Review

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Energy metabolism in cachexia

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Abstract

Cachexia is a wasting disorder that accompanies many chronic diseases including cancer and results from an imbalance of energy requirements and energy uptake. In cancer cachexia, tumor-secreted factors and/or tumor–host interactions cause this imbalance, leading to loss of adipose tissue and skeletal and cardiac muscle, which weakens the body. In this review, we discuss how energy enters the body and is utilized by the different organs, including the gut, liver, adipose tissue, and muscle, and how these organs contribute to the energy wasting observed in cachexia. We also discuss futile cycles both between the organs and within the cells, which are often used to fine-tune energy supply under physiologic conditions. Ultimately, understanding the complex interplay of pathologic energy-wasting circuits in cachexia can bring us closer to identifying effective treatment strategies for this devastating wasting disease.

Keywords adipose tissue; cachexia; inflammation; liver; skeletal muscle
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See the Glossary for abbreviations used in this article.

Introduction

A well-balanced and controlled energy homeostasis is critical for human health. Excessive caloric intake and insufficient physical activity lead to a plus in energy substrate storage, metabolic dysfunction, and obesity. Involuntary weight loss and an energy-deprived metabolic state on the other hand are also coupled to severe metabolic dysfunction, including insulin resistance, fatty liver, and dyslipidemia [1]. Chronic wasting conditions such as cancer-induced cachexia, sepsis, and burn injuries share many of these metabolic phenotypes, suggesting that distinct etiologies may trigger common downstream cellular events eventually responsible for systemic body wasting. These common biochemical wasting cycles may include the classical Cori Cycle [2], enhanced lipid turnover [3], and creatine kinase-dependent futile cycling [4] but in general remain still largely unexplored. In cancer cachexia, tumor metabolism may also be at least partially responsible for the wasting, since the aerobic glycolysis typical for tumor cells is energetically highly inefficient (Warburg effect).

The existence of tumors with identical origins and of equal size, one of which induces cachexia while the other does not, suggests that only a very limited number of genetic or gene expression events, e.g., in metabolic genes [5], may underlie the tumor-associated cachexia phenotype. This may also be extrapolated to non-tumorous wasting disorders as well as the peripheral target organs.

Interestingly, anorexia (loss of appetite, leading to reduced food intake) is a common hallmark of cancer, cancer therapies, and other wasting disorders. Multiple factors lead to anorexia, including secretion of proinflammatory cytokines from tumor and host, hormonal and neuroendocrine changes, and psychological changes such as depression or pain [6]. While these factors are fundamentally involved in cachexia development, they form only one part of the equation summing up to the disease-related weight loss. Indeed, body weight loss in cachexia cannot be reversed by treatment of anorexia, and conventional nutritional support neither improves muscle or adipose tissue loss nor functional impairment [7]. Thus, decreased energy intake and its central control alone cannot be the sole reason for the wasting, suggesting that peripheral energy metabolism must be altered in the cachectic state. By tracking the body's main peripheral organ systems, we here discuss our current knowledge on tissue-specific wasting mechanisms that impact systemic energy homeostasis and may thus represent key sites in the pathogenesis of severe human wasting disorders (Fig 1).

Absorption/malabsorption of energy substrates

Intestinal malabsorption can lead to reduced metabolic efficiency

Efficient recovery and absorption of nutrients by stomach and intestine are the first steps in whole-body energy metabolism. In patients with gastrointestinal cancer, mechanical limitations such as difficulties in swallowing, as well as feelings of satiety or nausea, restrict energy uptake and recovery. Hence, weight loss occurs in up to 83% of patients with upper gastrointestinal malignancy [8]. Further, nutrient malabsorption by the intestine can lead to reduced metabolic efficiency and, with equal energy intake, to wasting not only in patients with gastrointestinal cancer. Indeed, rodents with cancer-induced cachexia show a marked decrease in intestinal lipid and carbohydrate uptake [9,10]. Reduced lipid uptake is also observed in patients with cachexia induced by chronic congestive

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Glossary

AAV	adeno-associated virus
AIDS	acquired immune deficiency syndrome
Akt/PKB	protein kinase B
AMPK	adenosine monophosphate-activated protein kinase
Apc	adenomatous polyposis coli
AT	adipose tissue
Atg5	autophagy-related 5
ATGL	adipocyte triglyceride lipase
ATP	adenosine triphosphate
Atrogin 1	muscle atrophy F-box/MAFbx
BA	bile acid
BMI	body mass index
C26	Colon 26 cell line
CD36	cluster of differentiation 36
CEBP-β	CCAAT enhancer binding protein beta
eIF3f	eukaryotic translation initiation factor 3 subunit f
ER	endoplasmic reticulum
FITC-dextran	Fluorescein isothiocyanate-dextran
G6Pase	glucose 6-phosphatase
G6P	glucose 6-phosphate
GAA	acid α-glucosidase
Gabarap	gamma-aminobutyric acid receptor-associated protein
GIP	glucose-dependent insulinotropic peptide
GK	glucokinase
GKRP	GK regulatory protein
GLP-1	glucagon-like peptide 1
GLUT	glucose transporter
GTP	guanosine-5′-triphosphate
HSL	hormone-sensitive lipase
IL	interleukin
MAPK	mitogen-activated protein kinase
MGL	monoglyceride lipase
MHC	myosin heavy chain
mTOR	mammalian target of rapamycin
MuRF1	muscle RING finger-1
MUSA1	muscle ubiquitin ligase of SCF complex in atrophy-1
myoD	myogenic differentiation 1
NPC1L1	Niemann-Pick C1-Like 1
PYY	peptide yy
RIP140	receptor-interacting protein 140
S6K1	ribosomal S6 kinase
SCFA	short-chain fatty acids
SGLT1	sodium/glucose cotransporter 1
SNP	single nucleotide polymorphism
SRB1	scavenger receptor class B type 1
T3	triiodothyronine
T4	inactive thyroxine
TGR5	G protein-coupled bile acid receptor 1
TNFα	tumor necrosis factor alpha
TRAF6	TNF receptor associated factor 6
TSC22D4	TSC22 domain family member 4
UCP1	uncoupling protein 1
UPS	ubiquitin-proteasome system
ZAG	zinc-α2-glycoprotein

heart failure [11]. Protein or amino acid uptake, on the other hand, is either unaltered or slightly enhanced [10,12]. Malabsorption in cachexia due to chronic heart failure is thought to result from mesenteric ischemia and disturbed microcirculation of the intestine [13], while in cancer-associated cachexia, chemotherapies are likely to contribute to the development of intestinal absorptive dysfunction [14]. The molecular mechanisms contributing to intestinal malabsorption in cachexia are not clear yet. However, alterations in expression or localization of the major intestinal glucose (SGLT1, GLUT5, GLUT2) and lipid (CD36, NPC1L1, SRB1) transporters, as seen upon fasting and refeeding [15], are likely. Altered intestinal gluconeogenesis, a recently identified regulator of the central control of glucose and energy homeostasis, may further contribute to the energetic imbalance observed in cachexia: Tumor-bearing rats show ameliorated wasting when fed an l-glutamine-rich diet, activating intestinal gluconeogenesis and thereby improving glycemia [16].

Microbiota and inflammation by gut leakage

The intestine has yet another role to play in wasting diseases. Gut barrier dysfunction and subsequent endotoxemia occur when the intestinal mucosal barrier leaks or breaks down, causing gut microbiota or bacterial cell wall components to enter the circulation and cause an inflammatory response. Measuring gut permeability to the neutral hydrophilic polymer FITC-dextran, Puppa *et al* [17] have reported a marked reduction in intestinal gut barrier integrity in cachectic Apc(Min/+) mice with colorectal cancer. This is accompanied by significantly elevated plasma endotoxin concentrations. It may be speculated that the multiple intestinal lesions in this model contribute to gut dysfunction. Arguing against this and supporting a systemic effect also in gastrointestinal cancer, increased gut leakage is also apparent in an additional mouse model where colon cancer cells are injected subcutaneously, excluding a direct mechanical effect of the primary tumor. In the latter study, gut integrity is restored by treatment with an anti-IL-6 antibody, demonstrating the involvement of the inflammatory system in intestinal dysfunction in cachexia [18]. Inflammation therefore seems to be both cause and consequence of gut dysfunction, at least in rodent models. Causality is less clear in humans, but as shown in patients with gastric cancer, increased bacterial translocation through the intestinal mucosa is associated with increased cytokine production, altered levels and activation of T cells, and worse prognosis [19]. As discussed in Box 1, inflammatory mediators play a pivotal role in energy wasting in cachexia by multiple mechanisms.

Healthy energy metabolism is further modulated by the amount and quality (species) of gut microbiota. Balanced gut microbiota influence nutrition of the host as they determine nutrient metabolic efficiency, and microbiota-derived metabolites alter inflammation, gut barrier function, and energy expenditure. For example, colonocytes usually metabolize microbiota-derived SCFA such as butyrate but switch from oxidizing butyrate to fermenting glucose into lactate when butyrate is absent, resulting in an energetic defect of the host cell as insufficient ATP is produced [20]. The gut microbiota produces SCFA by fermentation of non-digestible carbohydrates, which may contribute to up to 10% of the daily energy requirements in humans. Dietary supplementation of the SCFA butyrate increases energy expenditure and mitochondrial function in mice [21].

The contribution of gut microbiota to metabolic health has been thoroughly studied in obesity/diabetes, in particular with regard to inflammation, SCFA action, and bile acids and cholesterol metabolism [22]. Gut microbiota and their metabolites have also been proposed as potential targets for the prevention and treatment of other metabolic diseases such as cardiovascular disease, heart failure, and chronic kidney disease. The role of gut microbiota for energy metabolism in cachexia is less clear, but a common microbial signature for cachectic mice has recently been demonstrated

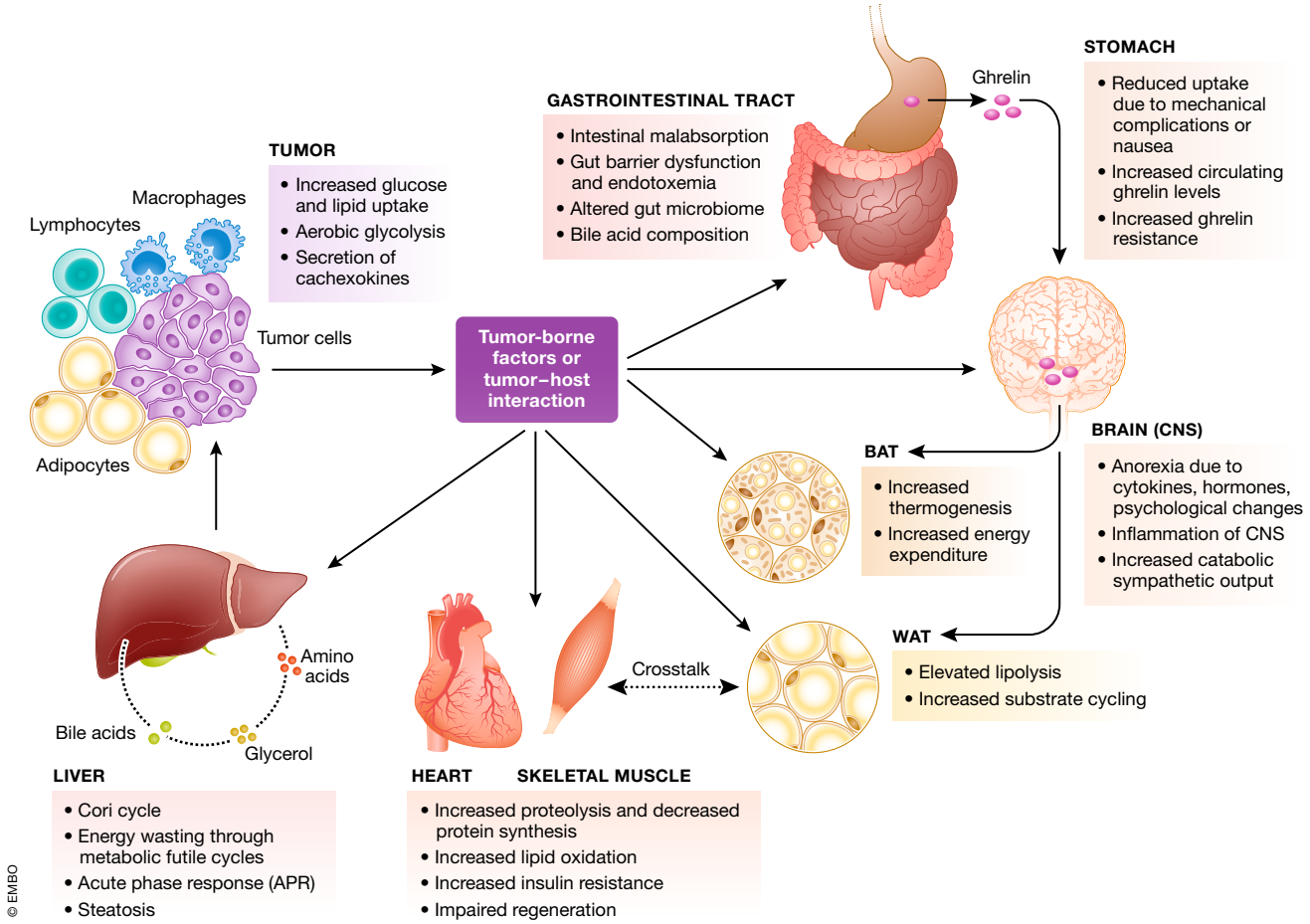

Figure 1. Overview of energy consuming processes in cachexia.
Tumor-secreted factors or tumor/host interactions reduce energy uptake and activate energy-wasting processes in different organ systems, acting on brain/CNS, adipose tissues, gastrointestinal system, liver, and muscles.

[23,24]. For example, the selective modulation of *Lactobacillus spp.* affects muscle atrophy, inflammatory marker levels, and cachexia in a mouse leukemia model [23], suggesting a gut-muscle signaling axis contributing to wasting. If tumor cells directly influence the gut microbiota through secreted factors or inflammatory mediators, or if the altered food and nutrient uptake are responsible for the observed changes is unclear so far. Likewise, the molecular mechanisms of this phenomenon are yet to be determined, but it is conceivable that microbiota-derived metabolites impact energy metabolism of muscle, liver, or adipose tissue. The gut microbiota also influences the regulation of bile acids and cholesterol metabolism [22], with impact on fat resorption and energy expenditure. Importantly, restoring the *lactobacilli* levels in a strain- and/or species-specific manner restores the molecular signs of muscle atrophy in cachectic mice [23]. In rodents, synbiotics restoring the gut microbial signature have since been used to successfully treat muscle atrophy and cachexia-associated body weight loss, independent of the site of the original tumor [24]. Transfer of gut microbiota from healthy patients has been shown to improve insulin sensitivity in obese patients with metabolic syndrome, as shown by a landmark study from Vrieze *et al* [25]. Thus, synbiotics or microbiota transplants may be tempting approaches for future cachexia therapy.

Ghrelin effects on wasting metabolism are closely linked to anorexia

Gut hormones have gained substantial interest with regard to body weight and metabolic regulation in recent years. In particular, the stomach-derived ghrelin [26], the so-called "hunger-hormone", has been extensively studied in the context of cachexia. Ghrelin was first found to improve cardiac cachexia in a rodent model of chronic heart failure (a syndrome also often associated with cachexia in patients) [27] and has since been explored for the treatment of other forms of cachexia and anorexia. Ghrelin's function in regulation of energy homeostasis has initially been described in the context of obesity [28], and ghrelin has since been shown to be involved in the regulation of appetite, gut motility and gastric acid secretion, white and brown adipose tissue function, and glucose metabolism, all of which influence energy homeostasis [29]. Ghrelin levels are elevated upon fasting [28] and in multiple forms of cancer cachexia [30,31], although this is not always the case [32]. This increase may be closely linked to anorexia: A study comparing anorectic, cachectic, and anorectic–cachectic patients with

Box 1: Inflammation and energy expenditure in brief

An inflammatory status is an established stimulator of resting energy expenditure in cancer [7], originating both from cytokine secretion by the tumor and from the immune response of the host. Inflammation, mainly high levels of IL-6 and TNFα, in cachexia triggers both high energy expenditure and muscle loss [7]. In fact, injection of TNFα-expressing tumor cells causes cachexia, while this is not the case for cells that do not express the cytokine [129]. TNFα inhibits both adipocyte and myocyte differentiation, stimulates lipolysis, impairs insulin signaling, influences food intake, and directly causes muscle atrophy [7,79,130]. It has also been shown to activate an intracellular futile substrate cycle between fructose 6-phosphate and fructose 1,6-bisphosphate, creating an energy sink [71]. Intracerebroventricular administration of TNFα induces body weight loss and brown AT stimulation [131]. In a recent retrospective cohort study with weight-losing patients, a SNP in the TNF gene was newly associated with weight loss and a low skeletal muscle index in cachexia [132]. SNPs in the genes influencing levels of other cytokines, such as IL-1β, IL-6, and IL-10, are associated with cachexia in pancreatic and gastric cancer [133]. Circulating IL-6 levels correlate with weight loss and survival in patients with cancer [7], and IL-6 has been shown to stimulate acute phase response in the liver [134]. In summary, inflammation influences energy expenditure on the level of most organs and cells and is therefore of central importance for cachexia development. In fact, hypermetabolism is commonly associated with inflammation in all forms of cachexia, be it cachexia associated with chronic kidney disease [135], AIDS [136], burn injury [137], rheumatism [138], or cancer [7,139].

non-small-cell lung cancer clearly demonstrated anorexia as determinant of circulating ghrelin levels [33]. However, opposite to fasting, the increased ghrelin levels in cachexia fail to induce appetite and energy storage, potentially hinting to ghrelin resistance in these patients [31]. Resistance to ghrelin action has been confirmed in cachectic rats [34].

Nonetheless, ghrelin has proven effective against both tumor- and chemotherapy-induced cachexia in mice, acting directly on muscle cells to prevent atrophy by reducing inflammation, p38/CEBP-β/myostatin, and activating Akt, myogenin, and myoD [35,36]. Ghrelin increases the energy intake in cancer patients with impaired appetite [37], and a large body of evidence from clinical trials now highlights the positive effect of ghrelin on patients with cachexia, in particular with regard to growth hormone plasma levels, weight gain, increases in lean mass, and reductions in loss of adipose tissue [38]. Anamorelin, a ghrelin receptor agonist with anabolic and appetite-enhancing activities, has successfully been tested in phase 3 studies in the treatment of non-small-cell lung cancer, where it ameliorates body weight and symptom burden [39]. It should be noted however that handgrip strength was unaltered in these studies.

Other gut hormones, GLP-1 and GIP, have less well-defined roles in cachexia, despite their profound influence on metabolism. GLP-1 promotes insulin secretion and has been extensively explored for the treatment of metabolic diseases such as obesity and type 2 diabetes. Altered glucose homeostasis and insulin sensitivity/insulin secretion have also been shown in cachexia [40], so a role for GLP-1 is likely. Indeed, the GLP-1 agonist and insulin sensitizer exendin-4 partially prevents cachexia in tumor-bearing rats [41]. Recent evidence further suggests that brainstem GLP-1 signaling influences body weight loss and lean/fat mass in cachectic rodents [42]. As for GIP, its plasma levels decrease in cachexia in rheumatoid arthritis patients [43]. Thus, gut hormones may be further explored for cachexia therapy in the future.

Bile acids as metabolic regulators

Bile acids (BA) are not only important for digestion and fat absorption but are also involved in the regulation of appetite and food intake, and plasma BA levels positively correlate with BMI, at least in obese patients [44]. BA administration has been shown to suppress appetite in patients with a high BMI, yet plasma BA levels are negatively correlated with cognitive restraint of eating in obese patients [44]. The high plasma BA levels in obesity may thus represent a compensatory mechanism to prevent further overeating. Treatment of healthy volunteers with the BA taurocholic acid dose dependently stimulates the secretion of GLP-1 and PYY and increases the feeling of fullness [45]. In mice, the administration of BA increases energy expenditure in brown adipose tissue and prevents obesity and insulin resistance upon high fat diet feeding [46]. Mechanistically, BA induce energy expenditure by promoting intracellular thyroid hormone activation via D2, which converts inactive T4 into active T3. In the study by Watanabe *et al*, brown adipose tissue D2 levels and activity are induced by BA treatment. The BA effects on D2 and subsequent increase of oxygen consumption are mediated by the G protein-coupled receptor TGR5. The BA-D2-TGR5 axis and positive effect on energy expenditure are also apparent in human primary myoblasts [46].

Opposite to what one might expect from these studies, plasma BA levels seem to be decreased rather than elevated in cachexia, at least in mice [47]. The fat malabsorption seen in patients with cardiac cachexia further hints toward lower BA levels in wasting [11]. Accordingly, the BA ursodeoxycholic acid has been successfully used to improve tissue loss in animals with progressive weight loss in the Yoshida hepatoma model of cancer cachexia, albeit to a low extent [48]. Thus, the role of BA in regulating energy expenditure and food intake in the wasting pathology is not fully elucidated yet. It is conceivable that the composition of BA rather than total levels may be important for regulation of appetite and energy expenditure. This is further supported by a study by Roberts *et al* showing the correlation between GLP-1 and ghrelin levels with a range of different BA. In response to a test meal in healthy patients, the levels of the BA glycochenodeoxycholic acid and glycodeoxycholic acid correlate positively with plasma levels of the anorexigenic GLP-1, while the orexigenic ghrelin correlates negatively with taurochenodeoxycholic acid and taurodeoxycholic acid [49]. In the context of cachexia, BA have shown limited potential under the tested circumstances so far. Thus, further studies are needed to fully understand the contribution of bile acids to energy metabolism in wasting diseases.

Dysfunctional peripheral handling of energy substrates

Energy dissipation through futile cycles in the liver

The liver as a highly metabolic organ contributes to energy wasting through metabolic futile cycles (Fig 2). This is true under both physiological and pathological conditions, such as in glycogen storage diseases, end-stage liver diseases, and cachexia. Futile cycles are

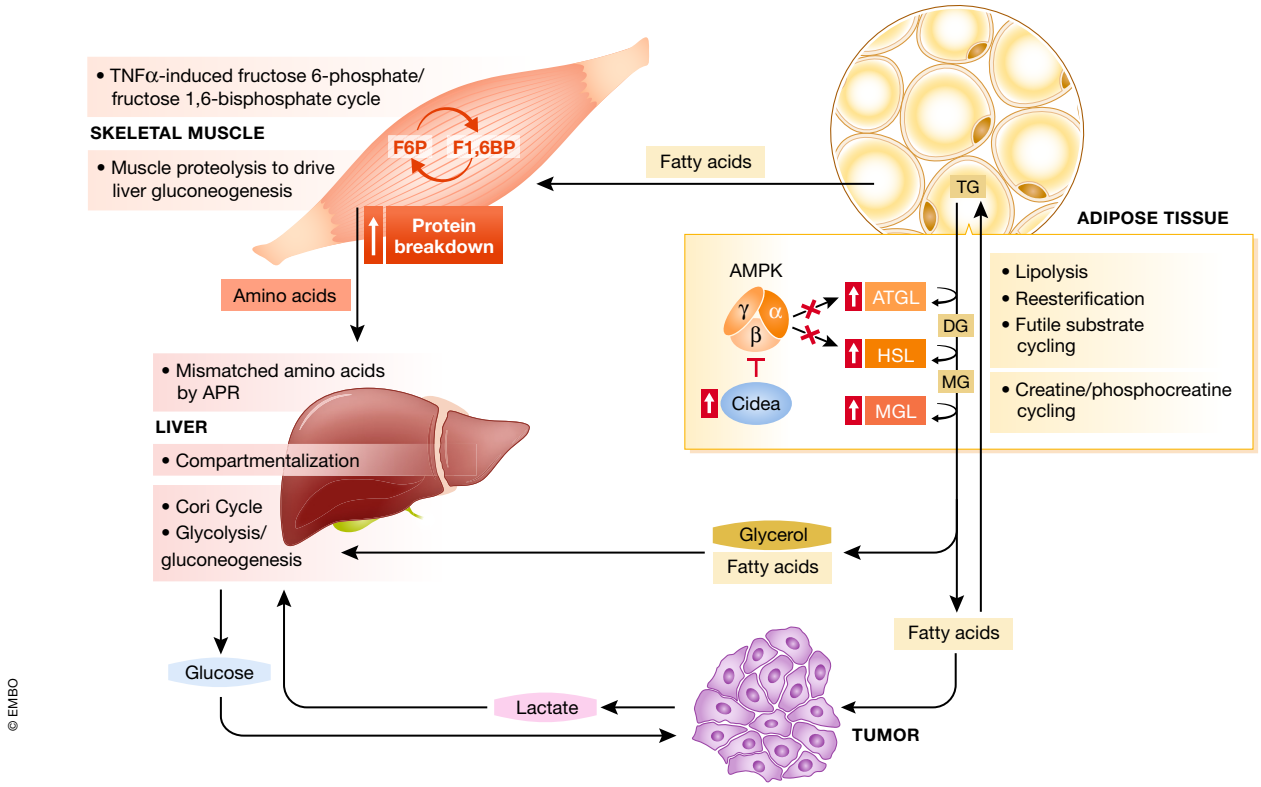

Figure 2. Overview of inter- and intra-organ futile energy-wasting cycles.
Futile cycles are mechanisms to regulate and fine-tune metabolic processes under physiologic conditions. In muscle, adipose and liver, futile cycling is increased in cachectic conditions, and released metabolites are involved in inter-organ cycles.

substrate cycles that dissipate energy without any anabolic or catabolic function. Futile cycles affecting the liver can be found in glycolysis/gluconeogenesis, where both pathways operate even under high glucose concentrations [50]. Glycolytic products such as lactate remain constant not through pausing of glycolysis but rather through equal rates of lactate production and removal. The use of anaerobic muscle derived lactate by the liver through gluconeogenesis for glucose production is part of a large substrate cycle known as the Cori cycle. This is particularly evident in cancer patients, where lactate derived from tumors is reconverted to glucose via hepatic gluconeogenesis in a very energy consuming futile cycle that accounts for a big portion of energy loss [51]. Hepatic gluconeogenesis can also be fueled by amino acids derived from muscle protein degradation [52,53]. It has further been suggested that energy is dissipated in a futile cycle initiated by mismatched amino acid composition originating from the liver acute phase response [54], which is activated in cachexia [55].

Interestingly, mathematical modeling of a genome-wide human metabolic network revealed high amounts of futile cycles in humans, which highlight the importance of compartmentalization present in eukaryotes [56]. These cellular compartments include cytosol, ER, Golgi apparatus, lysosomes, mitochondria, nucleus, and peroxisomes. Substrate cycles that employ multiple compartments are known to participate in energy dissipation through transport reactions between the different cellular organelles. An example in carbon metabolism is the hexokinase/glucose-6-phosphatase reaction, where in the liver hexokinase is replaced by GK, which is regulated by GKRP. Under fasting, GKRP inactivates and sequesters GK in the nucleus to prevent futile cycles of glucose phosphorylation during gluconeogenesis [57]. Liver hexokinase activity is markedly increased in cachexia [52]. However, it is not completely clear whether the amount of futile cycles changes between healthy individuals and patients with metabolic disorders, since the mathematical model is a combination of multi-omics data without distinguishing the origin. It would be very interesting to construct two different mathematical models for healthy and disease conditions to compare the different metabolic fluxes and futile cycles in the two states.

Energy wasting in the liver under cachectic conditions leads to a reduction in the oxidative phosphorylation capacity of mitochondria due to an increase in mitochondrial cardiolipin content [58]. This is accompanied by an increase of TNFα resulting in enhanced expression of phosphatidylglycerolphosphate synthase [59], which mediates cardiolipin expression [60]. In addition, decreased usage of hepatic triglyceride stores has been demonstrated in cancer cachexia, due to enhanced expression of the transcriptional cofactors RIP140 [61] and TSC22D4 [62], leading to hepatic steatosis. Increased liver lipogenesis, as observed in cachectic rats, may further contribute to the hyperlipidemia [9]. Hepatic steatosis is a prerequisite of nonalcoholic fatty liver disease and is associated with sarcopenia or muscle loss [63], which also occurs in the majority of patients with chronic liver disease. Liver cirrhosis causes an imbalance in the metabolic rate, leading to increased energy

expenditure, insulin resistance, and increased fat turnover, resulting in a hypermetabolic state [64]. Apparently, an increase in blood ammonia levels induces skeletal muscle autophagy and up-regulation of myostatins [65,66]; however, the direct underlying molecular mechanisms are not understood. In summary, there seems to be a strong inter-organ relationship between liver and muscle under energy-wasting conditions.

There are still many open questions regarding the role of the liver for cachexia, as exemplified by other forms of energy wasting in the liver, such as glycogen storage diseases, rare human diseases caused by abnormalities in proteins that regulate the synthesis or degradation of glycogen. Liver glycogen storage diseases are mainly characterized by hypoglycemia and, when occurring during infancy, are associated with poor prognosis. The importance of cellular compartments, such as the ER and lysosomes, is evident in glycogen storage disease type 1 (von Gierke disease or G6Pase deficiency) as well as glycogen storage disease type 2 (Pompe disease). G6Pase is an ER resident protein that catalyzes the terminal reaction of glycogenolysis and gluconeogenesis by hydrolyzing G6P to glucose and phosphate [67]. Multiple transport systems exist to shuttle the different substrates in and out of the ER. Deficiency of G6Pase or any of the transporters causes an accumulation of glycogen in the cytosol and a swelling of the ER probably due to the accumulation of glucose-6-phosphate. Pompe disease is a lysosomal storage disease characterized by mutations in the GAA enzyme, which is responsible for the cleavage of α-1,4- and α-1,6-glycosidic bonds of glycogen leading to lysosomal accumulation of glycogen in particular in skeletal and cardiac muscle, but also in liver [68]. The relevance of the liver in this storage disease is emphasized by a liver-specific enzyme replacement therapy approach using AAV8 vectors for GAA transgene expression in mice with Pompe disease. Expression of GAA in liver resulted in GAA secretion from the liver and enhanced GAA activity in plasma and peripheral tissues, leading to the correction of glycogen accumulation not only in liver but also skeletal muscles, emphasizing the importance of tissue crosstalk between liver and muscle in this disease [69]. Given its importance for other metabolic diseases, surprisingly, cellular compartmentalization in cachexia has not been studied so far.

Skeletal muscle and cardiac muscle atrophy are hallmarks of cachexia

Skeletal muscle is a highly plastic tissue with the ability to adapt its structure and metabolism in response to different physiological stimuli. Under pathological conditions like cancer cachexia, several cues derived either from the host or tumor compromise muscle homeostasis, resulting in wasting and impairment of function and metabolism of this tissue. Being the main site of protein storage in the body, muscle both balances the metabolic demands of other organs and serves as a protein reserve for energy production, for example, during starvation. It is well established that inflammatory mediators including IL-1b, IL-6, or TNFα play a crucial role in muscle wasting, and recent studies have identified additional candidates like soluble proteins, exosomes, and metabolites that are associated with cachexia and potentially induce muscle atrophy [70]. TNFα has been shown to activate a futile cycle between fructose 6-phosphate and fructose 1,6-bisphosphate which acts as ATP sink for elevated glycolytic activity, leading to increased energy expenditure, heat production, and tissue wasting in C2C12 myotubes [71]. An inter-organ futile energy-wasting cycle is generated by increased muscle proteolysis and release of amino acids to sustain tumor protein synthesis and liver gluconeogenesis [52,53]. Efficiency is low when amino acids are used for energy production, and the removal of waste nitrogen building up during this process requires additional energy, profoundly altering the normal homeostatic energy balance and contributing to energy wasting in cachexia [51].

Although increased futile cycling in the muscle occurs and might contribute to wasting, it is probably not a major factor causing atrophy. Instead, muscle atrophy during cancer cachexia is induced by increased protein breakdown mediated mainly by the activation of the UPS [72] and the autophagic–lysosomal system [73]. In the UPS, the 26S proteasome complex recognizes the substrates covalently attached to a chain of ubiquitin molecules for breakdown [74]. Many classes of enzymes (E1, E2, and E3) are involved in protein ubiquitination, but the E3 ubiquitin ligases are rate-limiting for the ubiquitination process and are well-known markers of UPS activity [74]. MuRF1 and Atrogin 1 were the first E3-ligases identified and are considered master markers of muscle atrophy. These E3-ligases are strongly upregulated in some mouse models of cancer cachexia [75–77]. MuRF1 is involved in the ubiquitination and degradation of muscle structural proteins including beta/slow MHC, MHCIIa, actin, myosin binding protein C and myosin light chains 1 and 2, and troponin I [74]. Atrogin 1-induced atrophy is mediated by degradation of eIF3f, which suppresses S6K1 activation induced by mTOR as well as MyoD breakdown [78], blocking differentiation and inhibiting myotube formation. These data might partially explain the reduced protein synthesis [74] and impaired muscle regeneration in atrophic muscle during cancer cachexia observed in previous studies [79,80]. Importantly, mice lacking Atrogin 1 [81] and MuRF1 [75] are partially protected from fasting- and denervation-induced muscle wasting, respectively. Current studies have shown the involvement of newly emerged E3-ligases TRAF6 [82] and MUSA1 [83] as potential targets of cachexia in rodent models of muscle atrophy. However, whether or not these E3-ligases spare muscle loss in cachexia still needs to be investigated.

Autophagy is an evolutionarily conserved process involved in the degradation of target cytoplasmic materials in a lysosome-dependent manner. Autophagy is activated during starvation, where its role is to recycle intracellular components to maintain mitochondrial metabolic function, thereby maintaining energy homeostasis. The recycled material can thus be seen as a cellular nutrient store which is released upon activation of autophagy. Although lysosome-dependent proteolysis has been shown to be activated in muscle cells during catabolic conditions several years ago [84–86], only in the last few years enhanced autophagy has been found in muscle [73] and heart [87] of tumor-bearing animals. As previously observed in atrophic models of muscle denervation or starvation [84,85], autophagy also plays a role in muscle atrophy in Apc(Min/+), C26 [73], and Lewis Lung Carcinoma tumor-bearing mice [86]. Reinforcing the role of autophagy in muscle atrophy, Penna *et al* [73] have observed that this proteolytic pathway was induced in muscle of three different models of cancer cachexia as well as in glucocorticoid-treated mice. Further, several autophagy markers such as Atg5, Beclin1, and Gabarap are induced in skeletal muscle of cachectic patients affected by pancreatic cancer, esophageal cancer, and gastric cancer [88,89]. There is conflicting evidence to whether or not cancer cachexia affects fiber type composition [90].

As often the case in this field, this can partly be explained by the criteria employed to define cachexia. Several studies have shown a predominant loss of type II fibers under different wasting conditions and in cachectic mouse models [90]. Interestingly, type II skeletal muscle fiber atrophy associated with altered autophagy is also observed in atrophic conditions induced by Pompe disease, fasting, and sarcopenia [91]. The relative preservation of the slow-twitch oxidative type I fibers potentially reflects the body's attempt at conserving energy. Taken together, these results demonstrate that autophagy, either excessive or defective, contributes to the complicated network that leads to muscle atrophy during cachexia [73].

Beyond the induction of UPS and autophagy, excessive muscle fatty acid oxidation has been demonstrated as a driver of muscle atrophy in a mouse model of kidney cancer [92]. Cachectic kidney cancer cell lines secret a cocktail of inflammatory factors that rapidly lead to high levels of fatty acid oxidation and activation of a p38 MAPK-response signature in skeletal muscles, which precedes the manifestation of atrophy [92]. Interestingly, the *in vitro* and *in vivo* pharmacological blockage of fatty acid oxidation rescues the muscle atrophy induced by kidney cancer cells [92], suggesting a possible crosstalk between adipose tissues and skeletal muscle. Aberrant fatty acid metabolism might also be involved in cardiac atrophy induced by C26 tumor-bearing mice. Importantly, this study by Schäfer *et al* [93] has identified a signature panel of "cachexokines" including Ataxin-10 which are sufficient and necessary to trigger the aberrant fatty acid metabolism and cardiac atrophy. Ataxin-10 serum levels are also elevated in cachectic cancer patients and might be a potential target to treat heart wasting [93]. Since cachectic patients in advanced cancer stages often become intolerant to anticancer therapies, and those with severe wasting of skeletal muscles and cardiac muscle often die prematurely due to respiratory and cardiac failure, identification of extracellular triggers or intracellular mediators of muscle wasting might be critical for the treatment of cancer cachexia and prolong the rate of survival.

Disturbed adipose tissue energy handling

White adipose tissue

The major role of the white adipose tissue is to store energy as fat, a storage form approximately sixfold more efficient than carbohydrates due to fat's hydrophobic nature. Complete oxidation of fatty acids yields about 9 kcal/g, while carbohydrates and proteins yield about 4 kcal/g. When needed, as upon exercise or after prolonged fasting, energy is mobilized from the adipose tissue by triglyceride hydrolysis (lipolysis), releasing fatty acids and glycerol into the circulation for oxidation by other organs. Tumor-bearing animals show increased lipid utilization, and hence, adipose tissue is degraded [3]. Lipolysis is a sequential process orchestrated by three lipases, ATGL, HSL, and MGL. Elevated lipolysis is a characteristic of cachexia in both patients and rodent models [94,95], leading to adipose tissue wasting and elevated circulating free fatty acid levels [96]. Altered levels and/or activity of ATGL and HSL in white adipose tissue are causal for this [95,97]. Knockout of ATGL or HSL in mice partly protects against cancer-induced wasting [95]. Signal for the increased energy demand in fasting are catecholamines, and lipolysis can also be activated by cortisol, natriuretic peptides, and proinflammatory cytokines, while insulin inhibits lipolysis. Adipocytes isolated from cachectic patients show stronger catecholamine- and natriuretic peptide-induced lipolysis [98]. Weight-losing patients are also more sensitive to catecholamine signaling [99]. Transcriptome profiling of adipose tissue from gastrointestinal cancer patients with cachexia reveals pathways regulating energy turnover are upregulated [100]. Further, insulin resistance or reduced insulin secretion often occur in patients with cachexia [101], potentially preventing insulin from exerting its antilipolytic effect. The importance of insulin for adipose tissue integrity is emphasized by the severe lipodystrophy of mice lacking the insulin receptor specifically in adipose tissue [102]. In cachexia, lipolysis has been shown to be further activated by tumor-secreted ZAG, levels of which are elevated in patients with cancer cachexia, contributing to weight loss in patients with cancer [103,104]. Similar to lipolytic hormones, ZAG binds to a β3-adrenergic receptor and stimulates adenylyl cyclase in a GTP-dependent process [105]. Inflammatory cytokines such as TNFα or IL-6 contribute to adipose loss both by directly activating lipolysis and by impairing insulin sensitivity [1,106].

Glycerol released from adipose tissue during lipolysis can serve as a substrate for gluconeogenesis in the liver, leading to an energy-wasting effect as part of futile substrate cycling. Fatty acids generated during lipolysis are mostly distributed to other organs for energy usage, but some are also re-esterified to triglycerides during lipogenesis in the adipose tissue, again creating a futile cycle (Fig 2). Adipocyte lipogenesis has indeed been shown to increase in cachexia [97,107]. With both lipolysis and lipogenesis induced upon stimulation by tumor-secreted factors, enhanced substrate cycling occurs. This is an energy costly process, creating an enhanced energy demand which, in light of the undersupply frequently occurring in cachexia, is seldom met and contributes to adipose tissue wasting. Indeed, intracellular ATP levels are low in cachectic adipocytes [97]. The enhanced lipolysis–lipogenesis futile cycling is mediated by impaired signaling through AMPK, activity of which is reduced in cachectic adipose tissue [97]. Interestingly, as shown by Mulligan *et al*, *de novo* lipogenesis occurs not only in adipose tissue but also in kidney and liver of cachectic mice. This may result in reduced glucose availability and hence loss of utilizable carbohydrate energy, further favoring catabolism by increasing overall energy requirements [107].

Brown and brite adipose tissue

While white adipose tissue serves mainly as energy storing organ, brown adipose tissue uses stored energy for heat production during thermogenesis, a highly energy costly process. Brown adipose tissue is found in cachectic mice and patients with cancer [108,109]. Catecholamine signaling in brown adipose tissue leads to expression of UCP1, causing heat generation by uncoupling oxidative phosphorylation from ATP production. Accordingly, catecholamine levels correlate with brown adipose tissue activity and BMI, also in humans [110]. Catecholamine signaling is enhanced in cachectic mice, but increased thermogenesis can be prevented by β-adrenergic blockade with propranolol [108]. Expression profiling of cachectic mice with colorectal cancer reveals alterations in key regulators of lipid accumulation and fatty acid β-oxidation, including increased UCP1 expression, indicative of active brown adipose tissue [111]. Brown fat activity also correlates positively with cancer stage when adjusted to ambient temperature [112]. Thus, there is ample evidence that brown adipose tissue is activated in various conditions of cachexia in mice and men.

It is estimated that humans possess up to 60 g brown fat, contributing to 15–25 kcal/day [113]. Other studies estimate the contribution of brown AT to total basal metabolic rate to be around 3–5% [114]. Considering the small overall amount of brown fat, it is thus questionable if this is sufficient to substantially contribute to increased energy expenditure and wasting. In contrast, skeletal muscle accounts for up to 40% of body weight, accounting for 20–30% of total resting energy expenditure [115].

In addition to classical brown adipose tissue, white adipose tissue can contain varying amounts of brite ("brown in white") adipocytes that are thermogenically active. Patients with pheochromocytoma (catecholamine-secreting tumors) display white-to-brown fat conversion as indicated by elevated UCP1 staining of the omental adipose tissue [116]. Unfortunately, no observations regarding body weight or energy expenditure were made in this study. Increased UCP1 mRNA and protein levels are also described in both patients and mice with cachexia [117,118], as is increased energy uptake, measured by oxygen consumption rate but also heat generation. IL-6 was identified as one of the drivers for this browning effect [106,117].

While multiple lines of evidence suggest that brite fat-induced thermogenesis contributes to increased energy expenditure in cachexia [106,117–120], there is also data questioning the prominent role of browning for adipose and body wasting. Brown or brite adipose tissue thermogenesis contributes to the body's ability to defend against cold temperatures, so more brown/brite AT would suggest elevated body temperature or cold tolerance. However, in temperature preference studies, mice carrying tumors select a higher ambient temperature than mice without tumors, indicating elevated cold stress in tumor-bearing mice [121]. Further, cachectic Apc (Min/+) mice experience a gradual decline in body temperature during development of body wasting [17]. Finally, mice housed at thermoneutrality develop cachexia exactly parallel to mice housed at room temperature (a mild cold stress activating brown/brite AT) [97]—in contrast, tumor growth and inflammation are aggravated by housing at room temperature [121]. While increased AT UCP1 levels are recorded for several murine and human cancers [106,117–120], this is not consistently seen, as some reports demonstrate unchanged or even reduced adipose UCP1 levels [97,122]. Mice lacking UCP1 are not protected from cachexia development or adipose tissue loss, questioning the prominent role of browning for wasting [97]. Further, 6-hydroxydopamine-induced adrenergic blockade does not protect from tumor-induced AT wasting [97]. However, other, UCP1 independent energy dissipation mechanisms have been described in brite fat, albeit not in the context of cachexia so far. These include activation of creatine/phosphocreatine cycling [4], and ATP-dependent Ca^{2+} cycling [123], again emphasizing the importance of cellular compartmentalization for energy homeostasis. Thus, to further clarify the role of adipose tissue it will certainly be helpful to gain further insights into futile energy-wasting cycles, quantify the capacity of brown/brite fat activation to increase whole-body energy expenditure, and to quantify its contribution to wasting in patients with cachexia.

Future directions

The present review discusses pathways in which energy metabolism is at fault under pathologic wasting conditions, be it through altered energy uptake or energy dissipation for example by inter-organ or intracellular futile cycles. Many of the presented studies show increased energy expenditure in cachexia. It is thus surprising that a large systematic literature review of domains associated with involuntary weight loss in cancer shows no correlation between energy expenditure and weight loss [124]. Indeed, after correction for changes in body composition, no alterations in energy expenditure are observed in patients with pancreatic cancer [125]. Likewise, in cachectic mice, even with severe cachexia, increased energy expenditure is not always seen [97], or only after dividing oxygen consumption by body weight, which is arguably lower in cachexia.

This may indicate a compensatory decrease in energy expenditure in response to poor caloric intake. Indeed, in a pilot study with 10 subjects, intensive, biometric parameter-oriented dietary counseling was sufficient to improve cachexia and prolong life in cachectic cancer patients [126]. However, meta-analyses have largely failed to show an improvement of mortality due to nutritional intervention [127], partially due to low compliance to the therapeutic intervention [128]. This overall suggests that even behavioral and/or psychological aspects have to be considered in order to improve metabolic dysfunction as associated with metabolic wasting.

While research over the past years has provided significant progress in our understanding of peripheral wasting mechanisms (Fig 1), the system-wide integration of site-specific contributions to organismal energy remains a grand challenge for future research and therapy development. This relates in particular to the

Box 2: In need of answers

As of now, we are still lacking an effective treatment regime against cachexia. Why is this the case? The often large discrepancies between studies demonstrate that we are facing the challenge of better defining or standardizing cachexia criteria, as even for clinical trials the readout is not always clear. Despite enormous improvement in recent years, this is still in its infancy. We further need better ways to measure and standardize energy expenditure in both mice and patients to understand at which point energy is wasted and when normal metabolism and futile cycling spirals out of control to cause cachexia. Investigating other diseases such as glycogen storage diseases in the liver, or cellular processes such as futile metabolic cycles or trafficking between cellular departments, where energy is lost, may help us uncover novel, targetable mechanisms of cachexia. We may also learn from other metabolic disorders: given the remarkable effect of gut hormones and their use in obesity, it is surprising that their role in cachexia is not more pronounced according to current studies, and the roles of microbiota or bile acids in wasting disorders are not well understood yet. Also, organ crosstalk, for example, by adipokines, myokines or reactive metabolites, needs to be better addressed in the future. As often the case in obesity, nutritional intervention also in cachexia is less effective than one should think, partly due to poor compliance. Malabsorption may pose an additional problem, in particular in patients with gastrointestinal cancers, where systemic and primary tumor effects cannot always be separated. Some studies show improved cachexia in parallel with a reduced tumor growth, suggesting the cancer cell metabolism, i.e., Warburg effect, also plays a critical role for the wasting. Yet other studies show wasting completely independent of tumor size. Are these different states still representations of the same disease, or do we have to start looking at different subtypes of cachexia depending on the tumor entity? Likely, there will be no single cure but combinatorial approaches to better treat cachexia in the future.

identification of common therapeutic targets between distinct wasting disorders as well as between distinct tumor entities.

In addition, the contribution of the brain-periphery axis to systemic wasting (beyond appetite control) has been largely ignored up to date but will definitely provide critical insights into integrative wasting mechanisms.

Given the remarkable similarity in metabolic phenotypes between obesity and metabolic wasting, addressing the abovementioned neglected areas as well as improving technical approaches to reliably determine energy expenditure particularly in humans will represent important research avenues for the years to come. It can be envisaged that key mechanisms in wasting disorders might eventually be used in anti-obesity therapies and vice versa, thereby further highlighting the necessity to intensify biomedical research and translation in wasting disorders in the future.

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Conflict of interest

The authors declare that they have no conflict of interest.

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