Tumor-muscle communication in cancer-associated cachexia (Review)

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Abstract. Cancer progression is characterized by the ability of cancer cells to grow uncontrollably, invade adjacent tissues and eventually metastasize, which is typically accompanied by systemic effects. Cachexia, a catabolic state characterized by the loss of skeletal muscle mass and anorexia, is thought to result from the release of inflammatory molecules and other mediators from the tumor niche. The loss of skeletal muscle mass that characterizes cachexia is due to an exacerbation of proteolysis in muscle cells, a catabolic process that is dependent on inflammatory factors and extracellular vesicles (EVs) released by tumor cells. EVs activate various cellular signaling pathways that result in the nuclear translocation of NF-κB. These EVs carry various cargoes, including interleukins, microRNAs and receptors for advanced glycation end-products. When reaching muscle cells, these factors lead to an energy imbalance, increased oxidative stress, and the transcription of ubiquitin ligases such as muscle RING finger 1 and muscle atrophy F-box (Atrogin-1). While EVs appear to play an important role in cachexia, more evidence is needed to determine the interaction of the different cellular signaling pathways involved in the communication between the tumor cells and skeletal muscle cells, as well as to characterize the EVs derived from tumor cells and understand how they may contribute to the varying severity levels of cachexia syndrome. In cachexia, muscle wasting is driven by pro-inflammatory and catabolic factors released by tumor cells, leading to a negative energy balance. These factors activate the ubiquitin-proteasome pathway and suppress the PI3K/AKT/mTOR pathway. This line of research may lead to the development of new therapeutic strategies aimed at improving survival in patients with cancer with cachexia.

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1. Introduction

Cancer is characterized by the uncontrolled growth of somatic cells driven by mutations in proto-oncogenes and tumor suppressor genes (1), leading to the invasion of surrounding tissues and the progressive spread to secondary organs (2). According to the World Health Organization, in 2020 cancer was responsible for nearly 10 million deaths globally, making it one of the leading causes of mortality (2). Tumor growth and progression is accompanied by systemic effects, including cachexia, that cannot be explained solely by the effects of

tumor cells on their immediate tumor microenvironment. In particular, cachexia, often associated with late stages of cancer as well as other chronic inflammatory diseases, markedly contributes to increased mortality, reduced quality of life and physical dysfunction of affected individuals (3).

Cachexia is defined as a multifactorial catabolic syndrome characterized by the loss of skeletal muscle mass, reduced appetite and persistent fatigue. Its prevalence ranges from 35-90% in patients with advanced stages of cancer, being particularly prevalent in patients with malignant neoplasms that arise in the digestive system (4,5). Indeed, loss of skeletal muscle mass, or muscle wasting, is a central feature of the cachectic syndrome (6). Among primary mechanisms underlying muscle wasting is the upregulation of catabolic pathways that create an energy imbalance favoring the degradation of myofibrillar proteins. This metabolic imbalance is the result of paracrine signals in the form of soluble proinflammatory cytokines and/or extracellular vesicles (EVs) released from tumor cells or stroma cells in response to tumor cells (7).

EVs are membrane-bound particles produced and released by most cells. It is currently considered that EVs represent a complex mechanism of intercellular communication that involves the simultaneous transfer of multiple biomolecules (such as cargoes) that may regulate various processes in target cells (8). In particular, EVs released by tumor cells can function as carriers of biomolecules destined to several different tissues, including skeletal muscles, likely contributing to the muscle wasting observed in patients with cancer (9).

In addition to a vast and functionally diverse array of proteins, EVs also contain micro RNAs (miRNAs), a group of small non-coding RNAs that participate in post-transcriptional mechanisms of control of gene expression by binding to the 3'UTR of the coding mRNAs, leading to silencing the respective target genes. While several miRNAs carried by EVs released by cancer cells can regulate the expression of tumor suppressor genes and proto-oncogenes, thereby controlling tumor development and progression (10), they may also regulate inflammatory processes, protein degradation and the inhibition of myogenesis in muscle cells. So far, however, there is limited evidence indicating that these miRNA-dependent mechanisms are important contributors to cancer-related cachexia (11).

The present review summarized the available information linking cancer-derived extracellular vesicles (EVs) to inflammation and proteolytic mechanisms of muscle wasting in patients with cachexia.

2. Cancer-associated cachexia

Cancer-associated cachexia is a systemic condition characterized by a negative energy balance due to increased energy expenditure and reduced food intake (anorexia), resulting in loss of adipose tissue followed by loss of muscle mass, ultimately leading to dysfunction of multiple organs (12).

Tumor cells are characterized by a deregulated and inefficient metabolism, which results in a high demand for glucose and an increase in the production of lactate, even in the context of normal concentrations of oxygen (Warburg effect) (13). Due to metabolic inefficiency and overactivation of the Cori cycle, catabolic pathways are activated in the adipose tissue and skeletal muscle cells in order to mobilize glucose precursors for hepatic gluconeogenesis needed to sustain the energy requirements of tumor cells (13). This systemic metabolic reprogramming leads to a higher resting energy expenditure and a decrease in muscle strength and function, ultimately leading to a poor quality of life and reduced survival rates of patients with cancer (14).

Cachexia is observed in >50% of patients with cancer and is responsible for nearly 20% of cancer-related deaths. The incidence of cachexia varies depending on the type and stage of the tumor, with rates >80% in advanced gastric and pancreatic cancers (15). Overall, the cachectic syndrome is clinically classified into three stages: i) Pre-cachexia, where patients lose <5% of body weight and begin experiencing early anorexia-related symptoms; ii) cachexia, where patients lose >5% of body weight over a 6 months-period; this stage is often accompanied by increased release of pro-inflammatory factors by cancer cells, leading to organ dysfunction; and iii) refractory cachexia, where patients have a survival prognosis of <3 months. This latter stage is characterized by an exacerbated catabolism, neural disorders and dysfunction of the immune system, all factors that contribute to the rapid progression of cachexia and multi-organ functional decline (16).

It is worth mentioning that, in addition to factors released by tumor cells (or by stromal cells in response to tumor cells), most antitumoral treatments are known to cause adverse effects, including nausea, vomiting, dysphagia and mood disorders, that likely contribute to the development of anorexia and thus can exacerbate cachexia (17). However, as aforementioned, the increase in energy expenditure observed in cachectic patients is mainly attributed to the effects of systemic inflammation and the energy demands of tumor cells. Thus, inflammatory mediators and the increase in energy requirements of tumors cells leads to the degradation of muscle proteins through activation of the ubiquitin-proteasome system. Released amino acids serve in turn as glucose precursors for the hepatic synthesis of glucose, a process known as gluconeogenesis. In addition, muscle protein synthesis is reduced due to inhibition of the PI3K-AKT-mTOR pathway, which further contributes to muscle wasting in patients with cachexia (18).

3. Role of proinflammatory cytokines in cancer-associated cachexia

Inflammation is a known enabling feature of cancer (19). Several aspects of chronic inflammation may contribute to tumorigenesis, including the release of local and systemic proinflammatory and mitogenic mediators, as well as the increased accumulation of reactive oxygen species (ROS), with the consequent oxidative stress and genotoxic damage (19). In addition to promoting tumor initiation, features of chronic inflammation are also present during tumor progression. Thus, the tumor microenvironment often encompasses a heterogeneous population of cells in addition to cancer cells. These 'stromal cells' may include cellular components of the immune system capable of releasing pro-inflammatory mediators such as cytokines that favor tumor progression (20).

Cellular components of the immune system, both innate and adaptive, contribute to inflammation through the release of soluble mediators, namely cytokines, chemokines and other

molecules (21). Cytokines may aid cancer cells through the promotion of angiogenesis and by increasing glucose availability within the tumor microenvironment, both processes being crucial for cancer progression (22). Proinflammatory cytokines and chemokines, such as IL-6, TNF-α, IL-8 and IL-1, can promote cachexia and rapid skeletal muscle functional deterioration (7). Indeed, the functional link between soluble proinflammatory mediators and muscle wasting is at the core of the most accepted mechanism through which chronic inflammation induces cachexia (23). Notably, it has been shown that increased expression and release of IL-5 by tumor cells leads to an increase in the serum levels of IL-6 and IL-8, which is accompanied by a reduction in the expression of the secreted glycoprotein Folistatin-like protein-1 (FSTl-1) in muscle cells; reduced expression of FSTI-1 leads, in turn, to decreased vascularization and hindered muscle regeneration in patients with cancer with cachexia (24). Other studies have shown that IL-6 causes atrophy of C2C12-derived myotubes (25-27). Not surprisingly, IL-6 produced by pancreatic adenocarcinoma cells contributes to systemic inflammation and chronic lipolysis in the adipose tissue, resulting in increased fatty acid accumulation around muscle cells, myosteatosis and lipotoxicity-driven cachexia (25). IL-6 is further linked to neuromuscular junction dysfunction by increasing Noggin expression in muscle cells (26). Noggin, a signaling protein that regulates tissue development and differentiation, inhibits the BMP-SMAD1/5/814 pathway in skeletal muscles, which is crucial for muscle growth and maintenance (26). Inhibition of this pathway during cancer-associated cachexia therefore may also promote neuromuscular junction denervation (27).

Local release of proinflammatory cytokines at the tumor microenvironment can also contribute to the generation of neuroinflammation and lead to changes in the hypothalamus-pituitary-adrenal (HPA) axis (28). This latter physiological axis, a key regulator of the stress response, includes corticotropin-releasing hormone, corticotropin, and the cortisol-glucocorticoid receptor interaction (29). Dysfunction of the HPA axis has been linked to the adverse effects of proinflammatory cytokines, potentially leading to systemic dysregulation of energy metabolism and increased fatigue in patients with cancer (28). For example, IL-1β has been shown to upregulate leukemia inhibitory factor mRNA in the central nervous system, which may in turn contribute to HPA axis dysfunction, becoming apparent as appetite loss, reduced muscle mass and increased release of amino acids from muscle fibers, in the context of the increased energy demands of tumor cells (30,31). In addition to these systemic, HPA-mediated effects, cytokines may also affect more directly muscle contractile abilities and strength. For example, IL-1α and IL-1β are implicated in the decrease of myotube width and reduced amounts of sarcomeric actin, through the activation of catabolic pathways that lead to an upregulation of muscle atrophy F-box (Atrogin1/MAFbx), as well as muscle RING finger 1 (MuRF1) mRNA levels, which are components of the ubiquitin-proteasome proteolytic system that promote muscle protein loss (32).

TNF-α, a key proinflammatory cytokine linked to cachexia, can stimulate the ubiquitin-proteasome system in muscle cells, resulting in muscle mass loss and altered metabolism in patients with cancer (33). Indeed, TNF-α has been used as a serum biomarker of muscle wasting in individuals with colorectal cancer (34). In addition, a positive correlation between TNF-α and the upregulation of high-mobility group protein B1 (HMGB1) in the serum has been reported (35). HMGB1, a non-histone nuclear protein that is released by cancer cells or cells subjected to stressful stimuli, stimulates the ATP-dependent ubiquitin-proteasome pathway via activation of the NF-κB pathway, leading to autophagy in skeletal muscle cells, the mobilization of amino acids from muscle cells and their release into the blood stream to finally be used for gluconeogenesis in the liver (34,35). TNF-α also modulates the production and function of various non-coding RNAs in muscle cells, including long non-coding RNAs (lncRNAs) that are linked to morphological alterations in C2C12 cells (36). Powrózek *et al* (36) reported an inverse correlation between TNF-α levels and the expression of the lncRNAs Gm4117 and Ccdc41os1, implying that increased TNF-α levels lead to the suppression of these lncRNAs and the upregulation of another lncRNA, 5830418P13Rik. According to this study, the functional interaction between Gm4117 and Npm1, the gene encoding the chromatin modifier protein Nucleophosphin, interferes with a phosphoprotein involved in the control of muscle differentiation, a process mediated by several transcription factors, including c-Myc, NF-κB, Yin Yang 1 and interferon regulatory factor 1 (IRF-1) (36). Thus, a TNF-α-mediated reduction in Gm4117 levels contributes to muscle breakdown. Conversely, targeting of miRNA-125 by 5830418P13Rik positively regulates proteolysis by activating MAPK and forkhead box O (FOXO) signaling (36).

IL-8, a chemokine-type inflammatory cytokine, plays a critical role in local and systemic inflammation by promoting neutrophil chemotaxis (37). Similarly, activation of macrophages, induced by IL-6 secretion, further intensifies inflammatory responses mediated by IL-8 (37). In patients with cancer and cachexia, elevated IL-8 levels are associated with a poorer prognosis, typically indicating reduced survival (38). High IL-8 levels have also been linked to muscle atrophy in cachectic patients (37). IL-8 exerts its biological effects through its binding to the G protein-coupled receptor CXCR2 (38). Activation of CXCR2 activates the ERK signaling, which has been shown to markedly reduce the diameter of C2C12 myotubes treated with IL-8-containing conditioned media derived from human pancreatic cancer cells (38).

Recent studies have identified other members of the interleukin family linked to cachexia, such as IL-17A, which is primarily released by CD8+ T cells and plays a critical role in inducing inflammation (39,40). By synergizing with TNF-α, IL-17A also promotes the progression of pancreatic ductal adenocarcinoma (41). Conversely, head and neck cancers with low IL-17A expression levels tend to be associated with more advanced cancer stages. Therefore, IL-17A may have a dual function being both pro- and anti-tumoral, depending of the type of malignancy (42). Notably, this suggests a mechanism involving the regulation of T and B cells that infiltrate the tumor (41). In terms of muscle wasting, a study by Ying *et al* (42) found that lung patients with cancer with reduced muscle mass exhibited elevated serum levels of C-reactive protein and IL-17A. Additionally, lung carcinoma cells have been shown to induce muscle wasting in part through the release of increased levels of IL-17A, leading to the phosphorylation

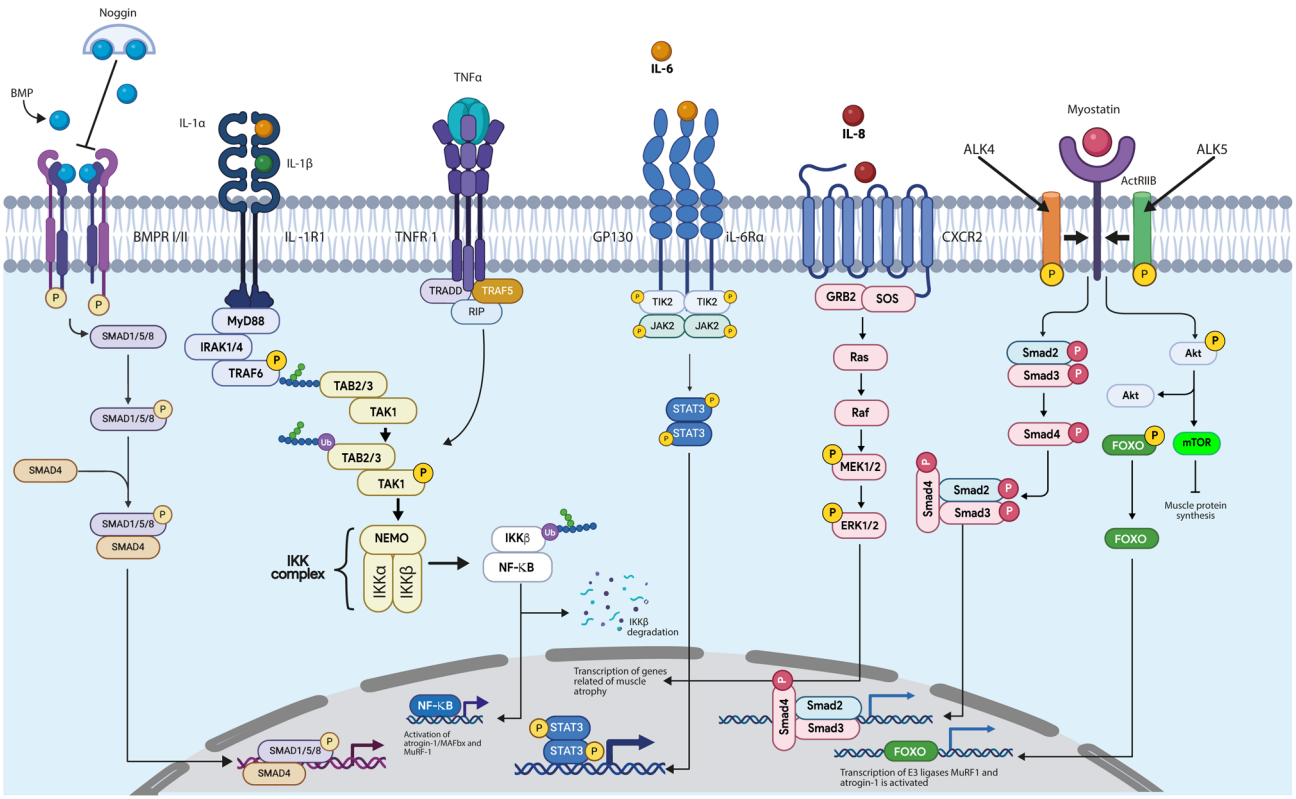

Figure 1. Main cell signaling pathways involved in myofibrillar protein degradation in cancer-associated cachexia. BMP, bone morphogenetic protein; BMPR I/II, bone morphogenetic protein receptor type I/type II; SMAD1/5/8, mothers against decapentaplegic homologs 1, 5 and 8; SMAD4, mothers against decapentaplegic homolog 4; IL-1R1, interleukin-1 receptor type 1; MyD88, myeloid differentiation primary response protein 88; IRAK1/4, IL-1R-associated kinase 1/4; TRAF6, TNF receptor-associated factor 6; IKK, IκB kinase; IκB, inhibitor of κB; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; TNF-α, tumor necrosis factor α; TNFR1, TNF receptor 1; TRADD, TNF receptor-associated death domain; RIP, receptor-interacting protein; TRAF5, TNF receptor-associated factor 5; TAB2/3, TAK1-binding protein 2/3; TAK1, transforming growth factor-β activated kinase 1; NEMO, NF-κB essential modulator; GP130, glycoprotein 130; JAK1/2, janus kinase 1/2; STAT3, signal transducer and activator of transcription 3; CXCR2, C-X-C chemokine receptor 2; GRB2, growth factor receptor-bound protein 2; SOS, son of sevenless; Ras, rat sarcoma viral oncogene homolog; Raf, rapidly accelerated fibrosarcoma kinase; MEK1/2, mitogen-activated protein kinase kinase 1/2; ERK1/2, extracellular signal-regulated kinase 1/2; ActRIIB, activin receptor type IIB; ALK4/ALK5, activin receptor-like kinase 4/5; Smad2/Smad3, mothers against decapentaplegic homologs 2/3; FOXO, forkhead box o; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; MuRF1, muscle ring finger 1; Atrogin-1 (MAFbx), muscle atrophy F-box protein.

and activation of the JAK2/STAT3 signaling pathway in muscle cells. Despite the identification of several inflammatory factors associated with cancer cachexia, further research is needed to pinpoint the specific interleukins involved in the etiology of cancer-associated cachexia (Fig. 1). An improved understanding of the pivotal role of proinflammatory cytokines, as well as of the intracellular pathways they activate in muscle cells, will set the stage for a deeper examination of the mechanisms governing myofibrillar protein degradation in cachectic patients.

4. Myofibrillar protein degradation in cancer-associated cachexia

It has now become clear that the metabolic and morphologic alterations in muscle fibers leading to muscle mass loss in cancer-associated cachexia is the result of an upregulation of the ubiquitin-proteasome system and/or the activation of the autophagy-lysosomal process (43). In a study by Zhang *et al* (44), changes in myocyte morphology, including misalignment of Z-lines and sarcomeres, were noticed in cachectic patients with gastric cancer. Additionally, these findings were accompanied by a reduction in the cross-sectional area of muscle fibers along with an increased expression of LC3B, an autophagy marker, and MuRF1 (45). MuRF1, a muscle-specific RING finger protein 1, acts as an E3 ubiquitin ligase in skeletal muscle catabolism (46). It binds directly to myofibrillar proteins, thereby initiating the proteolytic process that eventually leads to muscle wasting or atrophy (46). According to this model, increased proteolysis is mediated by cytokines and proinflammatory factors released by neoplastic cells, particularly TNF-α. Upon TNF-α binding to its receptor the signal transducer tumor necrosis factor receptor adaptor protein α (TRAF6) is activated (47), which phosphorylates the IKK kinase complex, leading to activation of NF-κB. This, in turn, activates the transcription of MuRF-1, which promotes the ubiquitination of sarcomere thick filaments (Myosin), ultimately resulting in proteasome-mediated myofibrillar protein degradation (47).

As aforementioned, autophagy is also involved in the pathogenesis of muscle wasting. In this multistep process, a double-membrane structure called a phagophore is first formed (48). The phagophore sequesters cellular components or protein complexes to be degraded; the fully formed cargo-containing doble-membrane vesicle, known as the autophagosome, then fuses with the lysosome to become an

autolysosome, the site in which the degradation of the sequestered cargoes occurs (49). Upregulation of LC3B, a protein essential for autophagosome formation, has been reported in the quadriceps femoris muscle of pre-cachectic and cachectic individuals with lung cancer (49). Similarly, elevated LC3B-II/I ratios (an indication of an increased autophagy flux) have been documented in the vastus lateralis muscle of patients with esophageal cancer (49). Such elevated levels of LC3B in muscle tissue are indicative of autophagosome accumulation, disrupted trafficking and cytoskeletal organization in myofibrils, all of which contribute to loss of muscle mass (49).

A study by Johns *et al* (50) set out to determine the structure and morphological composition of muscle fibers in cachectic patients, as well as various signaling pathways involved in cancer-associated-cachexia. The authors observed that an increase in the levels of SMAD3 protein was associated with >5% body weight loss in patients with pancreatic cancer (51). SMAD proteins constitute a family of intracellular proteins that act as signal transducers and transcriptional regulators downstream activated TGF-β receptors, thus transmitting signals involved in cell growth and differentiation (51). Specifically, it has been shown that SMAD3, in complex with SMAD2, is part of a signaling cascade that contributes to muscle wasting following the binding of myostatin to phosphorylated activin receptor type IIB, a serine/threonine kinase TGF-β receptor that is fundamental in muscle development, metabolism and other physiological processes in humans (52). Activation of this cascade inhibits the AKT/mTOR signaling pathway, which when active promotes muscle hypertrophy and protein synthesis (53). Additionally, SMAD3 activates the transcription factor FOXO3a, which regulates the autophagy pathway during muscle atrophy through an upregulation of LC3 (53). SMAD3 also increases the transcription of MuRF-1 and Atrogin-1, leading to increased protein degradation (53).

Regarding mechanistic target of rapamycin complex 1 (mTORC1), some discrepancy exists on its role in muscle wasting in the context of cancer-associated cachexia. Although mTORC1 inhibition does not directly lead to muscle atrophy, an upregulation of the process of mitophagy has been reported (54). Following the injection of C26 colon cancer cells in conditional knockout mice that are deficient in Raptor (a key protein of the mTOR complex 1, mTORC1) specifically in skeletal muscle cells, a significant increase in LC3 lipidation was observed in the gastrocnemius muscle compared to non-inoculated mice after colchicine treatment. Accordingly, AKT-mTORC1 activation alone in muscle fibers was sufficient to reduce myofibrillar protein ubiquitination and autophagy in the context of cachexia (55). These findings suggested the participation of mTORC1 as a integrating node in multiple signaling pathways that regulate muscle wasting in cachectic patients with cancer.

Furthermore, *in vivo* results using B16F10 mouse melanoma cells have demonstrated a markedly higher activation of the Ubiquitin-proteasome proteolytic system in the extensor digitorum longus muscle of tumor-bearing animals when compared to controls (56). This study also revealed a correlation between increased expression of MuRF-1 and reduced weight and muscle strength in tumor-bearing mice with cachexia. Reinforcing this association, inhibition of MuRF-1 led to a reduction in muscle mass loss (56). These and other findings highlight MuRF-1 as a key player in muscle wasting observed in tumor-bearing animals.

Another signaling pathway involved in muscle catabolism during cachexia is the JAK/STAT signaling pathway. Increased activation levels of STAT3, myostatin, as well as Atrogin-1 and MuRF1 ligases, have been reported in skeletal muscles of cachectic patients with liver cancer (57). In addition, the interaction between Heat Shock Protein 90 (HSP90) and STAT3 seems to be enhanced in muscles of cachectic individuals. HSP90, a chaperone protein that facilitates the proper folding of other proteins, also facilitates protein degradation and may regulate STAT3 activation during cancer-associated cachexia (58). STAT3 alone is sufficient to induce muscle atrophy both *in vivo* and *in vitro* models, resulting in a 30% reduction in the diameter of C2C12 myofibers (59). Conversely, STAT3 inhibition prevents IL-6-mediated muscle atrophy *in vitro* and attenuates cachexia in patients with colorectal or lung cancers (59,60). These findings suggest that JAK/STAT activation, driven by chronically elevated IL-6 levels, promotes skeletal muscle deterioration by activating autophagy and subsequently increasing myofibrillar protein degradation.

5. The effect of EVs derived from tumors on muscle cells in cachectic syndrome

EVs are lipid bilayer-encased structures that carry complex cargoes that include proteins, lipids, and nucleic acids (61). EVs are released from a variety of cells and act on distant target cells, facilitating paracrine or endocrine intercellular communication (61). EVs can be classified into different sub-types according to latest guidelines of 'Minimal information for studies of extracellular vesicles' (62). Small extracellular vesicles, typically with a diameters of <200 nm, are generated within the endosomal compartment region referred to as the multivesicular body (MVB), which must fuse with the plasma membrane in order to be released (61). Microvesicles, on the other hand, range in size from 50-1,000 nm and are shed directly from the plasma membrane through exocytosis (62). Finally, apoptotic bodies are even larger vesicles (1-5 μm) produced as a consequence of the fragmentation of apoptotic cells (62). The term 'exosome', although widely used, refers specifically to an EV of ~100 nm in diameter, formed as an intraluminal vesicle within an MVB and released outside the cell through the process of exocytosis. Essentially, an exosome is a specific type of EV, but not all EVs can be classified as exosomes (63).

It has been well established that, depending on the type of cargo, EVs released by cancer cells can regulate their growth, survival and dissemination to distant sites (64). For example, tumor-derived EVs can transport metalloproteinases that facilitate invasion of cancer cells through remodeling of the extracellular matrix (65). This process is accompanied by epithelial-mesenchymal transition, which enhances migration and invasiveness of cancer cells (66). In addition, EVs can provide spatial information for the formation of new blood vessels in tumor niches (67). Notably, some tumor-derived EVs display in their surface the protein programmed death ligand 1 (PD-L1), which facilitates the development of an immunosuppressive tumor microenvironment, thereby allowing the tumor cells to escape the detection of the adaptive immune

system (68). These findings highlight the crucial role of EVs in shaping the tumor microenvironment and in establishing a selection mechanism that ultimately increases intratumoral heterogeneity. Overall, tumor-derived EVs are emerging as important mediators of paracrine, autocrine and endocrine communication by virtue of their capacity to transport various cargoes that affect the behavior of target cells (64). This communication promotes interactions between cancer cells and non-cancerous cells, explaining, at least in part, how tumor cells exert distant effects on other tissues (69), including muscle cells in the context of cancer-associated cachexia.

A study shed light on the role of tumor-derived EVs in driving catabolism in tissues distant from the primary tumor in the context of cachexia (69). For example, C2C12 myoblasts exposed to conditioned-medium containing EVs derived from an AH-130 hepatoma cells exhibited delayed differentiation, marked by a reduced expression of Myogenin and Myosin Heavy Chain (MHC), as well as an overall decrease in protein synthesis compared to controls (70). Additionally, tumor-derived EVs carrying miR-21a-5p and miR-148a-3p enhance mitophagy in muscle cells by upregulating Bcl-2 interacting protein 3 (Bnip3) expression, leading to reduced mRNA levels of PPARGC1A (70), a gene encoding peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) that particularly regulates mitochondrial biogenesis (71). This suggests that an increased tumor burden triggers an energy crisis that prompts a shift from an oxidative to glycolytic metabolism, contributing to significant mitochondrial dysfunction and to an increased lactate production in muscle cells (70). In a study using a mouse model of esophageal squamous cell carcinoma-induced cachexia, the authors observed that tumor-derived EVs containing the beta subunit of prolyl 4-hydroxylase (P4HB), a protein disulfide isomerase (PDI) that can trigger cell death upon accumulation in response to misfolded proteins, could activate caspase-3 and caspase-8 in C2C12 myoblasts, accelerating the development of muscle wasting (72). Likewise, differentiated C2C12 myotubes treated with P4HB-containing EVs displayed reduced diameters and a downregulation in the expression of MHC, while the levels of MURF1, as well as the autophagy marker LC3, were concomitantly elevated (72). Finally, inoculating esophageal cancer cells overexpressing P4HB in mice generated a greater loss of body weight and a reduction in the cross-sectional area of myofibrils (72). Taken together, these observations suggest that P4HB may play a crucial role in inducing muscle wasting and therefore represent a key mediator of cachexia. However, further research is required to fully understand the role of P4HB in the proteolysis of myofibrils.

Hu *et al* (73) reported the effects of IL-6-containing exosomes released by Lewis lung carcinoma cells on muscle wasting. Notably, the authors noted that the activation of the STAT3-dependent proteolytic pathway initiated by ligand binding to IL6R resulted in atrophy of C2C12-derived myotubes, as well as adipocyte lipolysis. Similarly, it has been reported that EVs derived from a Lewis lung carcinoma cells contain the chaperone proteins HSP70 and HSP90, which, once incorporated into C2C12 myotubes, activate p38MAPK, resulting in an increased expression of the ubiquitin ligases Atrogin1 and UBR2 (74). Accordingly, the inhibition of HSP70 and HSP90 reduces the catabolic response triggered by Lewis lung carcinoma cells in C2C12 myotubes, as evidenced by the downregulation of the ubiquitin ligases Atrogin1/MAFbx and UBR2, as well as a reduced loss of myofibrillar protein (74). Finally, exosomes derived from colon adenocarcinoma cells containing Growth Differentiation Factor 15 (GDF-15) have also been reported to contribute to muscle wasting (75). In a study by Zhang *et al* (75), myocytes exposed to GDF-15-containing exosomes displayed a reduced expression of Bcl-2 and an increased expression of BAX which is associated with activation of caspase 3 and apoptosis, thereby promoting loss of muscle mass.

Kuang *et al* (76) reported that small EVs released from murine colon carcinoma-26 cells were enriched in miR-183-5p, a miRNA associated with a reduction in the diameter in C2C12-derived myotubes. In addition, it was observed that miR-183-5p, through activation of the Myostatin/Smad3 signaling pathway, upregulates the expression of MuRF-1 and Atrogin-1, promoting the degradation of proteins in myotubes. These responses were accompanied by a significant decrease in basal respiration and ATP production (76). It has also been observed that miR-195a-5p- and miR-125b-1-3p-containing EVs derived from colon adenocarcinoma cells can decrease Bcl-2 expression and induce apoptosis in muscle cells through caspase 3 activation (77). Another microRNA involved in muscle wasting is miR-122, found in EVs derived from MDA-MB-231 breast cancer cells. When added to C2C12-derived myotubes, these EVs induce a reduction in the expression of the tumor suppressor p53, Tfam, PGC-1α, SCO2 and MFN2, involved in negative regulation of mitochondrial function, thus leading to increased production of ROS, reduced ATP levels, decreased mitochondrial content and altered energy production (78). This may suggest that the induction of mitophagy upon inhibition of p53 might play a role in the disruption of energy homeostasis and mitochondrial regulation (79). Of note, while the effects of p53 inhibition in skeletal muscle were observed under stress conditions, there is no evidence for the relevance of this pathway in the context of muscle wasting observed in cancer-associated cachexia. Similarly, it has been shown that miR-122-containing EVs released by MDA-MB-231 breast cancer cells leads to a reduction in cytosolic O-GlcNAcylation with an upregulation of ryanodine receptor 1 (RyR1), a calcium release channel located in the sarcoplasmic reticulum of skeletal muscles, and the calcium-activated protease Calpain, ultimately promoting the calcium-dependent proteolysis of gastrocnemius myofibrillar proteins in female nonobese diabetic-scid-IL-2γ chain receptor null mice (80). On the other hand, it has been observed that myeloma-derived EVs contain receptors for advanced glycation endpoints (RAGE), which facilitate muscle wasting of myotubes through the activation of the Toll-like receptor 4/NF-κB p65 pathway (81).

Taken together, these data seem to indicate that EVs released by tumor cells may primarily induce mitochondrial dysfunction and an enhancement of glycolytic metabolism in skeletal muscle cells, leading to an energy imbalance that activate the Ubiquitin-Proteasome and/or autophagy, ultimately ending with the degradation of myofibrillar units that is typical of muscle wasting (Fig. 2). So far, however, little is

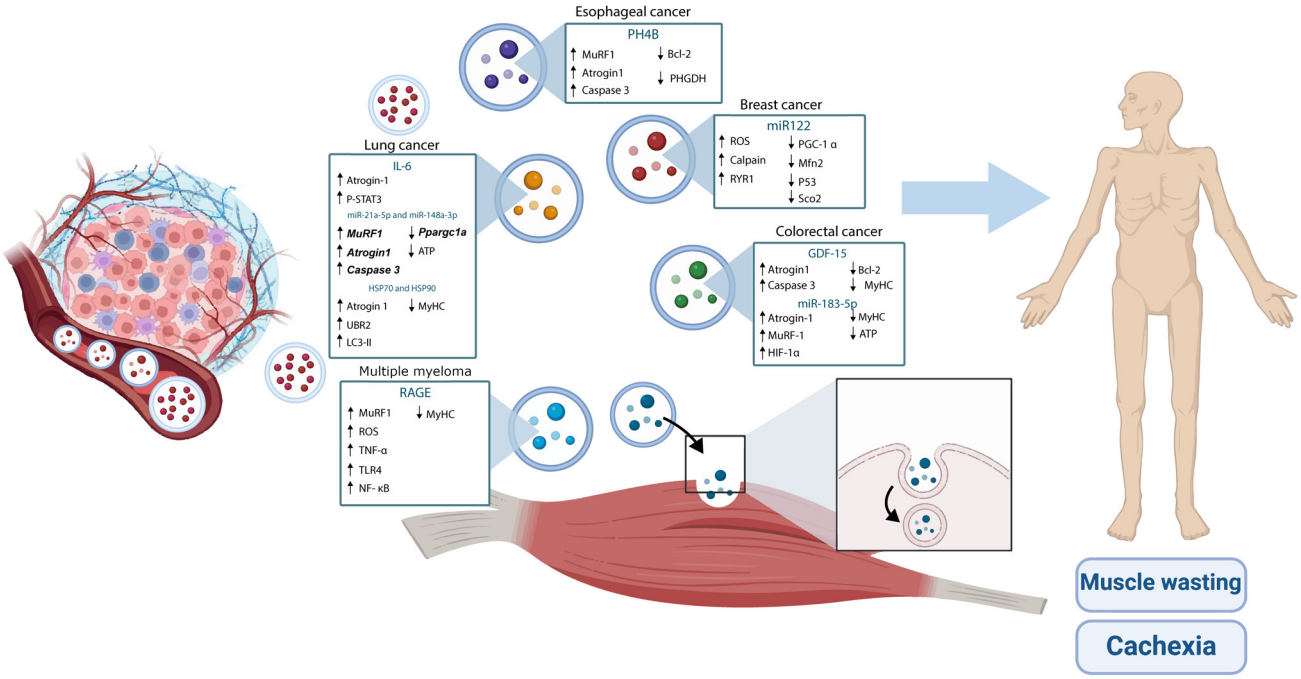

Figure 2. Characteristics of tumor EVs in cachectic syndrome. EVs, extracellular vesicles. ATP, adenosine triphosphate; Atrogin-1 (MAFbx), muscle atrophy f-box protein; Bcl-2, B-cell lymphoma 2; Caspase 3, cysteine-aspartic protease 3; GDF-15, growth differentiation factor 15; HIF-1α, hypoxia-inducible factor 1α; HSP90, heat shock protein 90; IL-6, interleukin-6; LC3-II, microtubule-associated protein light chain 3-II; miR-21a-5p, microRNA-21a-5p; Mfn-2, Mitofusin-2; MuRF1, muscle ring finger protein 1; MyHC, myosin heavy chain; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PHGDH, phosphoglycerate dehydrogenase; PPARGC1A (Ppargc1a), gene encoding PGC-1α; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; RyR1, ryanodine receptor 1; SOD2, superoxide dismutase 2; STAT3/p-STAT3, signal transducer and activator of transcription 3 (phosphorylated); TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor α; UBR2, ubiquitin protein ligase E3 component N-recognin 2.

known about signaling pathways that tumor-derived EVs activate or repressed in target cells (such as skeletal muscle cells). Similarly, we have a rather incomplete understanding of the cargoes carried by tumor-derived EVs that render them more or less likely to induce degradation of muscle components (Table I).

6. Clinical and therapeutic implications of tumor-derived EVs in cachectic syndrome

Currently, the clinical approach to cachexia involves a nutritional intervention based on the administration of food supplements, with enteral or parenteral nutrition depending on the clinical condition of the patient (82). This nutritional approach can be complemented with drugs such as Anamorelin, a potent and specific agonist of the ghrelin receptor that markedly stimulates appetite in patients with cancer (83). Nutritional and pharmacological approaches can both be effective in increasing body weight; however, no improvements in survival have been reported (82). Notably, Fan *et al* (84) showed that CT26 colon cancer cells treated with atractylenolide I, a component of a Chinese medicinal herb, produced and released fewer EVs, which was associated with an increase in food intake and an attenuation in the decrease of body weight in tumor-carrying BALB/c mice. Another study assessed the effects of the drug Amiloride (an inhibitor of Na/H and Na/K exchangers) on colon cancer cell lines (CT26) and primary Lewis lung carcinoma cells. The authors observed a significant reduction in the release of exosomes and reported drastic decreases in the plasma density of exosomes in a murine model (85).

Notably, a nanovesicular drug called Physiactisome has been recently patented. The drug is made up of vesicles containing the 60 kDa heat shock protein Hsp60, derived from HSPD1-overexpressing C2C12 cells (86). Although there is still no evidence regarding the effectiveness of Physiactisome, it is hypothesized that it could improve the expression of PGC-1α in cachectic muscle, increase mitochondrial biogenesis, thus reducing the generation of ROS and decreasing muscle waste (86). Furthermore, EVs have therapeutic potential when they contain IL-6 signal transducer decoy receptors, as they can inhibit STAT3 phosphorylation in skeletal muscle and reverse myotube reduction in the C2C12 cell line. This may contribute to reducing the activation of inflammatory cytokine signaling pathways and decreasing NF-κB translocation in cachectic syndrome (87). These preliminary data suggest the possibility of using EVs as therapeutic vehicles to counteract muscle wasting that occurs in cachexia or, alternatively, reduce the secretion of EVs released by tumor cells. Furthermore, nanovesicles can be generated to deliver drugs and/or proteins that may improve myofibrillar protein synthesis.

7. Conclusions and future perspectives

Cachexia-associated muscle wasting is driven by pro-inflammatory and catabolic factors released by the tumor cells or stromal cells in response to tumor cells. These factors create

Table I. Studies evaluating the effect of EVs tumor-derived on skeletal muscle.

First author/s, year	Cells of origin	Origin of the EVs	Isolation of EVs	Characteristic of EVs	Treatment in *in vitro* and *in vivo* models	Results	(Refs.)
Hu *et al*, 2019	•Lewis lung carcinoma cells. •C57BL mice	•Culture medium •Human serum and murine serum	•Ultracentrifugation	•Diameter: 106.4 nm •CD9 •TSG101 •HSP70 •IL-6	*In vivo* models •Male Lean C57BL mice •6 to 10 weeks old •Subcutaneous LLC injection •Sacrificed 28 days after tumor implantation. *In vitro* models •Conditioned culture medium for murine C2C12 myotubes •Concentration of 5 to 20 μg of EVs •EVs labeled with PKH67 internalization •Analysis at 12 h and 24 h of treatment	*In vivo* models •Body weight (↓) •Muscle mass TA, GN, quadriceps (↓) •Atrogin 1 (↑) •P-STAT3 (↑) •Myotube diameter (↓) *In vitro* models •Atrogin1 (↑) •P-STAT3/STAT3 (↑)	(73)
Gao *et al*, 2021	•Squamous cell carcinoma of the esophagus. •Human	•Culture medium	•Ultracentrifugation •ExoQuick□TC Exosome Isolation reagent kit	•Diameter: 30 -150 nm •ALIX •FLOT-1 •TSG101 •P4HB	*In vivo* models •Male BALB/c nude and C57BL/6J mice •6 weeks old •ESCC 100 μl subcutaneous injection. •Sacrificed 18 days after tumor implantation. *In vitro* models •Conditioned culture medium for C2C12 murine myoblasts •Concentration of 10 μg of EVs •Analysis after 24 h of treatment •EVs marked with PKH67-Internalization	*In vivo* models •Body weight (↓) •Muscle mass GA (↓) •*Myod1* (↓) •*Atrogin1* (↑) •*MURF1* (↑) •MURF1 (↑) •PHGDH (↓) •Cleaved caspase-3 (↑) *In vitro* models •MURF1 (↑) •PHGDH (↓) •Bcl-2 (↓) •Cleaved caspase-3 (↑) •Bax (↑)	(72)

Table I. Continued.

First author/s, year	Cells of origin	Origin of the EVs	Isolation of EVs	Characteristic of EVs	Treatment in *in vitro* and *in vivo* models	Results	(Refs.)
Miao *et al*, 2021	•Murine colon carcinoma cells C26	•Culture medium and mouse serum	•ExoQuick-TC Exosome Isolation reagent kit	•Diameter: ~100 nm •miR-195a-5p •miR-125b-1-3p	*In vivo* models •BALB/c and C57BL/6 mice •6-8 weeks •Subcutaneous injection $1x10^6$ of C26 cells •Intramuscular injection of C26 EVs (GN, TA) •Sacrificed 16 and 24 days after tumor implantation *In vitro* models •Conditioned culture medium for myoblasts and murine myotube C2C12 •Concentration of 50 μg of EVs •EVs marked with PKH67-Internalization •Analysis after 48 h of treatment	*In vivo* models •Grip strength (↓) •Body weight (↓) •Bcl-2(↓) •Muscle mass TA (↓) *In vitro* models •Myotube diameter (↓) •MyHC (↓) •MURF1 (↑) •Bcl-2(↓) •Cleaved caspase-3 (↑)	(77)
Pin *et al*, 2022	•Murine Lewis lung carcinoma cells •Murine colon carcinoma cells C26	•Culture medium and murine/rats plasma	•Ultracentrifugation	•Diameter: ND •miR-21a-5p •miR-148a-3p	*In vivo* models •Male Wistar rats •Subcutaneous injection $5x10^5$ of C26 cells •Sacrificed on day 7 and 14 after tumor implantation *In vitro* models •Conditioned culture medium for murine myotube and myoblast C2C12 •Analysis at 2, 4 and 6 days of treatment (myoblast) •Analysis at 24, 48 and 72 h of treatment (myotube)	*In vivo* models •Muscle mass GN, TA (↓) •*Becn1/Beclin1* (↑) •*MURF1*(↑) •*Atrogin1* (↑) *In vitro* models •*MURF1*(↑) •*Atrogin1* (↑) •Caspase 3 (↑) •*Myh7* (↓) •*Bnip3* (↑) •Lactate (↑) •*Ppargc1a* (↓) •ATP (↓)	(70)

Table I. Continued.

First author/s, year	Cells of origin	Origin of the EVs	Isolation of EVs	Characteristic of EVs	Treatment in *in vitro* and *in vivo* models	Results	(Refs.)
Yan *et al*, 2022	•Triple negative breast cancer cells •MDA-MB-231 •Human	•Culture medium	•Ultracentrifugation	•Diameter: ND •CD9 •CD63 •CD81 •miR-122	*In vivo* models •15-week-old NSG mice •Intravenous EV injection •~10 μg of EVs for 5 weeks (2x weeks) *In vitro* models •Conditioned culture medium for murine C2C12 myotube. •Concentration of ~ 2 μg of EVs	*In vivo* models •O-GlucosilNAcetilación RYR1 (↓) •Muscle mass GN-TA (↓) •Muscle Contractility(↓) •Desmin filament cleavage (↑) •Vimentin filament cleavage (↑) *In vitro* models •RYR1 (↑) •Calpain (↑) •Vimentin filament cleavage (↑) •Desmin filament cleavage (↑)	(80)
Liu *et al*, 2022	•Murine Lewis lung carcinoma cells	•Culture medium	•ExoQuick-TC Exosome Isolation reagent kit	•Diameter: ND •HSP70 •HSP90	*In vivo* models •8-week-old male C57BL/6 mice •Subcutaneous injection $1x10^6$ of LLC •Sacrificed on day 21 *In vitro* models •Conditioned culture medium for murine C2C12 myotubes. •48 h of treatment.	*In vivo* models •Body weight (↓) •Muscle mass TA, EDL (↓) •Grip strength (↓) •MyHC (↓) •LC3-II (↑) *In vitro* models •Atrogin1/MAFbx (↑) • p38 MAPK (↑) •Atrogin 1 (↑) •UBR2 (↑) •MyHC (↓) •Myotube diameter (↓)	(74)

Table I. Continued.

First author/s, year	Cells of origin	Origin of the EVs	Isolation of EVs	Characteristic of EVs	Treatment in *in vitro* and *in vivo* models	Results	(Refs.)
Zhang *et al*, 2022	•Murine colon carcinoma cells C26 and MC38	•Culture medium	•ExoQuick-TC Exosome Isolation reagent kit	•Diameter: 30 -150 nm •CD9 •CD63 •CD81 •TSG101 •GDF-15	*In vivo* models •Male BALB/c andC57BL/6 J mice •6-8 weeks •Subcutaneous injection of C26 tumor cells •Sacrificed on day 16 and day 22 *In vitro* models •Conditioned culture medium for murine C2C12 myotubes. •48 h of treatment	*In vivo* models • MyHC (↓) •Myotube diameter (↓) •Bcl-2/Bax (↓) •Atrogin1 (↑) •Cleaved caspase-3/caspase-3 (↑) *In vitro* models •MyHC (↓) •Bcl-2/Bax (↓) •Caspase-3/cleaved caspase-3 (↑)	(75)
Kuang *et al*, 2022	•Murine colon cancer C26 and MC38	•Culture medium	•ExoQuick-TC Exosome Isolation reagent kit	•Diameter: ND •miR-183-5p	*In vitro* models •Conditioned culture medium for C2C12 murine myotubes •Concentration of 50 μg of EVs •From the fourth day of differentiation •48 h of treatment	*In vitro* models •MyHC (↓) •FHL1 (↓) •HIF-1α (↑) •Atrogin-1 (↑) •MuRF-1 (↑) •ATP (↓)	(76)
Ruan *et al*, 2023	•Triple negative breast cancer cell line MDA-MB-231 •Human	•Culture medium	•Ultracentrifugation	•Diameter: ND •miR-122	*In vivo* models •8-week-old female NSG mice •Intravenous EVs injection ~10 μg •For 5 weeks (2 x weeks) *In vitro* models •Conditioned culture medium for murine C2C12 myotubes. •Concentration of 2 μg of EVs for 105 cells cultured in 2 ml of medium. •24 h of treatment	*In vivo* models •p53 (↓) •mtDNA (↓) •ROS (↑) •mitochondrial contents (↓) •Pgc-1 α (↓) •Mfn2 (↓) •Sco2 (↓) •Distance traveled (↓) *In vitro* models •p53 (↓) •ATP (↓) •ROS (↑) •Pgc-1 α (↓) •Mfn2 (↓) •Sco2 (↓)	(78)

Table I. Continued.

First author/s, year	Cells of origin	Origin of the EVs	Isolation of EVs	Characteristic of EVs	Treatment in *in vitro* and *in vivo* models	Results	(Refs.)
Wu *et al*, 2024	•Multiple myeloma •Murine Sp2/0-Ag14 cell line	•Culture medium	•Ultracentrifugation	•Diameter: 65-70 nm •CD9 •CD63 •CD81 •TSG101 •RAGE	*In vivo* models •6–8 weeks male BALB/c mice •Subcutaneous injection of Sp2/0-Ag14 tumor cells •Injected into the TA muscles 400 μg of EVs Sacrificed on day 22 *In vitro* models •Conditioned culture medium for murine C2C12 myotubes. •Concentration 50 μg of EVs •24 h of treatment	*In vivo* models •Body weight (↓) •Muscle mass TA, GA (↓) •CSA of muscle fiber (↓) •Grip strength (↓) •Serum levels ROS (↑) •Serum levels TNF-α (↑) •Serum levels IL-6 (↑) *In vitro* models •ROS (↑) •MuRF-1 (↑) •MyHC (↓) •IL-6 (↑) •TNF-α (↑) •TLR4 (↑) •NF- κB (↑)	(81)

C26 is a murine colon carcinoma cell line, MC38 are murine colon adenocarcinoma cells and C2C12 is a murine myoblast cell line. ND, not determined; EVs, extracellular vesicles; CD9, tetraspanin-29; CD63, cluster of differentiation 63; TSG101, tumor susceptibility gene 101 protein; HSP70, 70 kilodalton heat shock proteins; IL-6, interleukin-6; Atrogin 1, muscle atrophy F-box; PKH67, green fluorescent cell linker kit; ALIX, ALG-2 interacting protein X; FLOT-1, Flotillin-1; LLC, Lewis lung carcinoma cells; P-STAT3, phosphorylated activator of transcription 3; UCP 1, uncoupling protein one; *Bnip3*, Bcl-2 interacting protein 3 gene; BAX, Bcl-2-associated X protein; *Ppargc1a*, peroxisome proliferator-activated receptor gamma coactivator 1α gene; Pgc-1 α, peroxisome proliferator-activated receptor gamma coactivator 1α; ATP, adenosine triphosphate; MuRF-1, muscle ring-finger protein-1; ESCC, oesophageal squamous cell carcinoma; TA, tibialis anterior; GN, gastrocnemius; EDL, muscle extensor digitorum longus; P4HB, beta-subunit of prolyl 4-hydroxylase; Bcl-2, B-cell lymphoma 2; p38MAPK, p38 mitogen-activated protein kinases; UBR2, ubiquitin protein ligase E3 component n-recognin 2; LC3, microtubule-associated protein 1A/1B-light chain 3; *Myod1*, myoblast determination protein 1 gene; MyHC, myosin heavy chain; PHGDH, phosphoglycerate dehydrogenase; miR, microRNA; FHL1, four and a half LIM domains protein 1; ROS, reactive oxygen species; p53, cellular tumor antigen p53; NSG, NOD/SCID/IL2Rγ-null; HIF-1α, hypoxia inducible factor 1α; RYR1, ryanodine receptor 1; mt, mitochondrial; Mfn2, mitofusin-2; TNF-α, tumor necrosis factor α; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; SCO2, cytochrome c oxidase assembly protein; RAGE, receptors for advanced glycation end products; CSA, anatomical cross-sectional area.

an energy imbalance, activating the ubiquitin-proteasome signaling pathway while, at the same time, suppressing the PI3K/AKT/mTOR pathway. This cascade exacerbates myofibril proteolysis and autophagy and reduces protein synthesis. Despite the considerable amount of information available concerning the mechanisms of muscle wasting in cancer-associated cachexia, there is still rather limited evidence available on the role of tumor-derived EVs in these processes. Skeletal muscle mass markedly affects cancer patient prognosis, survival rates and treatment effectiveness. Therefore, investigating the mechanisms through which EVs contribute to tumor cells-muscle cells crosstalk in different malignancies is clinically relevant. It is considered that such a research program will lead to the development of novel therapeutic strategies aimed to improve the survival of patients with cancer with muscle wasting. Future research should focus on identifying systemic molecular markers associated with different stages of the cachectic syndrome and muscle wasting. Insights gained from such studies could help identify prognostic factors and enhance early pre-cachexia interventions to improve cancer patient functionality, quality of life and to reduce treatment-related side effects.

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Availability of data and materials

Not applicable.

Authors' contributions

LBC, MMV, NB, CV and RMC conceived the study and wrote the manuscript. LBC conducted the literature search/selection and data extraction. AFGQ, SB and FLS revised and edited the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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