressed migration and invasion in human lung adenocarcinoma cell lines, and also blocked tumor metastasis *in vivo* (92). These data suggest that skeletal muscle-secreted OSM during exercise can act as an anti-tumorigenic myokine.

However, it is controversial as to whether OSM is anti-tumorigenic or pro-tumorigenic. In addition to muscle-to-tumor effects, OSM can be released within TME by tumor cells and/or stromal cells (99, 100). TME-derived OSM seems to exert pro-tumorigenic functions. Treatment with OSM induced proliferation in ovarian and prostate cancer cell lines (101, 102). OSM upregulated the expression of EMT markers and cancer stemness in pancreatic and cervical cancer cells (103, 104). In consistent manner, paracrine expression of OSM promoted invasiveness and angiogenesis of the grafts *in vivo* (105, 106). Of note, OSM suppressed or maintained the tumor sizes in xenograft models, while promoting metastatic features (104, 106). This might be explained by the lack of OSMR complex. OSM inhibited the growth of OSMR-intact cell growth, while cells with OSMR loss showed OSM resistance (102, 107). Thus, OSM might differentially affect tumorigenesis, depending on the cellular and molecular contexts.

BDNF: BDNF is a member of the nerve growth factor family that is mainly produced by neurons, regulating neuronal survival, differentiation, and apoptosis (108). In addition to neuron cells, skeletal muscle can synthesize BDNF (109). BDNF-null mice exhibited abnormal differentiation of myoblasts, decreased myotube size, and delayed muscle regeneration, suggesting that BDNF is a myokine responsible for skeletal muscle physiology (110). Of note, BDNF can be secreted from stromal cells in TME (111, 112). Higher expression of BDNF was associated with poor prognosis in various types of cancers (112, 113). Moreover, BDNF promoted cancer cell proliferation, migration, and invasion (112, 114). These data suggest that TME-derived BDNF can act as an oncogenic regulator.

In the case of skeletal-muscle derived BDNF, exercise can induce the skeletal muscle expression of BDNF in murine and human (109, 115). However, exercise was not able to increase plasma BDNF levels in human subjects, which means that muscle-derived BDNF might not be directly involved in muscle-to-tumor signaling (115). Rather, exercise seems to stimulate BDNF production in the brain (116). Hypothalamic BDNF expression inhibited tumor growth, while enhancing the anti-cancer CD8 T-cell immunity in C57BL/6 mice subcutaneously implanted with mouse melanoma cells (117, 118). Furthermore, brain infusion of BDNF reduced migration and intratumoral macrophage infiltration in the glioma mouse model (119). Although there is no strong evidence yet that skeletal muscle-derived BDNF directly affects tumorigenesis, exercise-induced hypothalamic BDNF expression can inhibit tumor promotion and progression. Taken together, these data imply that BDNF exerts tumor suppressive functions rather indirectly through the muscle-to-brain effects. Further investigation is required to elucidate a direct role of skeletal muscle-derived BDNF as a myokine.

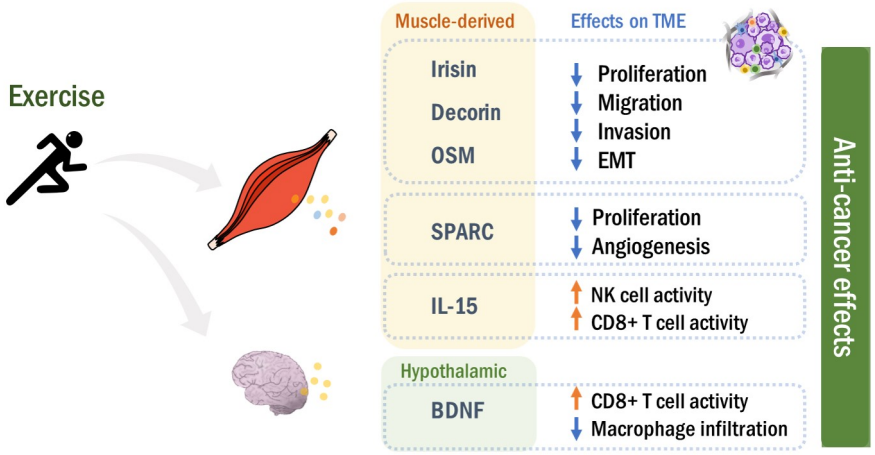

Fig. 2. Muscle-to-tumor effects. During exercise, muscle contraction stimulates the production of myokines. Muscle-derived myokines enter the circulation, and affect tumor promotion and progression by modulating TME in an endocrine fashion. In particular, BDNF seems to regulate TME rather indirectly through muscle-to-brain effects. Overall, exercise-derived myokines exert anti-tumorigenic functions in both direct and/or indirect manners.

CONCLUDING REMARKS

Currently, skeletal muscle is well recognized as a secretory organ (4). During exercise, skeletal muscle releases various types of myokines that control exercise adaptations in the autocrine and/or paracrine fashions (5). Moreover, myokines can travel through the circulation to the other organs, such as adipose tissues and brain, modulating pathophysiology (120, 121). Similarly, myokines play a crucial role in the interplay between skeletal muscle and tumor, which regulates tumor promotion and progression. While tumor-derived IL-6 and/or TNF-α contribute to skeletal muscle atrophy (Fig. 1), skeletal muscle-secreted myokines promote anti-tumor immunities and suppress tumor growth and metastatic abilities (Fig. 2). Thus, maintaining and/or recovery of skeletal muscle mass, a source of myokines, would be a novel and proactive approach to cancer treatment. Taken together, the integrative understanding of crosstalk between skeletal muscle and tumor will provide effective diagnosis/prognosis markers and novel chemotherapeutic targets.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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