Understanding cachexia in the context of metastatic progression

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Abstract | Tumours reprogram host physiology, metabolism and immune responses during cancer progression. The release of soluble factors, exosomes and metabolites from tumours leads to systemic changes in distant organs, where cancer cells metastasize and grow. These tumour-derived circulating factors also profoundly impact tissues that are rarely inhabited by metastatic cancer cells such as skeletal muscle and adipose tissue. In fact, the majority of patients with metastatic cancer develop a debilitating muscle-wasting syndrome, known as cachexia, that is associated with decreased tolerance to antineoplastic therapy, poor prognosis and accelerated death, with no approved treatments. In this Perspective, we discuss the development of cachexia in the context of metastatic progression. We briefly discuss how circulating factors either directly or indirectly promote cachexia development and examine how signals from the metastatic process can trigger and amplify this process. Finally, we highlight promising therapeutic opportunities for targeting cachexia in the context of metastatic cancers.

Our understanding of cancer progression has evolved from an emphasis on cancer cell-intrinsic changes to an appreciation of the critical interactions that occur between cancer cells and non-cancer cells in the primary tumour microenvironment[1,2]. These cancer cell-extrinsic interactions influence the growth, invasion and metastatic abilities of cancer cells through the release of soluble factors, exosomes and metabolites that alter host physiology and reprogram host metabolism[3]. Many of these systemic changes in peripheral tissues are often detrimental to the host. Indeed, 80% of patients with advanced cancer experience cachexia — a progressive loss of muscle mass (muscle atrophy) and function, which often (but not always) includes loss of adipose tissue mass[4,5] (BOX 1). Since effective muscle function is vital for breathing, movement, chewing and swallowing food, the quality of life for patients with cancer significantly diminishes with the development of cachexia[6]. Furthermore, debilitated muscles reduce the tolerance of patients with cancer cachexia to antineoplastic therapy, and weakened heart and diaphragm muscles often lead to premature deaths from cardiac and respiratory failures, respectively[7]. Anorexia (lack of appetite for food), a decreased ability to chew food, and a compromised ability to absorb and utilize nutrients are some of the underlying complications of cachexia that contribute to muscle loss[3,4]. However, clinical studies revealed that cachexia is not simply a nutritional deficiency disorder since neither oral (dietary) nor intravenous (parenteral) nutritional supplementation can completely reverse cachexia in patients with cancer[5]. Cachexia is therefore an important clinical problem associated with cancer, and the ability to understand and effectively target cachexia remains an unmet need in cancer biology and medicine.

Among patients with cancer, patients with pancreatic, gastrointestinal, colon and lung cancer have a high incidence of cachexia[7] (BOX 2). Symptoms of cachexia can appear early, even when primary tumours are still localized; however, cachexia in this context rarely becomes life threatening if tumours are surgically removed or effectively treated[8–10]. Indeed, in mouse models of cancer cachexia, markers of muscle wasting reduced after resection of localized tumours[11] but eventually reappeared with recurrence and metastasis (Unpublished, A.K.B. and S.A.). Complete tumour elimination is rarely achieved in patients with metastatic cancer, and, consequently, cachexia becomes a chronic problem[12]. Effective therapeutic interventions for cachexia are therefore expected to markedly improve outcomes for a large proportion of patients with metastatic cancer.

There are currently no effective therapies for patients with cancer cachexia despite more than 100 clinical trials aimed at targeting its mediators[7] (Supplementary Table 1). Two key considerations that were overlooked in some of the trials might have contributed to their failure in finding an effective therapy. First, most of the tested therapies targeted cachexia mediators identified in experimental cachexia models involving localized, early-stage cancers, yet many of the clinical trials that investigated the targeting of these mediators were conducted in patients with metastatic cancer[13]. Since the mediators of cachexia may differ in the context of either metastasis or localized primary tumours, preclinical models of metastasis-associated cachexia might be more appropriate to identify candidate cachexia treatments for patients with metastatic cancer. Second, tumour progression and anticancer treatments impact the development of metastasis-associated cachexia[14]; indeed, some chemotherapy agents, such as cisplatin, doxorubicin or FOLFIRI (5-fluorouracil, leucovorin and irinotecan), can promote cachexia[15–17]. Preclinical studies designed to model these features are likely to have more translational success in cachectic patients with metastatic cancer. Although such preclinical studies are scarce, some recent studies have addressed these shortcomings by studying cachexia specifically in the context of metastatic cancer[11,18–20] (Supplementary Table 2). These studies provide a framework to identify the mediators of cachexia in the context of systemic changes that occur as cancer cells disseminate and colonize distant organs. The objective of this Perspective is therefore to examine cachexia pathogenesis through the lens of metastatic progression in order to identify causal links between the two processes. In this Perspective, we discuss how molecular and cellular changes in invasive primary tumours, pre-metastatic

niches (PMNs) and metastatic microenvironments could contribute to cachexia development. We highlight the emerging tractable targets for cachexia therapy in patients with cancer and discuss challenges in the field.

Mechanisms of muscle atrophy

Three lines of experimental evidence form the basis for our current understanding of the underlying mechanisms that drive cancer cachexia. First, experimental studies have shown that the complete removal of cachexia-associated tumours (when feasible) can reverse cachexia[8]. Thus, tumours are not only necessary for cachexia induction but their continued presence is required to maintain cachexia. Second, parabiotic transfer experiments using tumour-bearing rats showed that anorexia/cachexia-inducing factors are humoral in nature since pro-cachectic circulating factors could be transferred via circulation between rats that were surgically connected[21]. Subsequent studies established that the humoral factors can be secreted directly either by tumour cells, by non-tumour cells in the tumour microenvironment, or from distant organs. Studies using both primary-tumour and metastatic models have shown that cachexia-inducing circulating factors are diverse in origin and function[22] and include both pro- and anti-inflammatory cytokines, metal ions, hormones and growth factors[3] (FIGS 1,2). Third, circulating factors induce cachexia by two distinct mechanisms, which are briefly discussed below: directly, by interacting with muscle cells and activating pathways to promote muscle catabolism or suppress protein synthesis (reviewed in REFS[3,23]), or indirectly, by the metabolic reprogramming of secondary organs, which in turn induces muscle wasting (reviewed in REF.[22]) (FIG. 1).

Circulating factors: direct effects

Systemic metabolic dysfunction. During cancer initiation and progression, cancer cells reprogram their own metabolic pathways to fulfil their increased bioenergetic and proliferation needs while simultaneously disrupting the systemic metabolism of their host[3]. As such, metabolic dysfunction of host tissues is a consistent feature of cancer cachexia that manifests as a derangement in carbohydrate, fat and protein metabolism (reviewed in REFS[3,7,23–25]).

In response to cancer, protein homeostasis in muscle is skewed towards reduced protein synthesis and increased protein breakdown[26] (reviewed in REFS[25,27]). This mainly results from the hyperactivation of the ubiquitin–proteasome and autophagy pathways, which promote muscle breakdown in cancer. Transcriptional upregulation of genes encoding several E3 ligases, including muscle-specific RING finger protein 1 (MURF1, also known as TRIM63), muscle atrophy F-box protein (MAFBX, also known as FBXO32), FBXO30 and FBXO31, increased the turnover of key muscle proteins (myofibrillar proteins), resulting in muscle atrophy[25]. Muscle gain is normally achieved by the simultaneous activation of protein synthesis and inhibition of catabolic mediators. Under anabolic conditions, the PI3K–AKT pathway inhibits Forkhead box O (FOXO)-mediated induction of the genes encoding MURF1 and MAFBX, and thereby prevents muscle atrophy[27,28]. While catabolic pathways contribute to cancer-induced muscle loss, a consensus is lacking regarding the contribution of reduced muscle protein synthesis to cancer cachexia.

Patients with cancer cachexia often develop insulin resistance[29,30]. In normal physiology, besides controlling carbohydrate metabolism, insulin regulates muscle protein synthesis and breakdown to maintain blood glucose levels[31,32]. Insulin resistance in the physiological context can accelerate muscle proteolysis through suppression of the anabolic PI3K–AKT pathway and activation of the ubiquitin-mediated proteasome pathway[33]. This mechanism also seems to play a role in cancer cachexia because insulin resistance or interrupted insulin signalling has been shown to contribute to cachexia in murine and *Drosophila* tumour models in vivo[34–37] (FIG. 1b). In addition, treatment with the insulin sensitizer rosiglitazone delayed weight loss and anorexia in the murine colon 26 (C26) cancer cachexia model[38] and reduced weight loss and prolonged survival in the Yoshida AH-130 hepatoma rat cachexia model[39]. Impaired insulin secretion from the pancreas also contributed to insulin resistance and triggered muscle breakdown in the Walker 256 cancer cachexia model[34]. Interestingly, studies using the fruit fly *Drosophila melanogaster* showed that tumours secrete ImpL2, a homologue of insulin growth factor binding protein (IGFBP) and a potent antagonist of insulin signalling, which induces systemic metabolic dysfunction and muscle wasting[37]. Therefore, disrupted insulin signalling can negatively impact muscle mass and function in the context of cancer.

Cytokines. As cancer progresses, abundant levels of cytokines are released into the circulation from cancer cells, immune cells and other non-cancer cells in the tumour microenvironment[2]. A large body of evidence has established that cytokines, such as tumour necrosis factor-α (TNFα), transforming growth factor-β (TGFβ) and IL-6, promote muscle fibre breakdown (reviewed elsewhere[3,23]) (FIG. 1a). As an example of pro-inflammatory cytokine action on muscle, cytokines of the TNF superfamily, TNFα and TNF-related weak inducer of apoptosis (TWEAK), can directly activate the classical nuclear factor-κB (NF-κB) pathway, which in turn activates E3 ligases and promotes proteasome-mediated protein catabolism in differentiated muscle cells[40,41]. Additionally, NF-κB activation suppressed muscle-cell differentiation through MyoD loss[42]. Alternatively, circulating factors can promote

Box 1 | Defining and diagnosing cancer cachexia

The 2011 Delphi International Consensus defined cancer cachexia as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle, with or without loss of fat mass, that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. The pathophysiology is characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism"[145]. The four criteria for the diagnosis of cancer cachexia are: the presence of anorexia and reduced food intake, especially protein consumption; the presence of hypercatabolic drive (that is, the breakdown of muscle proteins far exceeds their synthesis); decreased muscle mass and strength; and a decline in physical functioning and psychosocial capacity[145]. It is important to note that cachexia can remain undiagnosed using body weight or body mass index measurements since skeletal muscle mass loss can be offset by adipose tissue gain. Therefore, direct quantitative measurements of muscularity and changes in body composition (both adipose tissue and muscle) by computed tomography are essential for the precise diagnosis of cachexia (reviewed in REF.[146]). Besides muscle mass loss, muscle dysfunction is emerging as an important feature of cancers that are not typically associated with a high incidence of cachexia (for example, breast cancer) and in metastatic cancers associated with bone metastasis[18]. This is particularly important since a gain in lean muscle mass does not always correlate with improved muscle function, as observed in the myostatin-null mice[147] and in patients with cancer treated with the ghrelin agonist anamorelin[148]. The assessment of muscle mass and function has therefore become a necessity in measuring cancer cachexia both for diagnosis and as an efficacy end point for anti-cachexia therapies in clinical trials.

muscle wasting by impairing metabolism in muscle cells. Exposure of a cancer cell-secreted cocktail of pro-inflammatory circulating factors (TNFα, IL-6, IL-1β, leukaemia-inhibitory factor precursor (LIF), IL-8, vascular endothelial growth factor (VEGF)) induced excessive fatty acid oxidation in muscle cells, which led to oxidative stress, activated the p38 stress response pathway and impaired myotube growth[43]. TNF-family cytokines therefore cause muscle atrophy through direct interference with protein homeostasis in muscle cells.

Similarly, several members of the TGFβ pathway superfamily have been implicated in cancer cachexia (FIG. 1a). For instance, myostatin, the overexpression of which, in normal mice, caused profound fat and muscle loss[44], binds to the activin type II receptors ACVR2 and ACVR2B and activates the SMAD2/3 signalling pathway. Administration of soluble ACVR2B, a potent myostatin inhibitor, inhibited cancer cachexia in multiple mouse tumour models[45,46]. Other TGFβ superfamily members, growth differentiation factor 11 (GDF11) and GDF15 (also known as MIC1), have been recently implicated as mediators of both anorexia and cachexia, for example, indirectly via the hypothalamus[47–54] (FIG. 1b).

Cargo from extracellular vesicles. Cells secrete extracellular vesicles (EVs) that carry nucleic acids, lipids, proteins, and metabolites and aid in intercellular communication (reviewed elsewhere in REF.[55]). Fractionation experiments using conditioned media from cachexia-inducing tumour cell lines, including lung Lewis lung carcinoma (LLC) and H1299, colon C26, and gastric AGS adenocarcinoma cell lines, identified muscle catabolic activity in EVs containing the heat shock proteins HSP70 and HSP90, the release of which directly induced muscle catabolism in the LLC tumour cachexia model. Mechanistically, this occurred by activating Toll-like receptor 4 (TLR4) and the p38–MAPK pathway in muscle cells, a process that could be inhibited either by neutralization or silencing of HSP70 and HSP90 in the LLC cells[56] (FIG. 1a). Similar effects were also shown in pancreatic cancer tumour xenograft models[57]. Here, ZIP4, a zinc transporter, stimulated the release of EVs via the RAB27B GTPase, and mice bearing tumour xenografts from a pancreatic cancer cell line with ZIP4 knockdown lost less body weight and survived longer than control mice[57]. Tumour-derived EVs in the LLC tumour model carrying microRNA-21 stimulated apoptosis in myoblasts by signalling through TLR7 and contribute to muscle wasting[58]. Tumour-derived EV-induced apoptosis of myoblasts was also observed using cachexia-inducing human pancreatic cancer cell lines and patient sera and could be reversed by the TLR7/8/9 antagonist IMO-8503 (REFS[58,59]). These studies demonstrate how cargo packaged in EVs reach subpopulations of muscle cells and mediate cachexia.

Circulating factors: indirect effects

Loss of white adipose tissue. Loss of adipose tissue is often observed in cancer cachexia. Early studies showed that genetic ablation of the gene encoding adipose triglyceride lipase (ATGL), an enzyme that catalyses the initial step of triacylglycerol hydrolysis, not only protected tumour-bearing mice from white adipose tissue (WAT) loss but also reduced skeletal muscle wasting[60]. Three different types of adipose tissue (white, beige and brown) were subsequently characterized in relation to their role in cachexia development[61]. WAT stores energy as triglycerides, while brown adipose tissue expends energy. Beige adipose tissue is derived from the 'browning' of WAT. Increased lipolysis, elevated total energy expenditure and upregulated markers of brown adipose tissue thermogenesis occur in early phases of cachexia[62]. WAT browning was found to be an early systemic event during cachexia development that contributes to the increase in energy expenditure and lipid mobilization in a variety of cancer mouse models, including pancreatic, skin, lung, liver and colon cancer models[63]. Mechanistically, chronic inflammation and IL-6 increase uncoupling protein 1 (UCP1) in WAT, which uncouples mitochondrial respiration from ATP synthesis to promote thermogenesis. WAT browning can be reduced by either anti-inflammatory treatments, β-adrenergic blockade or by IL-6 signalling blockade[63]. In the LLC model, tumour-derived parathyroid hormone (PTH)-related protein (PTHrP) binds to the PTH/PTHrP receptor (PTHR) on white adipocytes and promoted WAT browning, and neutralization of PTHrP indirectly preserved skeletal muscle mass and function, thereby protecting against cachexia[64]. Collectively, these studies suggest that circulating factors and adipose tissue could indirectly impact skeletal muscle through a tumour–adipose tissue–muscle axis (FIG. 1b). However, although methodologies for measuring WAT browning in humans are now emerging[65], definitive evidence for WAT browning in patients with cancer cachexia is still lacking.

Circulating factors released from tumours alter liver function, which indirectly impacts muscle health by increasing energy expenditure and producing high amounts of inflammation-promoting, acute phase response (APR) proteins[22]. Cancer cells consume high amounts of glucose and release elevated amounts of lactate[66]. For example, bioluminescence-based metabolic imaging[67] was used to quantify glucose and lactate concentrations in human cervical cancer tissue sections, where high lactate levels in primary tumours correlated with a higher likelihood of metastasis and poor patient survival[68]. The liver can convert lactate derived from the circulation into glucose through gluconeogenesis, which can then re-enter the circulation to be used for energy production by other tissues (an energy-inefficient process that, when lactate is derived from anaerobic glycolysis

Box 2 | **Prevalence and staging of cancer cachexia**

Four different cachexia risk groups have been described based on the frequency of cachexia development in patients with different cancer types[149]. Patients with pancreatic, liver or lung cancers comprise the 'very high risk' group, with an 80–90% risk of developing cachexia, followed by patients with colon, gastric, or head and neck cancers ('high risk', 50–70% risk); those with endometrial, kidney, renal pelvis, urinary bladder or non-Hodgkin lymphoma cancers ('middle risk', 30–40% risk); and those with breast, melanoma, prostate or thyroid cancers ('lower risk', 20–30% risk).

Cachexia has been classified into three different stages by the Delphi consensus[145]: pre-cachexia, characterized by ≤5% body weight loss and the presence of early metabolic changes such as glucose intolerance; cachexia, characterized by unintended body weight loss of >5% over the prior 6 months (in the absence of simple starvation), a body mass index of <20 and weight loss >2%, or sarcopenia and weight loss >2%; and refractory cachexia, characterized by hypercatabolic drive resulting from either advanced cancer progression or cancer that is refractory to anticancer therapy. Patients with refractory cachexia have a low performance status (WHO score of 3 or 4) and a life expectancy of <3 months. The precise staging of cachexia has been further refined using measurements of weight, body mass index, CRP and appetite loss[150]; however, it remains particularly challenging to diagnose pre-cachexia. To facilitate the diagnosis, staging and management of cachexia, specialized cachexia clinics have opened in a few hospitals and cancer centres, representing a step forward in achieving personalized medicine for cancer patients with cancer cachexia[151].

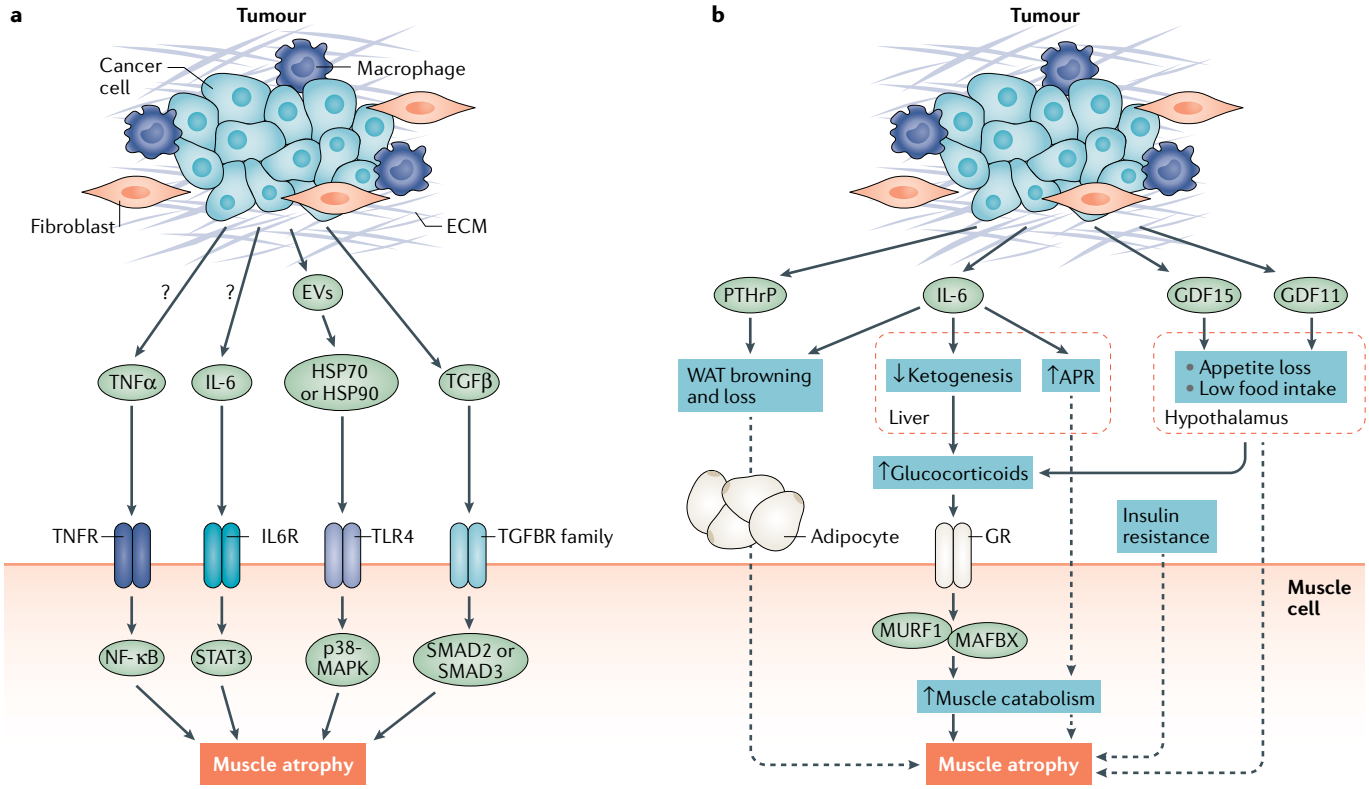

Fig. 1 | **Common mechanisms of muscle atrophy in cancer independent of stage.** The figure depicts how cues from the primary tumour microenvironment affect multiple distant organs, such as the liver, brain and adipose tissue, and contribute to muscle atrophy in cancer. Crosstalk between cancer cells and peripheral tissues is mediated by circulating factors, including soluble factors and extracellular vesicles (EVs) that could activate pro-cachectic programmes in muscles either by interacting directly with muscle cells and activating pathways to promote muscle catabolism or to suppress protein synthesis (part **a**) or by the metabolic reprogramming of secondary organs, which in turn induces muscle wasting (part **b**). Among the primary tumour microenvironment changes are molecular and cellular processes that enable migration and invasion (for example, epithelial–mesenchymal transition), many of which alter the secretome of the cancer and non-malignant cells in the tumour microenvironment. These include pro-inflammatory cytokines, such as tumour necrosis factor-α (TNFα) and IL-6, anti-inflammatory cytokines, such as transforming growth factor-β (TGFβ), and EVs carrying heat shock proteins HSP70 and HSP90, which could directly promote muscle atrophy. Other contributors of muscle atrophy include parathyroid hormone-related protein (PTHrP) and IL-6, which initiate white adipose tissue (WAT) browning and trigger muscle wasting. Cytokines such as growth differentiation factor 11 (GDF11) and GDF15 promote anorexia and also contribute to the muscle atrophy process in cancer. Insulin resistance of muscle cells and metabolic reprogramming of liver through increased acute protein response (APR), reduced ketone body formation and increasing glucocorticoids also contribute to muscle atrophy. ECM, extracellular matrix; GR, glucocorticoid receptor; IL6R, IL-6 receptor; MAFBX, muscle atrophy F-box protein; MURF1, muscle-specific RING finger protein 1; NF-κB, nuclear factor-κB; TGFBR, TGFβ receptor; TLR4, Toll-like receptor 4; TNFR, tumour necrosis factor receptor.

in muscle, converted to glucose in the liver and cycled back to muscle for energy production, is known as the Cori cycle). Although not experimentally shown, it has been estimated that the increased metabolic requirements of the tumour and an elevated Cori cycle inflicts a 40% increase in energy expenditure in patients with advanced cancer[69]. It has been postulated that amino acids released through muscle degradation can serve as an alternative source for energy production in the body in periods of glucose scarcity, either through the tricarboxylic acid cycle and oxidative phosphorylation in tissues, or in the liver by conversion to glucose, which can then re-enter the circulation and be consumed by tissues[70–73]. Dysfunction of these overall energy-inefficient metabolic processes in the liver can therefore sustain energy deficiency and the need for further muscle breakdown during cancer cachexia.

The presence of an APR has been linked to cachexia and shortened survival in patients with cancer[74]. The APR occurs in the liver and is a response to tissue injury and inflammation, leading to an immediate increase in the synthesis of plasma proteins needed for immediate defence[75,76] (FIG. 1b). To enable this immediate increase in protein synthesis, skeletal muscle (the predominant reservoir for amino acids in the body) are likely catabolized into amino acids and released into circulation, which can be utilized by the liver[75,76]. Yet, the amino acid composition of the APR proteins is significantly different to that of normal muscle tissue and therefore necessitates the breakdown and mobilization of excessive amounts of muscle proteins in order to meet the high APR protein demand[77]. Of note, transcriptomic analysis of cachectic muscles from mice bearing C26 tumours revealed a prominent upregulation of the IL-6–STAT3 pathway as well as of STAT3 target genes such as those encoding fibrinogen and serum amyloid A1 (SAA1), which belong to the APR[75]. Moreover, exposure to recombinant IL-6 or expression of activated STAT3 stimulated myotubes to produce fibrinogen. This IL-6–STAT3 dependent induction of APR proteins during cachexia in skeletal muscles has also been shown in the liver[74,76,78]. These observations suggest that APR activation could contribute to skeletal muscle wasting; however, direct experimental evidence for this phenomenon, either from in vivo experiments or from patients with cancer cachexia, is lacking.

Ketone bodies, produced from fatty acid oxidation-derived acetyl-CoA through ketogenesis in the liver, are transported via the blood to non-liver tissues, where they are used for energy production by skeletal and cardiac muscle and by the brain in starvation conditions[32]. Altered ketogenesis and metabolic reprogramming of the liver have been observed in lung and pancreatic cancer cachexia models[79,80] (FIG. 1b). Counterintuitively, even though ketogenesis is typically induced during starvation, serum metabolite profiling of cachectic muscles from mice with metastatic lung cancer showed low levels of ketone bodies[79]. Low ketogenesis along with reduced food intake markedly increased glucocorticoid levels[79], a pattern also observed in other models of cancer cachexia[80]. Reduced ketogenesis in cancer cachexia can be explained by tumour-induced IL-6, which impairs the response of the liver to reduced calorie intake, even in the pre-cachectic stages. As such, in pancreatic and colon cancer models, tumour-induced IL-6 suppressed peroxisome proliferator-activated receptor-α (PPARα)-controlled ketogenesis in the liver and, when challenged with caloric restriction, the resulting increase in glucocorticoid levels in turn suppressed intratumoural immunity[79,80]. Increasing ketogenesis using the PPARα agonist fenofibrate reduced muscle atrophy by decreasing circulating glucocorticoids in a lung cancer cachexia genetically engineered mouse model[79]. Although how reduced ketogenesis in the liver and elevated glucocorticoids mediate muscle atrophy was not explored in these studies[79,80], glucocorticoids are known to have both anti-anabolic and pro-catabolic functions in skeletal muscle that promote muscle atrophy (reviewed in REF.[81]) (FIG. 1b). One potential mechanism by which glucocorticoids mediate muscle wasting is by the induction of genes encoding MURF1 and MAFBX in muscle cells[27,28,82]. In the context of LLC-induced cancer cachexia, muscle-specific deletion of the gene encoding the glucocorticoid receptor in mice significantly reduced muscle wasting, with downregulated *Murf1* and *Mafbx* expression compared with control mice[83]. Therefore, tumours can induce myriad metabolic anomalies in the liver that both promote their own growth and indirectly induce cachexia in the host.

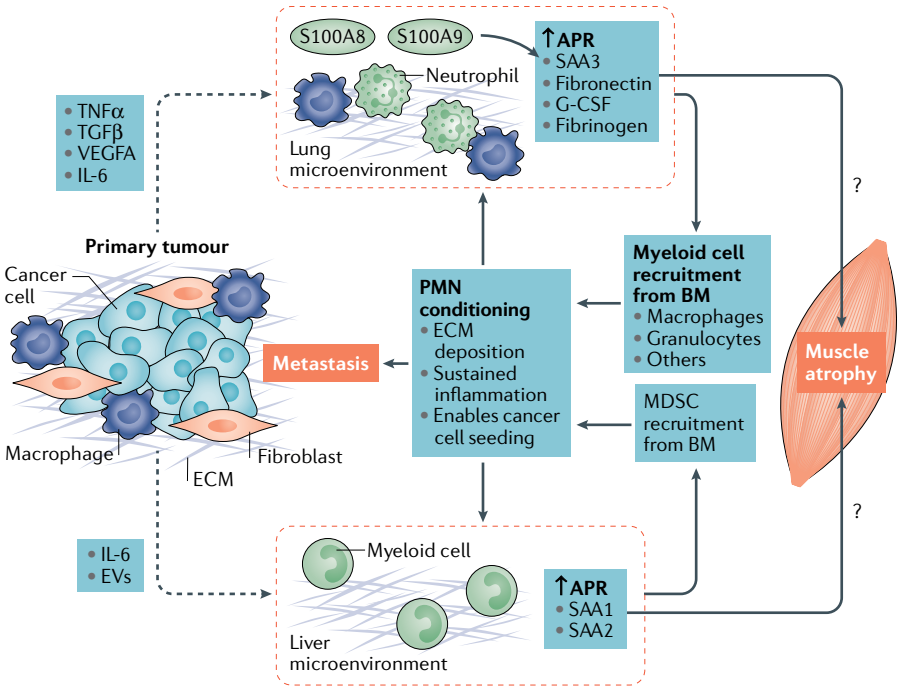

Fig. 2 | **Potential triggers of cachexia during pre-metastatic conditioning.** Systemic changes are detected in distant organs of future metastasis, namely pre-metastatic niches (PMN; for example, the lung or liver microenvironment) even before the arrival of cancer cells to these niches. These pre-metastatic changes are conditioned by circulating factors (cytokines, chemokines or cargo from extracellular vesicles (EVs)) from the primary tumours. These changes include the mobilization of bone marrow (BM)-derived cells to these niches and the establishment of a pro-inflammatory milieu that facilitates the chemotaxis, adhesion and extravasation of incoming cancer cells and increases the chances of successful metastasis. Multiple paracrine signalling cascades between different cell types have been observed in the lung and liver PMN: primary tumour-derived exosomes initiate a signalling cascade between Kupffer cells, liver stellate cells and BM-derived myeloid cells in the liver microenvironment that generates a PMN; IL-6 initiates a PMN through STAT3 signalling in hepatocytes and myeloid cell chemotaxis; the S100A8–serum amyloid A3 (SAA3)– Toll-like receptor 4 (TLR4) cascade is initiated in the lung microenvironment with recruited myeloid cells; secretion of multiple acute phase response (APR) proteins, SAA1–3, fibronectin, fibrinogen and granulocyte colony-stimulating factor (G-CSF) drastically increases in the PMN. These factors generate a fibrotic environment that arrests BM-derived myeloid cells and subsequently facilitates cancer cell homing and colonization. We propose that amplification of the APR, BM-derived myeloid cell recruitment and sustained systemic inflammation (amplified cytokine response) could be some of the concerted and shared changes during PMN conditioning that could serve as early triggers of cachexia. ECM, extracellular matrix; MDSC, myeloid-derived suppressor cells; TGFβ, transforming growth factor-β; TNFα, tumour necrosis factor-α; VEGFA, vascular endothelial growth factor A.

Cachexia during cancer progression

The incidence and severity of cachexia increases with metastatic progression[5]. This suggests that the development of cachexia could be molecularly linked to the metastatic process. Indeed, factors produced by cancer cells or host cells in the tumour microenvironment during metastatic progression exacerbate muscle mass loss and/or dysfunction[11,18,84]. In this section, we discuss how signals released during the various stages of metastasis (FIGS 1,2) could potentially orchestrate pro-cachectic signalling in muscle.

Migration and invasion

Migration is a fundamental property of cells that enables many biological processes, from embryogenesis to wound healing[85]. In cancer, migrating neoplastic cells within primary tumours breach the basement membrane and invade the stroma, thereby improving their access to nutrients and chance of survival. During epithelial–mesenchymal transition (EMT), epithelial cells from a primary tumour transiently 'trade in' their epithelial features (cell-to-cell junctions and cell polarity) for more motility-enabling mesenchymal features (fibroblast-like state, high protease secretion and stem cell-like features)[86]. Interestingly, EMT is accompanied by a shift in secretion of soluble cytokines and chemokines, including IL-6 and IL-8 (REFS[87,88]). IL-6 and IL-8 are secreted in response to TGFβ-induced EMT in lung cancer cell lines, and IL-8 promotes EMT through the autocrine IL-8–IL-8R axis in pancreatic cancer cell lines[88,89]. IL-6 and IL-8 can

also be induced through direct contact of EMT-induced cancer cells with tumour-associated monocytes and macrophages in the tumour microenvironment[90,91]. In addition, the IL-8 receptor CXCR1 was expressed on a subpopulation of tumour-initiating cells in the normal mammary gland and in breast carcinomas and contributed to metastasis in mice with breast cancer xenografts[92]. The common induction of IL-6 and IL-8 in cancer cells during the EMT is of relevance here because circulating IL-6 and IL-8 have prominent systemic effects on skeletal muscle[75,93–95]. As discussed above, IL-6 induces the APR, enhances lipid mobilization and ketogenesis, and increases energy expenditure, all of which contribute to muscle atrophy in cancer models[75,93,94]. It was also shown that IL-8 released into conditioned media from a coculture of human pancreatic cancer cells and tumour-associated stromal cells induced myotube atrophy in C2C12 muscle cells; however, this mechanism was not explored in vivo[95] (FIG. 1). While these disparate observations in different cancers neither establish causality nor prove that invasive cancer cells can induce muscle atrophy, they prompt the search for early cues from invasive primary tumours that might trigger muscle atrophy. The existence of heterogeneity and plasticity among primary tumour-derived cancer cell subpopulations also implies that their cellular state impacts their secretome, which in turn might influence distant tissues like muscle via circulation. Therefore, with respect to clinical translation, blocking the early triggers of cachexia might prove beneficial for patients with invasive primary tumours.

Pre-metastatic niche conditioning

Distant organs are primed for metastasis even before the arrival of cancer cells. During PMN conditioning, primary tumours secrete soluble factors, enzymes and EVs into circulation, which mobilizes bone marrow-derived cells to distant sites of future metastasis and establishes a pro-inflammatory milieu. Broadly, PMN conditioning facilitates the chemotaxis, adhesion and extravasation of incoming cancer cells and also serves as a rich source of growth-promoting factors, making it conducive for metastatic cells to thrive in a new microenvironment[96,97]. Studies on PMN conditioning are predominantly focused on understanding how it promotes metastasis. Here, we will discuss how PMN conditioning may also promote cachexia, a notion that has not been experimentally explored (FIG. 2).

Pancreatic ductal adenocarcinoma (PDAC)-derived exosomes can promote PMN formation in the liver, leading to increased liver metastasis in PDAC mouse models[98]. Specifically, fusion of PDAC-derived exosomes expressing migration inhibitory factor (MIF) with liver Kupffer cells led to the secretion of TGFβ, a cytokine known to induce cachexia in the context of bone metastatic cancer[18], which in turn stimulated fibronectin production by liver stellate cells[98]. These factors generate a fibrotic environment that arrests bone marrow-derived macrophages and neutrophils, which together generate a liver PMN (FIG. 2). Similarly, the secretion of TNFα, TGFβ and VEGFA from subcutaneous tumours of multiple cancer types induced lung PMN conditioning by activating the expression of the calcium-binding factors S100A8 and S100A9 (REF.[99]). S100A8 and S100A9 serve as chemoattractants to recruit macrophage subpopulations and create permissive docking sites for incoming cancer cells in the PMN[100]. Similarly, lung cancer cells can secrete versican, an extracellular matrix proteoglycan that acts as a potent macrophage activator. Versican promote the production of abundant TNFα and IL-6 in the niche[101], both of which are also potent inducers of cachexia[3] (FIG. 2). Cachexia was not assessed with PMN conditioning in any of these studies; however, these PDAC and lung cancer models are known to develop cachexia and might be of relevance for future investigations.

PMN conditioning constitutes a sustained inflammatory phase that overlaps with the kinetics and regulation of the APR response (FIG. 2). In the KPC pancreatic cancer model, IL-6–STAT3–SAA signalling constitutes a paracrine axis that was responsible for the generation of a pro-metastatic niche in the liver (FIG. 2). IL-6 is secreted from non-cancer cells in the primary tumour microenvironment, enters the circulation and activates STAT3 signalling in hepatocytes, thereby inducing APR proteins, SAA1 and SAA2, and leading to the recruitment of myeloid cells to the liver and to the deposition of extracellular matrix. Either genetic ablation or blockade of IL-6–STAT3–SAA signalling components significantly reduced the formation of the pro-metastatic niche in the liver as well as subsequent liver metastasis[102] (FIG. 2). Similarly, a S100A8/S100A9-dependent induction of SAA3 in pre-metastatic lungs in the LLC mouse model serves as an example of the contribution of APR proteins to PMN formation, recruitment of myeloid cells and the acceleration of lung metastasis[103]. Here, SAA3 then induced a positive feedback loop through TLR4 and sustained a chronic inflammatory state that promotes metastasis, which could be reduced by the blockade of SAA3 function[99]. In addition, increased levels of the APR protein fibrinogen were localized to hyperpermeable vascular foci in the lung PMN and enabled cancer-cell homing[100]. The APR proteins fibronectin and granulocyte colony-stimulating factor (G-CSF) were also important for the PMN priming process in the lungs of mice[104]. Fibronectin facilitated the seeding of circulating cancer and immune cells in the PMN, while G-CSF mobilized the granulocytic population to the PMN to promote metastasis. Thus, PMN conditioning is dependent on APR proteins, and protein synthesis demands during the APR along with limited nutrient supply may also initiate muscle catabolism[76] and serve as early triggers of cachexia during the pre-metastatic phases (FIG. 2).

We therefore propose that a unifying theme has emerged in which tumour-induced molecular and cellular changes that drive PMN conditioning bear striking parallels to those that induce cachexia (FIG. 2). This includes the shedding of EVs and the secretion of tumour-derived and host-derived factors that can activate pro-cachectic pathways in muscle cells and might be targetable during the pre-metastatic phases of cancer progression.

Signals from metastatic niches

As cancer cells colonize distant organs, a major remodelling of the metastatic niches ensues to accommodate the needs of expanding metastatic colonies[105]. Extracellular matrix modification, metabolic rewiring, stromal cell polarization and vascular remodelling further shape the metastatic niche and benefit the adaptation of cancer cells in their new tissue microenvironment. In this section, we will explore how signals from the metastatic niches can serve as amplifiers of cachexia after the cancer cells have already colonized and are detectably growing in the distant organs (FIG. 3).

Bone metastatic niches. One of the best-characterized metastatic niche remodelling events takes place in the context of bone metastasis[106], which has recently been mechanistically linked to muscle dysfunction[18]. Under normal, non-tumour conditions, bone homeostasis

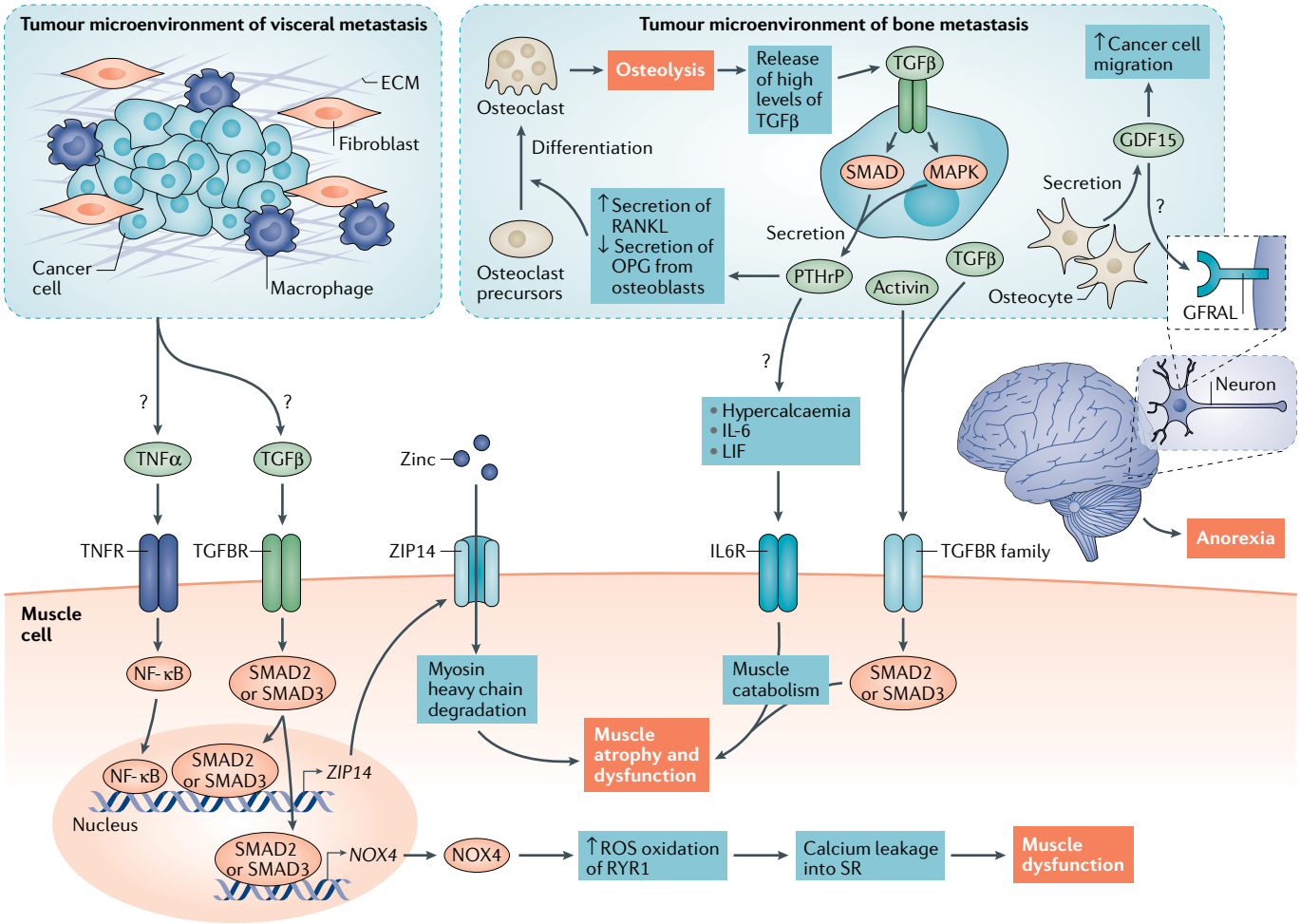

Fig. 3 | **Changes in metastatic microenvironments: amplifiers of cachexia?** Signals from visceral metastases (for example, lung and liver metastasis) (left panel) and bone metastasis (right panel) could trigger or even amplify muscle atrophy and/or dysfunction. Signalling inputs in muscle cells are shown in the centre. This includes regulation of the zinc transporter ZIP14 in muscle cells that mediates cachexia during visceral metastasis and the transforming growth factor-β (TGFβ)–NADPH-oxidase 4 (NOX4)–ryanodine receptor 1 (RYR1) pathway involved in calcium leakage into muscles, leading to muscle weakness during bone metastasis. Other factors include: parathyroid hormone-related protein (PTHrP) factors released by cancer cells that induce adipose tissue browning, promote the loss of muscle mass and initiate a vicious cycle of bone breakdown and tumour growth (osteolytic metastasis); and growth differentiation factor 15 (GDF15) released from the bone microenvironment that can promote cancer cell invasion and anorexia. None of these factors might be exclusive to metastasis; however, they indicate targetable pathways to treat cachexia in metastatic disease. In many instances, cancer patients are already diagnosed with existing metastatic disease and cachexia, and, therefore, the intervention strategy for treating cachexia would need to consider the pathophysiological changes associated with the later stages of the metastatic cascade, that is, post-colonization steps and accompanying anticancer therapy. ECM, extracellular matrix; GFRAL, glial-derived neurotrophic factor receptor-α-like; IL6R, IL-6 receptor; LIF, leukaemia-inhibitory factor precursor; NF-κB, nuclear factor-κB; OPG, osteoprotegerin; TGFBR, TGFβ receptor; TNFα, tumour necrosis factor-α; TNFR, TNF receptor; RANKL, receptor activator of NF-κB ligand; ROS, reactive oxygen species; SR, sarcoplasmic reticulum.

is maintained by osteoblasts, which create bone, and osteoclasts, which resorb bone. Osteoblasts secrete receptor activator of NF-κB ligand (RANKL) to direct the maturation of osteoclast precursors into functional osteoclasts and osteoprotegerin (OPG) to inhibit osteoclast differentiation[107] (FIG. 3). The secretion of high levels of PTHrP by cancer cells in the bone microenvironment alters this balance by inducing osteoblasts to increase their synthesis of RANKL and to reduce their synthesis of OPG, leading to greater bone demineralization. Copious amounts of active TGFβ normally stored in the bone are then released from the bone matrix, which further stimulates the production of PTHrP by cancer cells[108] (FIG. 3). This creates a powerful, self-perpetuating cycle of tumour growth and bone loss[106]. Indeed, neutralizing PTHrP or blocking TGFβ receptor signalling in cancer cells significantly reduced osteoclast-mediated bone resorption and bone metastasis in the MDA-MB-231 breast cancer xenograft model[108].

GDF15 is a cytokine that has been known to promote anorexia through its role in the central regulation of appetite via the hypothalamus[50,51,54]. As such, GDF15-expressing tumours are known to induce profound anorexia and weight loss in mice, mainly by affecting appetite control centres in the hindbrain and hypothalamus[50,51] (FIG. 1b) and in the context of cancer, GDF15 secretion can directly affect cancer cells and have pro-invasive and metastatic effects (FIG. 3). Prostate cancer cells stimulate osteocytes in vitro to secrete GDF15, which in turn can bind to its receptor, glial-derived neurotrophic factor receptor-α-like (GFRAL), on prostate cancer cells, promote prostate tumour growth in vivo and increase the proliferation of prostate cancer cells in the bone

microenvironment[109] (FIG. 3). This positive feedback loop can initiate a vicious cycle with the potential to promote the progression of bone metastasis[109]. Moreover, GDF15 is secreted by pancreatic cancer cells in response to solid stress through activation of the AKT–CREB1 pathway, and blocking GDF15 secretion decreased cancer cell migration[110]. GDF15 was also overexpressed in the tumour-associated stroma of human prostate cancer in tissue sections from patients with prostate cancer, and GDF15-expressing fibroblasts instigated outgrowth of indolent tumour cells at a distant site in the LNCaP prostate cancer model[111]. The overexpression of GDF15 in colon cancer cell lines induced the EMT through activation of the SMAD2/3 pathway and promoted metastasis in vivo[112]. Additionally, serum GDF15 levels increase with progressive cancer stages and correlate with a poor outcome and cachexia in patients with prostate cancer[113,114]. Therefore, blocking antibodies to GDF15 or its recently identified receptor GFRAL, or small molecule inhibitors against the GDF15–GFRAL axis[115] could serve as promising targeting strategies to inhibit both cancer progression and cancer anorexia–cachexia syndrome.

As discussed above, both the PTHrP and TGFβ signalling pathways play pivotal roles in mediating cachexia[64,116,117] and are also implicated in cancer progression. As such, elevated PTHrP levels are detected in squamous cell carcinoma and head and neck, renal and ovarian cancers, where PTHrP induce a state of hypercalcaemia and increases bone resorption[118]. Implantation of PTHrP-expressing HARA-B lung cancer cells into nude mice recapitulated humoral hypercalcaemia and induced cachexia, which could be partially reversed by PTHrP neutralization[117] (FIG. 3); however, the exact mechanism of action in this context remains unexplored. Since PTHrP increases IL-6 and LIF expression in osteoblastic cells[119,120], two cytokines with prominent roles as cachexia inducers[93,121], it has been speculated that part of the PTHrP function could be mediated by the IL-6–LIF signalling in muscle cells in vivo[117]. Among bone-derived cytokines, the release of TGFβ from the bone matrix during bone metastasis induces profound muscle weakness in mouse models of lung, breast and prostate cancer as well as multiple myeloma[18]. Mechanistically, the release of TGFβ from bone leads to the oxidation and nitrosylation of the ryanodine receptor and calcium release channel RYR1 in the muscles of mice with bone metastases. TGFβ upregulates NADPH oxidase 4 (NOX4), leading to RYR1 oxidation. Oxidized RYR1 leaks calcium ions (Ca^{2+}) and compromises muscle contraction by reducing Ca^{2+}-induced muscle force generation, thereby causing muscle weakness[18] (FIG. 3). Therefore, blocking TGFβ signalling, NOX4 or RYR1 could serve as promising approaches to prevent muscle weakness in cancers associated with bone metastasis[18]. A new generation of inhibitors of TGFβ signalling is now in preclinical and clinical trials for cancer, which could be utilized for anti-cachexia trials in patients with bone metastasis and muscle weakness (Supplementary Table 1). Furthermore, the bone matrix is also a storehouse of activin, another member of the TGFβ family, which is released upon bone resorption from osteolytic bone metastases and stimulates the activin receptor type 2B (ACTRIIB) signalling pathway[122]. Elevated levels of activins have been observed in the sera of patients with bone metastasis and associated with poor survival[123]. In normal mice, elevated circulating activin A induced the loss of muscle mass[124] and a soluble form of ACTRIIB increases muscle mass[125]. Inhibin-deficient mice that display ten-fold elevated serum activin levels develop gonadal tumours, severe weight loss and a cachexia-like syndrome[126]. Forced expression of activin A in vivo through the ACTRIIB pathway increased the transcription of atrophy-related E3 ligases and decreased AKT-mTOR protein synthesis pathways in muscle cells[124]. ACTRIIB blockade reversed muscle loss and prolonged survival in localized mouse models of cachexia without affecting tumour growth[45,46] (FIGS 1,3). Preclinical studies that test ACTRIIB blockade in metastatic cancer models in combination with anticancer therapies as a strategy for preventing cachexia in advanced cancers are warranted. Encouragingly, an antibody targeting both ACTRIIA and ACTRIIB receptors (BYM338/bimagrumab) promotes muscle hypertrophy in adult mice and is currently in clinical trials[127] (Supplementary Table 1). Therefore, activation of the TGFβ pathway by multiple members of the TGFβ superfamily represents a common underlying mechanism of cancer cachexia.

Visceral and brain metastatic niches. Aside from bone, the liver, lung and brain represent additional common sites of metastasis[128]. Recent studies have revealed a common mechanism of cachexia development in cancer models harbouring liver, lung, bone or brain metastases (FIG. 3). Studies from our laboratory showed that perturbed zinc homeostasis through aberrant expression of ZIP14 in the muscle can promote cachexia in a variety of metastatic cancers (colon, pancreatic, breast and lung)[11,129]. Cytokines such as TNFα and TGFβ upregulated ZIP14 in muscle cells, which allows excess zinc entry into muscle cells. Excess zinc is detrimental to muscle cells since it induces myosin heavy chain protein loss in myotubes and blocks differentiation in muscle progenitor cells, which together promote loss of muscle mass and function[11,129] (FIG. 3). Our studies showed that ZIP14 overexpression alone was not sufficient to induce muscle loss; therefore, excess zinc and, potentially, other cancer-induced cofactors collaborate with ZIP14 to induce cachexia in metastatic cancers[11]. Although zinc is required for normal growth and development, excess zinc accumulation in muscle cells had detrimental effects, which could be reversed by *Zip14* deletion[11] or intermittent zinc chelation in metastatic mouse models (unpublished, A.K.B. and S.A.). Zinc homeostasis is perturbed in many metastatic cancers, as observed by a decrease in serum zinc levels in patients with advanced cancer[130]; however, whether zinc uptake concomitantly increases in other tissues remains currently unexplored. It also remains to be determined whether ZIP14 functions during earlier stages of cancer in other models of cachexia. *Zip14*-inducing clones originating from the primary tumour became enriched during the processes of in vivo selection[131] and spontaneous metastasis selection[11] in mouse models. Low expression levels of muscle *Zip14* in primary tumour models of cachexia may therefore account for the absence of *Zip14* from lists of 'top' differentially expressed genes in published data sets[75,132], although it can indeed be detected in these models by analysing the raw data[75,132]. Still, it is not clear whether the primary tumour models used in these studies harboured disseminated cells or micrometastases, as, contrary to the dogma[133], dissemination from primary tumours can occur early and may remain undetected by currently available imaging modalities[134,135]. Based on these observations, blocking ZIP14 in muscle cells to prevent excess zinc entry into muscles represents a novel approach to preventing cachexia, irrespective of its induction by primary tumours, disseminated cancer cells or metastatic cancer cells.

The impact of brain metastasis on cachexia development remains elusive. However, it is well established that the brain plays a central role in regulating anorexia and

cachexia since it acts as both a sensor and an amplifier of inflammation and regulates feeding behaviour and energy homeostasis[136]. As such, direct IL-1β injection into the brain of mice activated the hypothalamic–pituitary–adrenal (HPA) axis and induced a glucocorticoid-dependent programme of muscle catabolism, thereby inducing muscle atrophy[137]. As alluded to above when discussing GDF15, the hypothalamus plays an important role in anorexia–cachexia syndrome development through its ability to regulate feeding responses[138,139]. Activation of AMP-activated protein kinase (AMPK) in the hypothalamus promoted food intake in tumour-bearing rats in an attempt to restore energy balance[140]. Additionally, activation of calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus contributed to anorexia and loss of lean muscle mass in the LLC mouse model[141]. A recent study showed that the presence of gliomas in mice induced anorexia and cachexia, which was associated with suppression of the AKT pathway and activation of the proteasome and autophagy pathways, although the mediators were not explored[142]. Given the predominance of neuroinflammation in brain metastases[143], it is likely that feeding responses and energy balance are altered in cachectic mice with brain metastasis, which remains an area of future investigation.

Conclusion and future directions

Cachexia associated with metastatic cancers has debilitating and lethal consequences for patients with cancer[7]. The widespread failure of candidate cachexia therapies in patients with metastatic cancer led to the realization that critical mediators of metastasis-induced cachexia could be distinct from those that drive primary tumour-induced cachexia. As discussed here, the clinical context of advanced cancer with metastasis is critical for studying and targeting cachexia associated with metastatic cancer[14]. Localized primary tumour models mimic the cachexia phenotype but do not fully recapitulate the systemic changes and molecular mediators associated with metastatic disease[18]. A repertoire of genetically engineered mouse models as well as orthotopic and experimental metastasis models are now available for the study of metastasis-induced cachexia (Supplementary Table 2); however, the existing data are still limited and do not allow for a clear distinction between mediators of cachexia that originate from primary tumours or from metastases.

Nevertheless, these observations prompt further exploration in this area with the hope that cachexia, even if detected in patients with metastatic cancer, can be effectively treated alongside the tumour. Future studies aiming for clinical validation of promising therapies as well as the identification of biomarkers to stratify patients who might benefit from such treatments are necessary. Additionally, it is important to separate the pre-metastatic and metastatic events that contribute to cachexia development. As yet, the knowledge gained from the limited work in this area is inadequate to comment on the potential existence of mediators of cancer cachexia that either overlap or function distinctly during the pre-metastatic and metastatic stages of cancer and is a subject of future investigation. Patients with established metastatic disease, especially with pancreatic and gastrointestinal cancers, often present with cachexia. Therefore, the focus of intervention trials should be to target known mediators of cachexia that are relevant for the specific metastatic context. It is important to note that 20% of patients with pancreatic, breast and kidney cancer, 40% of those with oral cancers and 30% of those with colon, lung and stomach cancers present with invasive primary tumours that are at high risk of developing metastasis but have no detectable disease progression[144]. Such patients currently represent a missed window of opportunity for cachexia prevention trials. Therefore, cachexia mediators will need to be identified in pre-metastatic disease. Thus, if both pre-metastatic and cachexia-promoting changes are already present in these patients, rationally designed therapies could interfere with both cancer progression and the development of cachexia to drastically improve the outcomes for patients with cancer. Given the complexity of metastatic disease, rigorous preclinical studies in the context of progression and therapy as well as robust clinical validation of promising therapeutic candidates are warranted before launching translational efforts or the next generation of clinical trials targeting cachexia.

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