Cancer-Associated Cachexia: A Systemic Consequence of Cancer Progression

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Abstract
Cancer is a life-threatening disease that has plagued humans for centuries. The vast majority of cancer-related mortality results from metastasis. Indeed, the invasive growth of metastatic cancer cells in vital organs causes fatal organ dysfunction, but metastasis-related deaths also result from cachexia, a debilitating wasting syndrome characterized by an involuntary loss of skeletal muscle mass and function. In fact, about 80% of metastatic cancer patients suffer from cachexia, which often renders them too weak to tolerate standard doses of anticancer therapies and makes them susceptible to death from cardiac and respiratory failure. The goals of this review are to highlight important findings that help explain how cancer-induced systemic changes drive the development of cachexia and to discuss unmet challenges and potential therapeutic strategies targeting cachexia to improve the quality of life and survival of cancer patients.

Keywords
cancer progression, systemic effects, cachexia, inflammation, muscle wasting, muscle atrophy
INTRODUCTION

With disease progression, cancers induce systemic changes in tissues such as the bone, liver, adipose tissue, and skeletal muscles (Argiles et al. 2018, Kaplan et al. 2006, McAllister & Weinberg 2010). These changes perturb tissue homeostasis and create a metabolic imbalance in the host. As such, patients with advanced cancer experience a metabolic wasting syndrome known as cachexia where muscle and often adipose tissues are lost (Baracos et al. 2018). Nutritional supplementation is unable to reverse this syndrome, and effective treatment for cachexia is still lacking. What is perplexing is that not all cancer patients with a similar tumor burden develop cachexia. The ones who do suffer from cachexia experience a lower tolerance to anticancer treatments, a drastic reduction in mobility and feeding ability, and a poor quality of life (Fearon et al. 2013). Patients with cachexia succumb to accelerated death resulting from respiratory and cardiac failure due to weakened diaphragm and cardiac muscles (Baracos et al. 2018). To date, there have been no satisfactory answers to the fundamental question of what initiates the cachexia cascade in cancer patients. Possibilities include tumor-derived factors, metabolites from a secondary organ that is indirectly impacted by the tumor, or perhaps circulating factors derived from the altered immune system (Fearon et al. 2012). It is also unclear whether there exists a master regulator of cachexia or whether unique combinations of already-identified mediators, which may differ depending on the type and stage of cancer, drive cachexia. Finally, it is unknown whether cachexia is in fact an unintended and futile consequence of cancer progression or if cancer cells somehow benefit from the breakdown of muscle and fat. We discuss advances in cancer-associated cachexia research in light of these questions and highlight the challenges and promising areas of research.

CANCER-ASSOCIATED CACHEXIA

Definition

Cachexia is a debilitating wasting syndrome associated with involuntary weight loss and is derived from the Greek words “kakos,” meaning bad, and “hexis,” meaning condition (Fearon et al. 2012). Cachexia occurs in multiple diseases such as chronic kidney, heart and obstructive pulmonary diseases, AIDS, and cancer (Fearon et al. 2013, von Haehling et al. 2016). In 1858, the English ophthalmologist John Zachariah first used the term “cancerous cachexia” to describe the wasting syndrome associated with malignancy (Bennani-Baiti & Walsh 2009, Laurence 1858). However, a formal definition for cancer-associated cachexia was only recently conceptualized (Fearon et al. 2011) as “a multifactorial syndrome characterized by 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” (p. 490). The pathophysiology of cachexia is characterized by a negative protein and energy balance, which is driven by a variable combination of reduced food intake and metabolic abnormalities. The diagnostic criteria for cachexia in a cancer patient are unintended weight loss that is greater than 5%, unintended weight loss greater than 2% in individuals already showing depletion according to current body weight and height (a body mass index less than 20 kg/m²), or loss of skeletal muscle mass from sarcopenia (Fearon et al. 2011). Cachexia occurs in 80% of advanced cancer patients, with higher incidences in pancreatic, gastrointestinal, and lung cancers (Baracos et al. 2018, Fearon et al. 2012). A characteristic feature of cachexia is a reduction in muscle mass, also known as muscle atrophy, that results from the loss of proteins, organelles, and cytoplasm from muscle cells (Sandri 2016). Skeletal muscle breakdown in cachexia results from increased protein degradation by hyperactivation of the ubiquitin-proteasome system (UPS) and autophagy-lysosome system (Cohen et al. 2015, Mitch & Goldberg 1996, Sandri 2016). FOXO transcription factors activate both UPS and lysosomal pathways and contribute to muscle...
atrophy (Zhao et al. 2007). A set of E3 ligases (MuRF1, MAFbx/atrogen 1, MUSA1, TRAF6, and FBXO31) are transcriptionally activated during muscle atrophy in multiple catabolic states including cancer (Bodine et al. 2001a, Gomes et al. 2001, Milan et al. 2015, Paul et al. 2010, Sartori et al. 2013). MuRF1 ubiquitinates sarcomeric proteins, myosin heavy chain protein, and actin (Polge et al. 2011), while atrogin 1 degrades MyoD, a muscle differentiation transcription factor, and EIF3F, an activator of protein synthesis, in muscle cells (Tintignac et al. 2005), thus contributing to muscle atrophy. Autophagy, the process of degrading and recycling proteins, bulk cytoplasm, and organelles in cells using lysosomal machinery, contributes to muscle atrophy. However, the exact role of autophagy is still controversial. Muscle-specific inactivation of a crucial autophagy gene, ATG7, results in muscle atrophy and aging-related muscle dysfunction from an accumulation of abnormal mitochondria and disorganized sarcomeres (Masiero et al. 2009). In contrast, overexpression of a positive regulator of autophagy, TP53INP2/DOR in muscle, upregulates the E3 ligases MuRF1 and atrogin 1, represses mitochondrial function, and exacerbates cancer-induced muscle wasting (Penna et al. 2019). Therefore, these studies indicate that both excess and defective autophagy promote muscle atrophy.

Differences Between Starvation, Cachexia, and Sarcopenia

Weight loss and wasting states can result from starvation, cachexia, or sarcopenia. While these three conditions are sometimes indistinguishable by appearance, their etiology and biochemical features are different. Starvation-induced weight loss results from caloric deprivation and is often associated with loss of adipose tissue. It is characterized by unchanged resting energy expenditure, a lack of inflammation, and a reduction in protein catabolism in prolonged starvation (Morley et al. 2006). The key feature of starvation-mediated weight loss is that the wasting state is transient and can be reversed by nutritional support. By contrast, cachexia involves skeletal muscle loss with or without loss of adipose tissue and is often associated with a major increase in resting energy expenditure, the presence of inflammation, and increased protein catabolism. Muscle protein catabolism is primarily driven by the activation of the UPS and autophagy pathways (Acharyya & Guttridge 2007, Argiles et al. 2014, Cohen et al. 2015, Egerman & Glass 2014, Fearon et al. 2012, Sandri 2016). Importantly, wasting from cachexia cannot be completely reversed by nutritional supplementation. Sarcopenia is a geriatric syndrome characterized by the loss of muscle mass and function that occurs as part of the normal aging process in humans (Kalyani et al. 2014, Short et al. 2004). Features of sarcopenia include reduced resting energy expenditure, the absence of inflammation, and normal/reduced protein catabolism, but it is not associated with an underlying illness or disease pathology (Ali & Garcia 2014). Importantly, sarcopenia is preventable and, to a large extent, reversible (Evans 1996). It is often difficult to assess loss of muscle mass through body weight measurements when it is masked by adipose tissue in obese patients. However, new advances in imaging analysis now allow us to determine body composition changes in cancer patients from routine computerized tomography (CT) images (Prado et al. 2009). Below we discuss some of the key mediators, systemic interactions, and new directions in the field of cancer-associated cachexia.

HUMORAL FACTORS AS MEDIATORS OF CACHEXIA

It has long been speculated that humoral factors serve as mediators of cachexia. However, the first experimental evidence for the presence of humoral factors causing anorexia/cachexia came from a parabiotic transfer experiment where two rats were surgically joined by their skin to allow parabiotic partners to share circulation (Norton et al. 1985). The authors demonstrated that
unidentified humoral factors that induce anorexia/cachexia in the methylcholanthrene-induced sarcoma tumor–bearing (TB) rats could also induce anorexia/cachexia in their non-tumor-bearing (NTB) parabiotic partners. Moreover, each of the parabiotic partners between two NTB rats gained the same amount of weight, which was significantly higher than the weight gained by the NTB halves that were paired with TB rats. Importantly, the NTB rats that were joined parabiotically to the TB rats remained tumor-free during the experiment, which ruled out that metastatic infiltration caused the phenotype and demonstrated that circulating factors mediate cancer-associated anorexia/cachexia in this context.

Tumor-induced systemic factors (TISFs in this review) secreted directly by tumor cells, or by nontumor host cells, in response to tumor growth are potential cachexia mediators and can negatively impact host physiology (Fearon et al. 2012). TISFs can either signal directly to muscle or fat cells or induce metabolic reprogramming of the peripheral organs to create a chronic negative energy state (Figure 1). TISFs can simultaneously activate catabolic processes in muscle and inhibit muscle protein synthesis, resulting in a sustained loss of muscle mass (Egerman & Glass 2014, Fearon et al. 2012). TISFs such as TNF-α (tumor necrosis factor alpha), IL-1β (interleukin 1 beta), IFN-γ (interferon gamma), TGF-β (transforming growth factor beta), and IL-6 cytokines, which often increase in the serum of cachectic patients, serve as mediators of cachexia (Fearon et al. 2012). TISFs promote both skeletal and cardiac muscle atrophy (reviewed in Argiles et al. 2009, Cohen et al. 2015, Egerman & Glass 2014, Fearon et al. 2012, Murphy 2016, Zimmers et al. 2016). In this review, we discuss cachexia in the context of skeletal muscle wasting, highlight some of the challenges in targeting these mediators, and discuss new advances in the field.

**Cachectin/TNF-α**

TNF-α is a well-established prototypical ligand of the TNF superfamily implicated in inflammation, apoptosis, and immune regulation (Baud & Karin 2001). Its role in promoting cachexia was first revealed in the early 1980s (Beutler et al. 1985, Kawakami et al. 1982) and further supported when nude mice implanted with Chinese hamster ovary (CHO) cells expressing TNF-α exhibited body weight reduction and cachexia-like symptoms (Oliff et al. 1987). Impaired TNF-α signaling in mice with either transgenic overexpression of soluble TNF-R1 or deletion of endogenous TNF-R1 partially reduces tumor-induced muscle wasting (Llovera et al. 1998a,b). Mechanistically, TNF-α blocks adipocyte and muscle cell differentiation (Chen et al. 2007, Guttridge et al. 2000, Ruan et al. 2002) and promotes muscle protein degradation (Li et al. 1998, 2005). Nonetheless, TNF-α blockade has not been successful in treating patients with cancer cachexia in clinical trials conducted in multiple cancer types (Jatoi et al. 2010, Wiedenmann et al. 2008). The failure of TNF-α blockade to improve muscle wasting in these patients may be due to the presence of multiple cachexia mediators, redundancy of TNF-α effectors, or immune complications arising from sustained TNF-α inhibition. In addition, many of the trials for cachexia were conducted in advanced metastatic cancer patients, although the mediators of cachexia were identified in early-stage localized tumor models. Based on newly emerging evidence (Wang et al. 2018, Waning et al. 2015), it is possible that the mediators of cachexia in metastatic cancers might be different from those in early-stage cancers, which could also contribute to the failure of previous clinical trials for cachexia. Moreover, enhanced muscle wasting can also be driven independently by chemotherapy treatment, a phenomenon that is often overlooked when TNF-α-blocking antibodies are combined with chemotherapy drugs (Barreto et al. 2016, Damrauer et al. 2018, Gilliam & St. Clair 2011, Gilliam et al. 2011). Collectively, these studies suggest that TNF-α inhibition is not likely to represent an effective therapeutic strategy for reversing cachexia in advanced cancer.
A reduction in muscle size and function (muscle atrophy) results from the loss of proteins, organelles, and cytoplasm from muscle cells in cancer-associated cachexia. Tumor-induced systemic factors (TISFs), such as proinflammatory cytokines and exosomes, induce muscle catabolism through increased proteolysis from hyperactivation of the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system and are often coupled with reduced protein synthesis. TISFs can be secreted directly by tumor cells, by nontumor cells in the tumor microenvironment, or by host tissues in response to tumor growth. TISFs either directly interact with muscle cells to cause muscle atrophy or induce metabolic reprogramming of other peripheral organs, which indirectly leads to muscle atrophy. Some examples illustrated in the figure include: Metastatic cancers upregulate the zinc transporter ZIP14, which increases zinc influx into skeletal muscle cells, promotes myosin heavy chain protein loss, and induces muscle mass and function loss. Muscle weakness can occur independent of muscle mass loss in cancers with bone metastasis by TGF-β pathway activation and altered calcium influx in muscle cells. TISFs can also induce excessive fatty acid oxidation, oxidative stress, and p38 activation in muscle cells and thereby impair muscle growth. Insulin resistance can trigger muscle catabolism through reduced PI3K activity and reduced AKT phosphorylation. Additionally, systemic changes in the brain, liver, adipose tissue, and microbiota can indirectly promote cachexia through altered appetite regulation, metabolism, and energy balance, as well as inflammation.

The IL-6 Family of Cytokines
IL-6 is a pleiotropic cytokine implicated in acute phase response, tissue regeneration, lipid mobilization, and energy expenditure (Narsale & Carson 2014). IL-6 activates the JAK-STAT, ERK, and PI3K/AKT-mediated transcriptional pathways (Heinrich et al. 2003). Animal models...
have convincingly demonstrated a role for the IL-6 family of ligands in promoting cancer-associated cachexia. The Apc\(^{Min/+}\) mouse, a genetic model of intestinal tumorigenesis (McCart et al. 2008), and C-26.IVX, an allograft model of murine colon cancer derived from the C26 cell line (Strassmann et al. 1992), develop IL-6-dependent loss of skeletal muscle mass and adipose tissue (Baltgalvis et al. 2008, 2009; Zaki et al. 2004). Moreover, an IL-6R antibody was shown to rescue muscle atrophy and proteolysis in IL-6 transgenic mice (Tsujinaka et al. 1996) and to reduce the loss of muscle mass in both the C26 (Fujita et al. 1996) and Apc\(^{Min/+}\) cachexia models (White et al. 2011). CNTO328, a human-mouse chimeric IL-6 antibody, also reduced tumor-induced cachexia in a nude mouse model injected with human melanoma or prostate cancer cells (Zaki et al. 2004), and treatment with the anti-IL-6 receptor antibody tocilizumab reduced weight loss and increased the survival of mice transplanted with IL-6-expressing Lewis lung carcinoma cells (Ando et al. 2014, Ohe et al. 1993). In a case study of a patient with lung cancer and advanced cachexia (Ando et al. 2013), treatment with tocilizumab improved appetite and body weight with no discernible impact on tumor growth or progression. In addition, a small phase II clinical trial showed that the humanized monoclonal anti-IL-6 antibody clazakizumab reduced loss of lean muscle mass and improved lung symptoms and fatigue score in lung cancer patients with cachexia (Prado & Qian 2019). Still, it is important to consider that sustained blockade in IL-6 signaling can increase the risk of infection from neutropenia and result in compensatory increases in the activity of other proinflammatory cytokines (Kopf et al. 1994). Future clinical trials are therefore needed to determine whether IL-6 represents a useful target for reversing cachexia in advanced cancer patients.

Additional IL-6 family cytokines, such as ciliary neurotrophic factor and leukemia inhibitor factor, have also been shown to promote muscle atrophy at least in part through the activation of STAT3 (Bonetto et al. 2011, Espat et al. 1996, Henderson et al. 1994, Kandarian et al. 2018). Transcriptomic analysis of cachectic muscles has revealed a prominent STAT3 signature in the C26 cachexia model (Bonetto et al. 2011), and STAT3 activation in muscle is necessary and sufficient for muscle wasting (Bonetto et al. 2012). It is encouraging to note that blocking STAT3 with pharmacological inhibitors or through genetic manipulation of the JAK/STAT3 pathway showed significant improvement in cancer-induced muscle atrophy (Bonetto et al. 2012). Thus, rather than systematically neutralizing individual members of the IL-6 family of cytokines, targeting STAT3 may represent a more effective strategy to treat cancer-associated cachexia (Zimmers et al. 2016).

The TGF-β Family of Ligands

Several members of the TGF-β superfamily have been implicated as important therapeutic targets against cancer-induced muscle wasting in advanced cancer. The TGF-β family member GDF8 (growth and differentiation factor 8), also known as myostatin, binds to the activin type II serine/threonine kinase receptors ACVR2 and ACVR2B and causes the downstream activation of SMAD2/3. Myostatin was first recognized as a potent inhibitor of muscle growth and development when myostatin-null mice were shown to exhibit up to 200% larger muscles due to myofiber hyperplasia and hypertrophy (McPherron et al. 1997). Similar findings have been reported in a child with a myostatin gene mutation (Schuelke et al. 2004). Moreover, systemic overexpression of myostatin in mice caused profound fat and muscle mass loss, which could be reversed by the myostatin inhibitor follistatin (Zimmers et al. 2002). In primates, however, simultaneous inhibition of activin A and myostatin was required to induce robust hypertrophic effects with enhanced force production (Latre et al. 2017). These findings are important to consider when designing anti-TGF-β pathway strategies to overcome cachexia in the clinic. In the context of cancer, the function of myostatin in muscle growth and development is less clear. While some studies report
an improvement in muscle wasting when tumor cells are injected into myostatin-knockout mice (Gallot et al. 2014), others have observed the opposite (Benny Klimek et al. 2010), which could be attributed to compensatory shifts in muscle fiber type or metabolism from the developmental loss of myostatin (Amthor et al. 2007).

Targeting the myostatin receptors ACVR2 and ACVR2B, on the other hand, has consistently shown considerable promise for reversing muscle wasting in independent studies. Bimagrumab is a human anti-ACVR2 antibody that prevents the binding of the ACVR2 ligands to their receptors (Lach-Trifilieff et al. 2014). The mouse version of this antibody was found to enhance muscle hypertrophy in the myostatin-mutant mice and to protect wild-type mice from glucocorticoid-induced muscle atrophy and weakness. In a recent randomized clinical trial (https://www.clinicaltrials.gov/ identifier NCT01433263), pancreatic and lung cancer patients treated with bimagrumab showed favorable increases in lean body mass (Yakovenko et al. 2018). In two landmark studies using a myostatin ligand trap strategy, systemic administration of soluble forms of Acvr2b, either Acvr2b-Fc secreted from implanted CHO cells (Benny Klimek et al. 2010) or the decoy receptor sActRIIB (Zhou et al. 2010), caused a striking inhibition of tumor-induced cachexia and prolonged survival in mouse models of cachexia (Zhou et al. 2010). Of note, sActRIIB treatment reduced the hyperactivation of the UPS in muscle cells and muscle protein turnover (Zhou et al. 2010). Since ACVR2B binds to other TGF-β family ligands, such as GDF11 and activin other than myostatin (Lee et al. 2005), the protective effect of soluble ACVR2B in vivo could be mediated by one or more of these ligands. These and subsequent studies (Busquets et al. 2012, Nissinen et al. 2018) have provided compelling evidence that the soluble form of ACVR2B could serve as a potent therapeutic target in cancer-associated cachexia.

Other members of the TGF-β superfamily, such as GDF11 and GDF15, have been recently implicated as mediators of both anorexia and cachexia. The role of GDF11 in aging-related muscle regeneration has been controversial (Egerman et al. 2015, Loffredo et al. 2013, Sinha et al. 2014). With respect to cachexia, sustained GDF11 induced whole-body wasting and reduction in organ sizes with profound skeletal and cardiac muscle wasting (Zimmers et al. 2017). In addition, high levels of Gdf11 reduced food intake, body weight, and muscle mass in mice (Jones et al. 2018). Gdf11-induced muscle loss was driven by increased plasma activin A and reversed by blockade of Acvr2b signaling. Gdf11 also induced appetite loss through upregulation of Gdf15 (also known as macrophage-inhibitory cytokine 1), and this effect was reversed through treatment with a Gdf15-neutralizing antibody. GDF15 influences the appetite regulation centers in the brain (Tsai et al. 2013). It originally emerged as a potent regulator of appetite when elevated levels of Gdf15 were found to be associated with decreased food intake and loss of fat and lean tissue in mice (Johnen et al. 2007). It was later found that tumors with Gdf15-induced activation of mitogen-activated protein kinase Map3k11 led to cachexia in mice (Lerner et al. 2016). Three groups identified glial cell line–derived neurotrophic factor receptor alpha-like (Gfra1) as the receptor for Gdf15 (Emmerson et al. 2017, Hsu et al. 2017, Yang et al. 2017) and found that germline deletion of the Gfra1 gene blunted the anorectic response induced by recombinant Gdf15. These studies established GDF15 as an important regulator of appetite and feeding responses, which could be important for targeting cachexia.

**SYSTEMIC REGULATION OF CANCER-ASSOCIATED CACHEXIA**

A large body of literature suggests that multiple organs contribute to the wasting of skeletal muscle in advanced cancer patients (Baracos et al. 2018, Fearon et al. 2012). This section discusses how these various systemic changes act as signals that trigger muscle atrophy in cancer (Figure 1).
Central Nervous System Regulation of Cachexia

The central nervous system (CNS) has emerged as a sensor and amplifier of inflammation that regulates anorexia and muscle wasting (Burfeind et al. 2016). In this setting, peripheral inflammatory cues are amplified in the mediobasal hypothalamus in the brain, which regulates the neuronal populations that control feeding behavior and energy homeostasis. Direct administration of IL-1β in the CNS by intracerebroventricular injection induces muscle atrophy through a glucocorticoid-dependent transcriptional program (Braun et al. 2011), a phenotype that can be abrogated by adrenalectomy. Hypothalamic inflammation is then followed by a marked activation of the hypothalamic-pituitary-adrenal axis, and in response to a neuroendocrine signaling cascade, cytokines enter the CNS and promote the catabolism of carbohydrates, proteins, and lipids in peripheral tissues, such as skeletal muscle (Burfeind et al. 2016). These studies demonstrated a key role for hypothalamic inflammation in muscle homeostasis.

The hypothalamus regulates feeding behavior through specific centers in the brain. Understanding this process is important during cancer progression or in response to cancer treatments, when lack of appetite or anorexia often exacerbates cachexia. The ventromedial hypothalamus has an appetite-suppressing or anorexigenic function, while the lateral hypothalamus has an appetite-increasing or orexigenic function (Anand & Brobeck 1951). Two distinct neuronal populations drive these functional outputs, the anorexigenic proopiomelanocortin (POMC) neurons and the orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons (Sohn 2015). Both types of neurons integrate central and peripheral signals to mediate feeding responses. Of relevance, the adipocyte-secreted hormone leptin induces anorexigenic effects by exciting the POMC neurons and suppressing the NPY/AgRP neurons (Cowley et al. 2001), whereas the gut hormone ghrelin increases appetite by suppressing POMC neurons and exciting NPY/AgRP neurons (Cowley et al. 2003). Moreover, hypothalamic serotonin can modulate both anorexigenic and orexigenic signaling (Dwarkasing et al. 2014). Even intraperitoneal injection of TNF-α or IL-6 in mice changes their hypothalamic transcriptome, causing alterations in inflammatory and serotonin pathways and reduced food intake (Dwarkasing et al. 2014, 2015, 2016). In addition, activation of AMP-activated protein kinase (AMPK) in the hypothalamus promotes food intake in TB rats to restore energy balance (Ropelle et al. 2007). The CNS has therefore emerged as an important contributor to the development of cancer-associated cachexia through its ability to regulate energy balance, appetite, and body weight.

The Intricate Link Between Adipose Tissue and Muscle Wasting

Adipose tissue was once considered an inert fat depot but has now emerged as an important compartment that exerts both endocrine and paracrine effects and actively engages in cross talk with skeletal muscle. Genetic ablation of the adipose triglyceride lipase gene (Atgl), which encodes an enzyme that catalyzes the first step of triacylglycerol hydrolysis, was found to protect mice from loss of white adipose tissue (WAT) when injected with cachexia-inducing tumor cell lines (Das et al. 2011). This protection was independent of tumor type or feeding status, and surprisingly, Atgl deficiency also conferred resistance to muscle protein degradation and loss of muscle mass (Das et al. 2011). These findings suggest that WAT loss precedes muscle mass loss and that lipolysis of WAT with fatty acid mobilization can activate muscle proteolysis in cancer.

White, beige, and brown adipocytes comprise three kinds of adipose tissue with distinct locations and functions. WAT depots mainly function to store energy in the form of triglycerides. Brown adipose tissue (BAT) depots mainly function to expend energy (Cypess et al. 2009). Brown adipocytes in the BAT depots are known as constitutive or classical brown adipocytes. Beige, or so-called brite, adipocytes are derived from the browning of WAT. They function like brown
adipocytes but appear in WAT as an adaptive response to stimuli such as prolonged cold exposure or β3 adrenergic receptor activation (Sidossis et al. 2015). The browning of WAT results in increased energy expenditure, body weight loss, and improved insulin sensitivity and represents a promising strategy for controlling obesity (Petruzzelli & Wagner 2016). By contrast, in pathological states such as cancer, kidney failure, or postburn injury where energy conservation is vital, the browning of WAT can be detrimental (Kir et al. 2014, 2016; Petruzzelli et al. 2014). Using the C26 cachexia model, the Belury group showed that during the early phases of cachexia when weight loss is less than 10% of initial body weight, mice showed enhanced lipolysis, elevated total energy expenditure, and upregulation of markers of BAT thermogenesis (Kliewer et al. 2015). Therefore, prevention of WAT browning could be beneficial for cachectic cancer patients, who are already suffering from a state of negative energy balance (Kir et al. 2014).

Recent studies have analyzed the underlying mechanisms that drive the browning of WAT. The Spiegelmangroup identified parathyroid hormone–related protein (PTHrP), a small polypeptide that modulates calcium homeostasis, as a mediator of the browning process (Kir et al. 2014). They found that either neutralizing PTHrP or blocking the PTHrP receptor in fat cells can inhibit browning, suppress tumor-induced hypermetabolism, and reduce fat wasting. Interestingly, neutralization of tumor-derived PTHrP preserved both fat and muscle mass and improved muscle function, a surprising result since the PTH/PTHrP receptor is not expressed in muscle fibers. This suggests that adipose tissue factors or metabolites that promote muscle wasting are released in response to PTHrP. The browning of WAT can also be induced by intermediate metabolites such as lactate or by the ketone body β-hydroxybutyrate as an adaptive mechanism to alleviate redox changes (Carriere et al. 2014). Lactate is a product of anaerobic glycolysis and is generated in skeletal muscles in high amounts during intense exercise and in response to increased glycolysis and glutamine metabolism in cancer cells (Doherty & Cleveland 2013). Recent studies have shown that circulating lactate can serve as a TCA (tricarboxylic acid) cycle carbon source (Faubert et al. 2017, Hui et al. 2017). Therefore, lactate acts as a fuel for cancer cells and a potential inducer of cachexia through adipose tissue browning. Moreover, the muscle-derived factor irisin induces WAT browning and increases thermogenesis (Bostrom et al. 2012, Zhang et al. 2016). WAT browning is an early event in the cachexia cascade (Petruzzelli et al. 2014). In genetic models of cancer, treatment with an anti-IL-6 antibody reduced WAT browning, prevented body fat reduction, and reduced the severity of cachexia. IL-6 is known to drive the expression of uncoupling protein 1, an inner mitochondrial membrane protein that is responsible for uncoupling the respiratory chain from ATP synthesis, allowing the proton gradient to be used instead for thermogenesis (Nedergaard & Cannon 2014, Petruzzelli & Wagner 2016, Petruzzelli et al. 2014). In addition, a decrease in AMPK activity and an increase in cell death–inducing DNA fragmentation factor, alpha subunit-like effector A (CIDEA), a key metabolic regulator and component of the WAT remodeling process, are common features of adipose tissue dysfunction in cancer-associated cachexia (Rohm et al. 2016). CIDEA interacts with and causes the destabilization of AMPK in WAT (Qi et al. 2008) and thereby promotes tumor-induced lipolysis. As such, WAT wasting can be inhibited by a peptide that blocks the CIDEA-AMPK interaction (Rohm et al. 2016). Interfering with WAT remodeling may therefore represent a viable strategy for inhibiting the onset of cancer-associated cachexia.

Pancreas Dysfunction and Cancer-Associated Cachexia

Dysfunction and metabolic alterations of the pancreas have been implicated in cachexia development. The pancreas has two distinct roles in physiology, an exocrine function involving the production of enzymes for digestion and an endocrine function that produces hormones that
regulate blood glucose levels. The exocrine pancreas produces key enzymes in the pancreatic juice that are essential for nutrient digestion (Vujasinovic et al. 2017). Pancreatic insufficiency or pancreatic tumors can induce maldigestion and contribute to weight loss (Vujasinovic et al. 2017, Wigmore et al. 1997), although the negative impact of altered exocrine pancreas function on patient survival is controversial (Danai et al. 2018). In healthy condition, pancreatic beta cells secrete the hormone insulin when blood glucose levels rise after a meal (Wilcox 2005). Insulin signals the transport of glucose into insulin-dependent tissues like muscle and suppresses proteolysis (Honors & Kinzig 2012). However, in cancer-associated cachexia, the muscle cells become insulin resistant and muscle catabolism ensues (Honors & Kinzig 2012). Indeed, glucose intolerance and decreased insulin sensitivity are observed in cachectic animal models and cancer patients (Asp et al. 2010, Fernandes et al. 1990, Heber et al. 1985). Reduced insulin secretion from the pancreas has been reported in animal models of cancer cachexia (Fernandes et al. 1990). Interestingly, insulin resistance occurred prior to overt weight loss in the C26 cancer cachexia mouse model and could be partially reversed by treatment with an insulin-sensitizing agent, rosiglitazone (Asp et al. 2010, 2011), suggesting that targeting insulin resistance in this way could prove useful in the treatment of cancer-associated cachexia.

Liver Metabolism in Cancer-Associated Cachexia

The liver serves as a central metabolic organ that possesses remarkable flexibility in sensing and adapting to both a changing nutrient supply and the metabolic demands of other tissues. The liver contributes to cancer-associated cachexia by increasing energy expenditure and by overproducing inflammation-promoting, acute-phase proteins at the expense of structural proteins (Argiles et al. 2018). Under normal physiological conditions, the brain, erythrocytes, and skeletal muscle produce lactate through anaerobic glycolysis and release it into the circulation. Lactate is taken up by the liver and converted to glucose by gluconeogenesis. It is then either released into the circulation or stored as glycogen in the liver, depending on the blood glucose level. In cancer, glucose utilization and lactate production increase markedly based on the aberrant metabolic needs of the cancer cells, a phenomenon known as the Warburg effect. Moreover, the rate of the Cori cycle increases and thereby maintains a perennial negative energy state in the host (Holroyde et al. 1975). To help compensate for this continuous loss of energy, muscle proteins are broken down to release amino acids, which may then be converted into glucose by the liver. An increase in the Cori cycle rate, as well as anomalies in carbohydrate metabolism, has also been observed in advanced cancer patients with cachexia (Holroyde & Reichard 1981, Holroyde et al. 1984) and may therefore contribute to muscle loss in these patients. The metabolic function of the liver is also compromised in cancer-associated cachexia by reduced PPAR-α (peroxisome proliferator–activated receptor alpha)-dependent ketone production, decreased very low-density lipoprotein secretion, hypobetalipoproteinemia, and impaired hepatic triglyceride export through upregulation of TGF-β-1-stimulated clone 22 D4 (Jones et al. 2013). However, very few studies have focused on the contribution of abnormal liver metabolism to cancer-associated cachexia.

Bone and Muscle Interactions: Implications in Cachexia

Bone and muscle are neighboring tissues that interact and physiologically influence one another (DiGirolamo et al. 2013, Waning & Guise 2015). The bone-derived factor Ihh (Indian hedgehog) promotes muscle growth (Bren-Mattison et al. 2011), while the muscle-derived factors IGF-1 (insulin-like growth factor 1) and FGF-2 (fibroblast growth factor 2) stimulate bone formation.
(Liang et al. 1999, Power et al. 2004, Yakar et al. 2002). Of relevance, cancer patients with bone metastases experience skeletal muscle weakness (Waning & Guise 2014), a phenomenon that is heavily influenced by bone-derived factors (Guise & Mundy 1998, Waning & Guise 2015, Waning et al. 2015). Pathological levels of TGF-β released from osteolytic bone metastases induce profound skeletal muscle weakness by reducing Ca\(^{2+}\)-induced muscle force production (Waning et al. 2015). This study provided three important insights into cachexia in advanced cancers. First, it established the importance of metastasis in compromising muscle function by demonstrating that the same cells injected at the primary site do not lead to muscle weakness; instead, bone breakdown and TGF-β release are required to induce muscle weakness. Second, it found that muscle dysfunction can occur even in the absence of muscle mass changes. Finally, it provided new therapeutic targets against cachexia (TGF-β-Nox4-RyR1 calcium leak) that are relevant for cancers with bone metastasis.

The Link Between Gut Microbiota Changes and Cachexia

A new gut microbiota-muscle axis has been uncovered that regulates host inflammation and metabolism in cancer. Early studies using lean and obese mice showed that colonization with microbiota from an obese (but not lean) mouse resulted in increased body fat in germ-free mice, indicating that obesity can be conferred by gut bacteria (Turnbaugh et al. 2006). In this study, obesity was associated with changes in the relative abundance of two dominant bacterial divisions, Bacteriodetes and Firmicutes (Turnbaugh et al. 2006). Furthermore, analysis of the bacterial flora in obese, lean, and anorexic human patients revealed significant differences in the concentration of bacterial species depending on the metabolic state. That is, the concentration of Lactobacillus species was higher in obese patients whereas the concentration of the archaeon Methanobrevibacter smithii was higher in the anorexic patients (Armougom et al. 2009). Interestingly, TB Apc\(^{Min/+}\) mice that were fed Lactobacillus reuteri, a probiotic that can ameliorate gastrointestinal disorders, had a lower intestinal tumor burden and gained protection against muscle wasting (Varian et al. 2016). In addition, reduced muscle atrophy was observed in a mouse model of acute leukemia that was given oral supplementation with L. reuteri and L. gasseri, which correlated with decreased circulating proinflammatory cytokine levels (Bindels et al. 2012). In the context of infection-induced cachexia, gut colonization by the O21:H\(^+\) strain of Escherichia coli induces systemic levels of IGF-1 that protect against muscle wasting from both Salmonella typhimurium–induced intestinal infection and Burkholderia thailandensis–induced pneumonic infection (Schieber et al. 2015). In C26 TB mice, a murine model of colon cancer, microbiota of cachectic mice showed an increase in the Enterobacteriaceae species Klebsiella oxytoca associated with an IL-6-driven disruption in gut barrier function (Bindels et al. 2018). Reduced cecal content and increased villi length and crypt depth were also associated with enhanced gut permeability in this model, with no effects on food intake. Gut microbiota have recently been shown to metabolize bile acids (Wahlstrom et al. 2016), which are known to enhance fat absorption in the intestine and regulate fat metabolism by acting as signaling molecules and metabolic integrators (Bindels & Delzenne 2013, Kawamata et al. 2003). Bile acids are synthesized in the liver, and gut microbiota influence the relative composition and abundance of bile acids across different tissue compartments from liver to kidney (de Aguiar Vallim et al. 2013, Swann et al. 2011). Bile acids can also promote energy expenditure in fat cells by increasing intracellular thyroid hormone activation (Watanabe et al. 2006). They do so by inducing cyclic-AMP-dependent thyroid hormone–activating enzyme D2 (type 2 iodothyronine deiodinase) and oxygen consumption, a phenomenon observed in both brown adipocytes and skeletal muscle cells (Watanabe et al. 2006). Therefore, the link between gut microbiota and bile acid metabolism may be important in the development of cachexia.
NEW DIRECTIONS

In this section, we summarize the findings of few recent studies that have provided new insights into cachexia pathogenesis. New insights have come from studies in Drosophila that have elucidated how TISFs induce insulin resistance and muscle wasting. The Drosophila IGF-binding protein homolog ImpL2, an antagonist of insulin signaling, promotes muscle wasting upon secretion from a Drosophila tumor (Figueroa-Clarevega & Bilder 2015). Similarly, an independent study showed that a reduction in systemic insulin/IGF signaling associated with increased ImpL2 expression also resulted in a muscle-wasting phenotype in Drosophila (Kwon et al. 2015). It is well established that IGF-1 signaling normally regulates muscle mass (Rommel et al. 2001) and has been found to promote muscle protein catabolism upon downregulation (Bodine et al. 2001b, Sandri et al. 2004).

The effects of insulin signaling disruption in peripheral tissues in Drosophila are consistent with the insulin resistance observed in cachectic patients and mouse models (Honors & Kinzig 2012), and these studies elucidated their underlying mechanisms.

To understand how a disrupted metabolism drives muscle atrophy, Shyh-Chang and colleagues exposed human muscle cells to conditioned media from cachexia-inducing human cancer cell lines (Fukawa et al. 2016). The muscle cells rapidly increased fatty acid oxidation, which led to oxidative stress, p38 activation, and impaired muscle growth. Interestingly, pharmacological blockade of fatty acid oxidation rescued cancer-associated cachexia. These studies demonstrate that tumor-secreted cytokines converge to trigger excessive fatty acid catabolism in muscle fibers and that early metabolic stress responses in muscle fibers may lead to muscle atrophy.

Studies from our laboratory have shown that altered zinc homeostasis in muscle promotes muscle wasting in the context of metastatic cancer. The metal ion transporter ZRT- and IRT-like protein 14 (ZIP14) is induced in muscle cells in both cachectic patients and mouse models of metastatic cancers (Wang et al. 2018). An increase in ZIP14 expression leads to a concomitant increase in zinc uptake, which induces myosin heavy chain loss in mature muscle cells and blocks differentiation in muscle progenitor cells. Moreover, muscle wasting is further accelerated in TB mice with zinc-supplemented water in a Zip14-dependent manner. Modulating zinc intake and blocking ZIP14 function therefore represent two new therapeutic strategies for the prevention or treatment of cancer-associated cachexia. Interestingly, expression of ZIP4, another zinc transporter, in pancreatic cancer cells promotes tumor growth and activates RAB27B, causing the release of high levels of extracellular vesicles into circulation. These vesicles serve as carriers of tumor-derived heat shock proteins HSP70 and HSP90, which were shown to induce muscle catabolism and cachexia through the p38 MAPK pathway (Liu et al. 2018, Yang et al. 2019). Therefore, zinc chelation or blockade of a zinc transporter (ZIP4 in tumor cells and ZIP14 in muscle cells) might be beneficial for preventing cancer-associated cachexia. Collectively, aberrant zinc regulation has also been observed in dexamethasone-induced muscle atrophy (Summermatter et al. 2017) and muscular dystrophy (Crawford & Bhattacharya 1987), suggesting that it may represent a common underlying mechanism of multiple muscle-wasting pathologies.

Finally, recent studies have sparked new interest in cancer prevention and combination therapies for cachexia (Argiles et al. 2019). Regular exercise in mice can reduce tumor incidence and growth across tumor models through an interaction with the immune system (Pedersen et al. 2016). Experimental and clinical studies have also shown that exercise reduces symptoms of cachexia in cancer models and human patients (Aversa et al. 2017, Ballaro et al. 2019, Lonbro et al. 2013, Peddle-McIntyre et al. 2012, Pigna et al. 2016). Although enrolling advanced cancer patients with cachexia into exercise programs could be a clinical challenge, the idea has emerged as a promising noninvasive, multimodal approach that might benefit cancer patients and improve their survival and quality of life (Muscaritoli et al. 2015, Solheim et al. 2018).
PERSPECTIVES AND CONCLUSIONS

The syndrome of cachexia, with its debilitating symptoms and manifestations resulting from lack of appetite, loss of muscle mass and function, fatigue, and metabolic dysfunction (Baracos et al. 2018, Fearon et al. 2013), adds an additional layer of complexity to the already challenging task of conquering advanced stages of cancer. Moreover, a cachexia diagnosis in cancer patients has become increasingly difficult in the current age of obesity, where the loss of muscle mass can be easily masked by fat gain (Esfandiari et al. 2014). However, subtle changes in body composition can now be measured using imaging analysis from CT scans from cancer patients and can be followed up longitudinally (Mourtzakis et al. 2008). Despite an accurate diagnosis, however, effective treatment options for cachexia patients are still lacking, so the search for cachexia mediators, mechanisms, and treatment strategies needs to be accelerated. Great strides have been achieved in the field of cancer-associated cachexia due to mechanistic studies that have identified how muscle and fat cells respond to TISFs and perturbed signaling pathways; however, the great majority of experimental studies designed for treating cachexia have performed poorly in over 100 clinical trials. Whether this is due to limited efficacy of the targeting agent or whether inactivating a single mediator is insufficient to reverse cachexia in advanced cancer patients is being reevaluated.

To model cachexia in the advanced cancer context, researchers are developing new preclinical cachexia models that can more accurately recapitulate the human syndrome (Penna et al. 2016). These include patient-derived orthotopic models (Go et al. 2017), genetically engineered mouse models (Goncalves et al. 2018, Wang et al. 2018), and allograft models (Greco et al. 2015, Wang et al. 2018, Waning et al. 2015) that metastasize and develop cachexia. These preclinical models can accelerate testing of combined anticachexia and anticancer therapies for translational studies. Additionally, validated molecular markers of human cachexia across cancer types are needed for translating these experimental studies successfully in the clinic. While cachexia was once ignored as a mere side effect of advanced cancer, it is now widely accepted as a formidable obstacle that undermines current treatment regimens. The early diagnosis and effective treatment of cachexia should therefore improve the outcome of current anticancer therapies and ultimately enhance the quality and duration of life for cancer patients suffering from this syndrome.

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