OPINION

# Cancer cachexia: understanding the molecular basis

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Abstract | Cancer cachexia is a devastating, multifactorial and often irreversible syndrome that affects around 50–80% of cancer patients, depending on the tumour type, and that leads to substantial weight loss, primarily from loss of skeletal muscle and body fat. Since cachexia may account for up to 20% of cancer deaths, understanding the underlying molecular mechanisms is essential. The occurrence of cachexia in cancer patients is dependent on the patient response to tumour progression, including the activation of the inflammatory response and energetic inefficiency involving the mitochondria. Interestingly, crosstalk between different cell types ultimately seems to result in muscle wasting. Some of the recent progress in understanding the molecular mechanisms of cachexia may lead to new therapeutic approaches.

Etymologically, cachexia is a term originating from the Greek, *kakos* and *hexis*, meaning 'bad condition'. Although in the last few years several definitions of cachexia have appeared[1,2], a certain consensus[3] indicates that they all share two common factors: weight loss — mainly from loss of skeletal muscle and body fat — and inflammation. Therefore, the main symptoms that are associated with cachexia in cancer patients are related to these factors and involve asthenia, anorexia, anaemia and fatigue — altogether, contributing to a reduced quality of life. From all of the different definitions of cachexia, one concept becomes very clear: it is a multifactorial syndrome involving changes in several metabolic pathways, in many tissues and organs. It is well accepted that cachexia is indirectly responsible for the death of at least 20% of all cancer patients[4]. The incidence of the syndrome among cancer patients is very high, although it varies by tumour type; in patients with gastric or pancreatic cancer, the incidence is more than 80%, whereas approximately 50% of patients with lung, prostate or colon cancer are affected, and around 40% of patients with breast tumours or some leukaemias develop the syndrome[5-6].

Despite several attempts to classify and stage patients with cancer-induced cachexia[7–10], the only methodology available that provides a quantitative approach involves the use of the so-called CAchexia SCOre (CASCO)[11], which has recently been validated[12]. The staging of cachectic cancer patients is an important aspect of the syndrome, as the design of the appropriate treatments depends on the degree of cancer cachexia. Although several blood biomarkers for cancer cachectic patients have been suggested, they are far from being universal and applicable to all patients. They include tumour-derived compounds[13], inflammatory cytokines[14,15], acute-phase proteins[16], and skeletal muscle degradation markers[17].

As a result of both the presence of the tumour and the patient's treatment (chemotherapy or radiotherapy), the need to maintain homeostasis forces important metabolic changes involving carbohydrate, lipid and nitrogen metabolism (FIG. 1). These changes are linked with the need to maintain glycaemia and to sustain, at the same time, tumour growth. Indeed, tumours consume very large amounts of glucose and amino acids, particularly glutamine[18]. Insulin resistance and other hormonal changes, such as increased levels of glucagon and glucocorticoid in plasma, are also present in cancer patients[18]. While these are clearly compensatory mechanisms to protect the homeostasis of the patient, some of these metabolic changes are actually harmful for the patient — a 'double-edged sword' — and result in metabolic inefficiency and wasting.

This Opinion article focuses on the molecular mechanisms underlying the cancer cachexia syndrome; rather than concentrating on possible therapies, this article concentrates on cachexia as an energy-wasting syndrome that leads to muscle wasting and atrophy. Special emphasis is given to the inflammatory response to tumour growth, which seems to be the trigger of many metabolic changes associated with the syndrome. This Opinion article also focuses on the role of the different cell types that make cachexia a multi-organ syndrome. At present, when cancer rates (and therefore the number of cachectic patients) are increasing, it seems particularly appropriate to analyse the different metabolic adaptations that are involved in cancer, with the aim to facilitate the development of a more focused therapeutic approach.

## Cachexia as an energy-wasting syndrome

Cachexia is a type of energy balance disorder, in which energy intake is decreased and/or energy expenditure is increased. The different contribution of the two components — intake or expenditure — of the energy balance depends on the tumour type and its growth phase. Although alterations of energy intake are often associated with cachexia, increased resting energy expenditure is a possible cause of the wasting syndrome. Thus, patients on total parenteral nutrition — and therefore with a perfectly controlled energy intake — still lose weight and suffer from cachexia symptoms[19] that are associated with different types of pathological conditions, including cancer.

Different types of molecular mechanisms contribute to energy expenditure and, therefore, involuntary body weight loss. First, increased futile cycle activity is observed and contributes to energetic inefficiency. One example of this is the lactate recycling that is associated with the 'Cori cycle' between the liver and the tumour mass (FIG. 1). Another futile cycle takes place within the mitochondria and is responsible for the recycling of protons; this cycle could be activated in cancer as a consequence of uncoupling. Second, a study involving the mouse Lewis lung carcinoma model suggests that mitochondrial ATP synthesis in skeletal muscle is decreased in cancer[20]. Indeed, the proton electrochemical gradient between the external and internal mitochondrial membrane that drives mitochondrial ATP synthesis is disrupted through the activation of the so-called uncoupling proteins (UCPs) (FIG. 2). The activity of different UCPs has been shown to be increased in skeletal muscle (UCP2 and UCP3) and brown adipose tissue (BAT) (UCP1) in both experimental animals and human subjects affected by cachectic tumours[21–23]. This phenomenon is linked with mitochondrial uncoupling of oxidative phosphorylation. Indeed, we have recently

shown that this is the case in mice bearing cachectic Lewis lung tumours[24]. Third, in addition to uncoupling, there are other important abnormalities in skeletal muscle mitochondria that occur in cancer patients, such as decreased oxidative capacity[25,26], disrupted protein synthesis[27], changes in membrane fluidity[25] and oxidatively modified mitochondrial proteins[28]; all of these result in impaired mitochondrial function.

Some of the above-mentioned alterations could well be attributed to an increased production of peroxisome-proliferator-activated receptor-γ co-activator 1α (PGC1α), which has been observed in skeletal muscle of mice bearing the Lewis lung carcinoma[29]. Indeed, this protein seems to have a major role in regulating mitochondrial biogenesis by upregulating nuclear respiratory factors and the mitochondrial transcription factor A (TFAM)[30]. In addition, cytokines such as tumour necrosis factor-α (TNFα; generated as a consequence of high tumour burden) activate p38 MAPK, which results in stabilization and activation of PGC1α[31]. Overexpression of PGC1α causes increased respiration and expression of genes linked to mitochondrial uncoupling and energy expenditure[32].

Both mitochondria and sarcoplasmic reticulum (SR) share a key role in muscular function. Thus, $Ca^{2+}$ released from SR stimulates mitochondrial ATP production contributing to increased energy demand during muscle contraction, a process known as excitation–contraction coupling; whereas functionally intact mitochondria inhibit undesired localized SR $Ca^{2+}$ release by controlling the local redox environment of the calcium release units[33]. Thus, bidirectional SR–mitochondrial communication provides a powerful local control mechanism for integrating $Ca^{2+}$ release and reuptake and ATP utilization during muscle contraction with ATP production and skeletal muscle bioenergetics[34]. During cachexia, an increase in the activity of SR $Ca^{2+}$ pumps (SERCA) occurs[35]; these pumps promote energy inefficiency as they consume ATP associated with $Ca^{2+}$ export to the cytosol and generate $Ca^{2+}$ overload. In addition, the gene expression of mitofusin 2 (*Mfn2*) is increased in skeletal muscle of rats during cancer cachexia[36]. MFN2 is a mitochondrial protein that is involved in the regulation of mitochondrial morphology. In addition, MFN2 is related to the interactions between SR and mitochondria — it tethers SR to mitochondria — which control interorganellar $Ca^{2+}$ signalling; MFN2 also has a key role in SR morphology. Moreover, the SR–mitochondrial connection that is promoted by MFN2 predisposes mitochondria to $Ca^{2+}$-overloading, eventually leading to apoptosis by excessive $Ca^{2+}$ transfer. Furthermore, it is known that PGC1α participates in the stimulation of MFN2 expression under various conditions characterized by enhanced energy expenditure[36]. Hence, in cachexia the overexpression of PGC1α can activate MFN2 expression, thus leading to a $Ca^{2+}$ deregulation, which is intimately associated with muscle wasting.

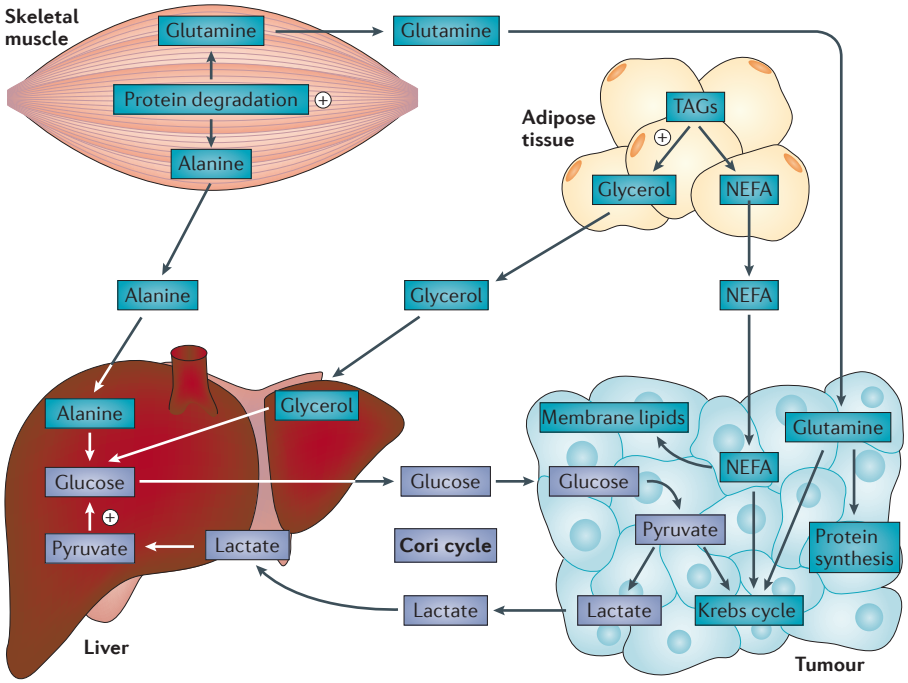



Figure 1 | **Main metabolic adaptations associated with tumour burden.** During tumour growth, substantial metabolic alterations take place in cancer patients. Thus, protein degradation is stimulated in skeletal muscle, which results in a massive amino acid efflux to the circulation. Therefore, a flow of nitrogen (mainly in the form of alanine) from skeletal muscle reaches the liver, where this amino acid is used to sustain gluconeogenesis and also the synthesis of acute-phase proteins. Glutamine is also exported from the muscle and used mainly in the tumour as a nitrogen donor for the synthesis of both protein and DNA. The tumour, depending on the availability of glucose, can also oxidize some glutamine. Adipose tissue mass is reduced owing to the activation of lipases, which participate in the lipolytic breakdown of triacylglycerols (TAGs), which produces both non-essential fatty acids (NEFAs) and glycerol. Glycerol can also be used to sustain liver gluconeogenesis while the NEFAs are used by the tumour mass, albeit at very low levels. Instead, tumour cells use huge amounts of glucose and thereby generate lactate, which is then exported to the circulation. The liver also uses lactate as a gluconeogenic substrate, partly to compensate for the acidosis associated with lactate production. The recycling of lactate constitutes a 'Cori cycle' (shown in purple) between the liver and the tumour, which is linked with high energetic inefficiency, as the conversion of glucose into lactate by the tumour generates much less ATP than the amount required to produce glucose from lactate. Circled "+" symbols indicate pathways that are activated during cachexia.

## Muscle wasting and atrophy

Cancer cachexia is invariably associated with muscle wasting and atrophy. Loss of myofibrillar proteins in muscle cells[37] (BOX 1) is of key relevance in cancer cachexia, as it results in muscle weakness and fatigue. In fact, skeletal muscle loss is a very powerful prognostic factor, independent of the actual body weight loss[38]. Many metabolic alterations are responsible for the loss of muscle mass[39]. Thus, abnormalities in protein (synthesis and degradation) and amino acid metabolism (transport and branched-chain amino acid oxidation) are seen in the cachectic muscle (FIG. 2a). Furthermore, an increase in apoptosis and an impaired capacity for regeneration contributes to muscle wasting. All of these alterations clearly contribute to the negative nitrogen balance observed in the skeletal muscle of cancer patients. In fact, in addition to tumour burden, some of these alterations may be a consequence of cancer treatment — mainly chemotherapy[40]. The pathway that seems to be most involved in the wasting process is protein degradation

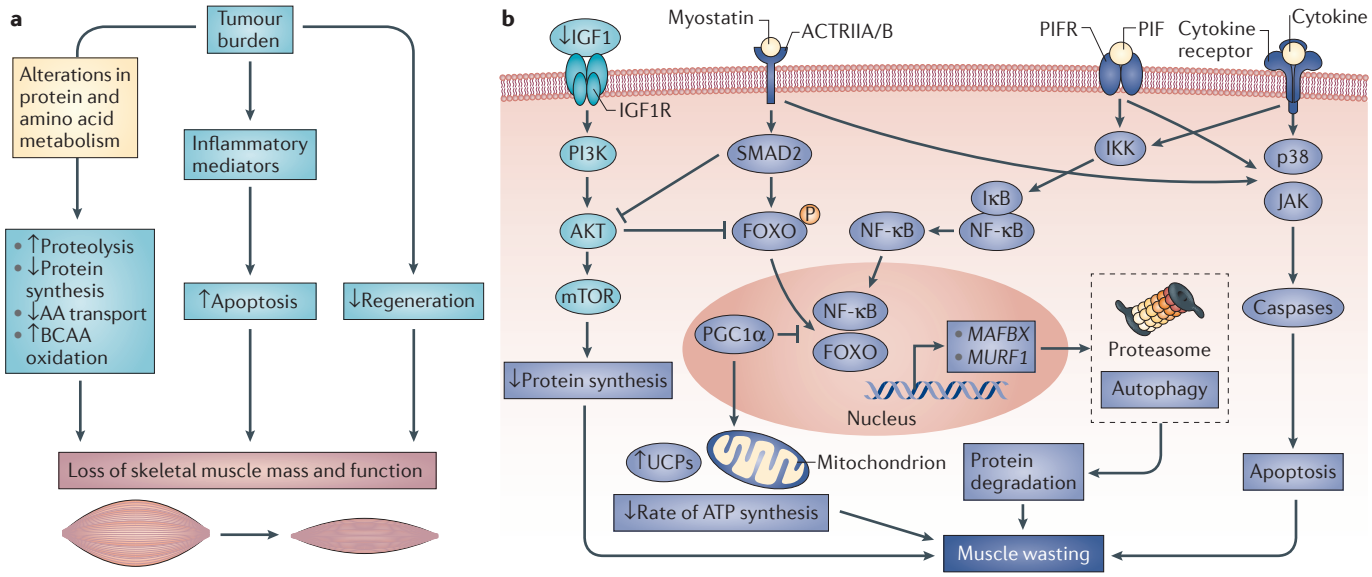



Figure 2 | **Skeletal muscle wasting during cachexia.** **a** | Alterations in metabolic pathways, apoptosis and regeneration. Muscle wasting involves alterations in protein and amino acid (AA) metabolism, together with activation of apoptosis and decreased regeneration. All of these alterations are linked with inflammation. **b** | Intracellular signals that participate in skeletal muscle wasting. Many intracellular signals are activated (shown in purple) by inflammatory mediators (such as cytokines and myostatin) and tumour-derived factors (such as proteolysis-inducing factor (PIF)). Basically, cytokines and PIF increase protein degradation via nuclear factor-κB (NF-κB) by activating forkhead (FOXO) family transcription factors; this allows for the increased transcription of genes encoding ubiquitin ligases (muscle atrophy F-box protein (MAFBX) and muscle RING finger-containing protein 1 (MURF1)) that are involved in the proteolysis of myofibrillar proteins. The same mediators (PIF and cytokines) can also activate the p38 and Janus kinase (JAK) MAPK cascades leading to increased caspase activity and, thus, apoptosis. Insulin-like growth factor 1 (IGF1) normally promotes protein synthesis via AKT and mTOR; a decrease (shown in blue) in IGF1 during muscle wasting suppresses protein synthesis. Myostatin can also decrease protein synthesis (through AKT via SMAD2) and activate both protein degradation (via FOXOs) and apoptosis — through the MAPK cascade. Overexpression of peroxisome-proliferator-activated receptor-γ co-activator 1α (PGC1α) causes increased respiration and expression of genes linked to mitochondrial uncoupling and energy expenditure (such as uncoupling proteins (UCPs)). ACTRIIA/B, activin receptor type IIA/B; BCAA, branched-chain AA; IGF1R, IGF1 receptor; IκB, inhibitor of NF-κB; IKK, IκB kinase; P, phosphorylation; PIFR, PIF receptor.

that is mediated by the activation of the ubiquitin-dependent proteasome pathway[41]. However, intact myofibrillar proteins seem to be degraded by mechanisms upstream of the ubiquitin–proteasome pathway to allow for the release of myofilaments from the myofibrils and the subsequent ubiquitylation and proteasome-dependent degradation of myofilaments. One such mechanism seems to be the calpain-dependent cleavage of myofilaments and proteins that anchor myofilaments to the Z disc[42,43]. Another mechanism that is involved in protein degradation is autophagy[44]. However, although blockade of the ubiquitin-dependent proteolytic system (for example, using the proteasome inhibitor bortezomib) has been shown to preserve muscle[45], the blockade of autophagy during development results in muscle weakness and myofiber disorders[46].

Many intracellular signals are involved in protein turnover and, therefore, in the wasting process[47] (FIG. 2b). Thus, inflammatory cytokines that are secreted by either immune cells or tumours directly induce signalling pathways that upregulate enzymes inducing skeletal muscle protein turnover. On the one hand, pro-inflammatory and pro-cachectic cytokines such as TNFα or interleukin-1 (IL-1) are involved in two established pathways, the nuclear factor-κB (NF-κB) pathway and the p38 MAPK pathway. These mediators induce an upregulation of the expression of the key E3 ligases — muscle RING finger-containing protein 1 (MURF1; also known as TRIM63) and muscle atrophy F-box protein (MAFBX; also known as atrogin 1 and FBXO32) — which mediate structural muscle protein breakdown and inhibition of protein synthesis[48]. MURF1 is responsible for facilitating the ubiquitylation of the thick filament of the sarcomere[49], as well as other thick filament components[50]. Thus, NF-κB inhibition results in a significant decrease in tumour-induced muscle loss, at least in experimental animals, in part, by blocking the upregulation of MURF1 (REFS 51,52). In addition to proteolysis, an impaired regenerative capacity of myogenic cells may also be involved in muscle wasting in cancer. Thus, paired box 7 (PAX7) — a protein involved in muscle regeneration — also participates in the decreased regenerative capacity and response to NF-κB[53].

In contrast to the pathways related to muscle atrophy are the ones that involve muscle hypertrophy. Understanding how muscles can reach hypertrophy not only contributes to the understanding of muscle development but also may provide clues for the design of anabolic therapies for skeletal muscle. Thus, insulin-like growth factor 1 (IGF1) signalling is perhaps the best-characterized mechanism for inducing hypertrophy. IGF1 activates insulin receptor substrate 1 (IRS1)–PI3K–AKT[54] signalling (FIG. 2b), and AKT induces protein synthesis by blocking the repression of mTOR. Moreover, AKT also phosphorylates the forkhead (FOXO) family of transcription factors. These have a key role in inducing transcriptional upregulation of MURF1 and MAFBX[55]. These transcription factors seem to be essential, as IGF1–AKT-mediated FOXO phosphorylation — followed by inhibition of FOXO transport to the nucleus — is sufficient to block the upregulation of the E3 ligases that participate in muscle proteolysis.

In addition to cytokines, protein degradation is increased and protein synthesis is decreased by the transforming growth factor-β (TGFβ)-family ligand myostatin through pathways involving the activation of the SMAD complex and by p38 and Janus kinase (JAK) MAPKs[56] (FIG. 2b). This results in activation of degradation-related gene expression and inactivation of protein synthesis. In addition, myostatin inhibits the myogenic programme, thereby resulting in a decrease of myoblast proliferation.

Recent studies have identified several microRNAs (miRNAs) that can modulate the muscle IGF1–AKT pathway[57]. A recent study by He *et al.*[58] describes a unique pathway involving lung cancer- and pancreatic cancer-derived microvesicles containing miR-21, which signals through the Toll-like receptor 7 (TLR7) to promote apoptosis of skeletal muscle cells. In addition to skeletal muscle wasting, miRNAs also seem to be involved in stimulating adipose tissue lipolysis[59], another feature that is characteristic of the cachectic state that is discussed further below.

## Adipose tissue wasting

In cancer cachexia, skeletal muscle loss is accompanied by a profound loss of white adipose tissue (WAT). The consistent dissolution of this white fat mass is the result of three different altered processes (reviewed in REF. 60). First, there is an increase in lipolytic activity, which results in an important release of both glycerol and fatty acids[60] (FIG. 1). The mechanism of increased lipolysis is associated with activation of hormone-sensitive lipase (HSL) in adipose tissue. In addition, in human cancer cachexia there is a decreased antilipolytic effect of insulin on adipocytes[60], together with an increased responsiveness to catecholamines and atrial natriuretic peptide, which stimulate lipolysis[60]. Second, an important decrease in the activity of lipoprotein lipase (LPL), the enzyme responsible for the cleavage of both endogenous and exogenous triacylglycerols (present in lipoproteins) into glycerol and fatty acids, occurs in WAT and, consequently, lipid uptake is severely hampered, as the activity of the enzyme allows for the entry of fatty acids into WAT. Third, *de novo* lipogenesis in adipose tissue is also reduced in tumour-bearing states in mice and humans, resulting in decreased esterification — as the availability of fatty acids for triacylglycerol synthesis is decreased — and, consequently, decreased lipid (triacylglycerol) deposition[60].

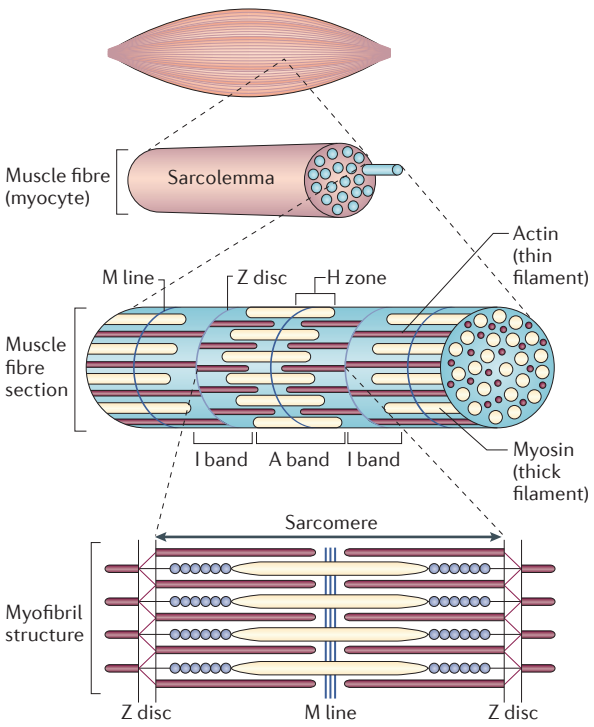
In adipose tissue, a clear interplay of adipokines and myokines in cancer has been shown[61], thereby supporting the importance of inter-organ signalling between skeletal muscle and adipose tissue[62]. From this point of view, Das *et al.*[63] found that genetic ablation of adipose triglyceride lipase in mice resulted in prevention of increased lipolysis and, therefore, prevention of the decrease in WAT mass that occurs during cancer. Ablation of HSL leads to similar but less marked effects[63]. Interestingly, decreased lipolysis occurs together with a preservation of skeletal muscle mass, suggesting that the breakdown of fat precedes that of skeletal muscle proteins and implying that some signal (or signals) generated during the breakdown of adipocyte triacylglycerols may actually be responsible for the activation of muscle proteolysis. The inactivation of HSL also resulted in a lack of activation of the muscle ubiquitin–proteasome pathway[63], which is considered to be the main proteolytic system involved in muscle wasting during tumour growth. It can be suggested, therefore, that infiltration of adipose tissue in skeletal muscle could contribute to wasting in this tissue. Thus, Stephens *et al.*[64] have reported an increased presence of intramyocellular lipid droplets in rectus abdominis muscle of cancer patients, which seems to be related to body weight loss.

Very recent studies[65,66] suggest that, during cancer cachexia, WAT cells undergo a 'browning' process in which they convert into BAT-like cells (also called beige cells). Browning is associated with increased expression of UCP1, which switches the use of mitochondrial electron transport from ATP synthesis to thermogenesis, resulting in increased lipid mobilization and energy expenditure.

Tumour-derived compounds, such as the inflammatory mediator IL-6 (REF. 65) — which may also be released by immune cells — and parathyroid-hormone-related protein (PTHRP)[66], seem to be responsible for driving the expression of UCP1. Neutralization of PTHRP in mice bearing the Lewis lung carcinoma was able to block WAT browning and decrease the loss of muscle mass and strength[66]. Also, anti-inflammatory

### Box 1 | Muscle cells and muscle anatomy

Skeletal muscle consists of cells called myocytes that form thread-like fibres (see the figure); the fibres are bundled into fascicles, which are grouped together to form muscles. Within the myocytes are myofibrils, which are bundles of protein filaments that organize together into repeating units known as sarcomeres. The striated appearance of muscle results from the regular pattern of sarcomeres within myocytes. The filaments in a sarcomere are composed of actin and myosin. A skeletal muscle fibre (myocyte) is surrounded by a plasma membrane called the sarcolemma, which contains sarcoplasm, the cytoplasm of muscle cells. The dark areas that correspond to where thick filaments are present are called A bands, whereas I bands are light areas that contain only thin filaments. The Z disc is within the I band and anchors the thin filaments and connects adjacent myofibrils, whereas the H zone is located in the middle of each A band, this lighter stripe corresponds to the region between the thin filaments. The M line is made up of protein fibres that connect neighbouring thick filaments. The sarcomere is the region of the myofibril between two Z discs. When a sarcomere contracts, the Z discs move closer together, and the I band becomes smaller. The A band stays the same width. At full contraction, the thin and thick filaments overlap.



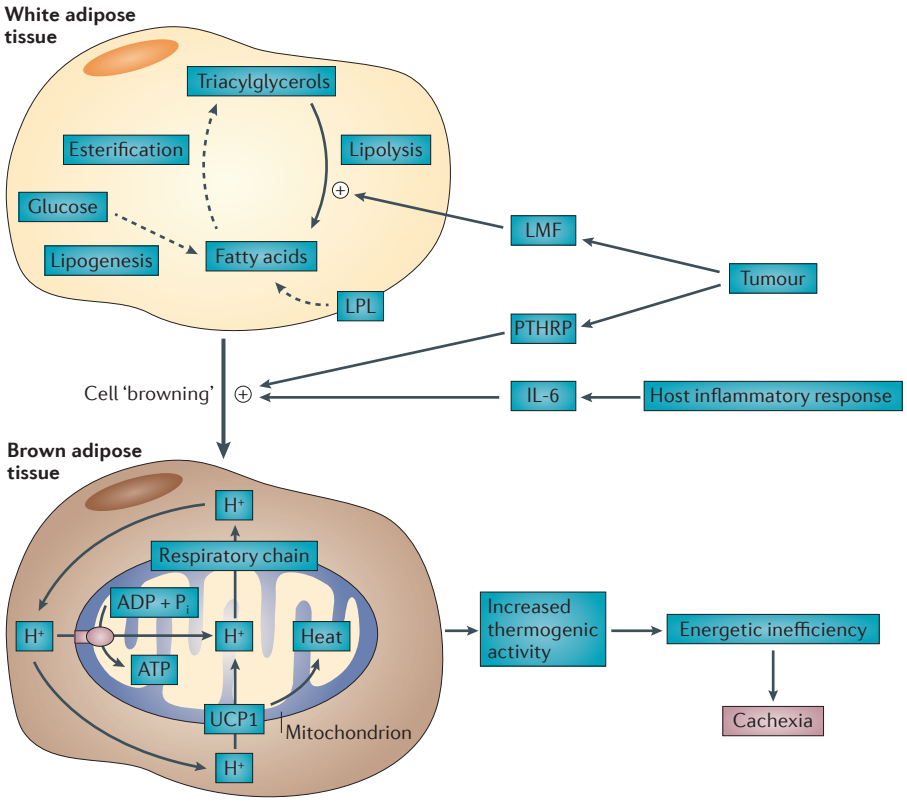



Figure 3 | **Browning of white adipose tissue in cachexia.** In addition to massive lipolysis, decreased lipogenesis from glucose and impaired entry of fatty acids owing to decreased activity of lipoprotein lipase (LPL) contribute to adipose tissue wasting. In addition, very recent data suggest that, during cancer cachexia, white adipose cells acquire some of the molecular machinery that characterizes brown adipose cells. This represents a 'browning' of white cells, in which uncoupling protein 1 (UCP1) is expressed and promotes uncoupling and, consequently, heat production and energetic inefficiency. This cell conversion can be triggered by both humoral inflammatory mediators, such as interleukin-6 (IL-6), and tumour-derived compounds, such as parathyroid-hormone-related protein (PTHRP). Circled "+" symbols indicate pathways that are activated during cachexia. Dashed arrows indicate pathways that are suppressed. LMF, lipid mobilizing factor; $P_i$, inorganic phosphate.

treatments or β-adrenergic blockade reduced WAT browning, resulting in a reduction in the severity of cachexia[65]. These approaches represent interesting and promising pharmacological strategies to ameliorate cachexia in cancer patients.

Several studies using tumour-bearing animals report a clear activation of BAT by lipolysis during cancer cachexia, which results in energy uncoupling at the mitochondrial level and the release of heat[67,68]. As BAT has a key role in thermogenesis and energy balance in rodents, it may potentially contribute to the energy wasting mentioned above, which occurs in cancer patients. In 2009, Virtanen *et al.*[69] showed that BAT was present in adult humans in the upper back, neck, between the clavicle and shoulder, as well as along the spine, which suggests that BAT also has a function in humans. Molecular imaging techniques have allowed detailed *in vivo* localization of BAT in disease[70]. Unfortunately, no information is available, at present, on the role of BAT in human cancer cachexia; therefore, future research on this field is highly encouraged.

## Tumour-driven inflammation

Systemic inflammation is a hallmark of cancer patients[71]. In fact, the inflammatory response is the main driving force behind the metabolic alterations observed in cancer. There are multiple origins of the inflammation: tumour cells and activated immune cells release cytokines, chemokines and other inflammatory mediators. Although the tumour is mainly responsible for the activation of immune cells, the gut seems to also have a role in this process. Indeed, gut barrier dysfunction and bacterial translocation are associated with cancer[72]. Thus, the release of lipopolysaccharide (LPS) and other bacterial toxins activates cytokine synthesis and release by immune cells. Cytokines promote the activation of transcription factors associated with wasting, both in adipose tissue and skeletal muscle. In addition to inflammatory mediators, other molecules also contribute to the metabolic abnormalities present in the cancer patient. Tumour-derived factors other than cytokines have been proposed as triggers of the wasting process associated with cancer cachexia. Two of these molecules, lipid mobilizing factor (LMF) and the proteolysis-inducing factor (PIF), have been found in tumour-bearing animals and in cancer patients[73]. LMF is a zinc-α2-glycoprotein (ZAG; also known as AZGP1) that can sensitize adipocytes to lipolytic stimuli and has a direct lipolytic effect in WAT[73] (FIG. 3). PIF is a major contender for promoting skeletal muscle atrophy; increasing protein degradation through the ubiquitin–proteasome pathway and depressing protein synthesis through phosphorylation of eukaryotic translation initiation factor 2α (eIF2α)[73].

Another interesting molecule that is associated with muscle wasting is myostatin, which operates through activin receptor type IIB (ACTRIIB)-mediated signalling. Myostatin is involved in skeletal muscle wasting in different catabolic conditions, including cancer[74]. Myostatin may be released not only by tissues such as skeletal muscle and adipose tissue (to a lesser extent) but also by cachexia-inducing tumours[75]. In fact, inactivation of myostatin and other TGFβ family proteins by treatment with a soluble form of ACTRIIB (sACTRIIB) ablates the symptoms of cancer cachexia in mice bearing the Lewis lung carcinoma[76,77]. It has recently been demonstrated that glucocorticoids could also be a determinant of inflammation-driven atrophy, possibly having an important role in the pathogenesis of cancer cachexia[78]. Understanding the interactions among cytokines, chemokines, tumour factors (PIF and LMF) and myostatin may possibly accelerate the development of novel therapeutic interventions against cancer-induced inflammation and, thus, cachexia.

## Cachexia as a multi-organ syndrome

In spite of the fact that skeletal muscle contributes to more than 40% of body weight and seems to be the main tissue involved in the wasting that takes place during cancer cachexia, recent developments suggest that tissues and organs such as adipose tissue (both BAT and WAT), brain, liver, gut and heart are directly involved in the cachectic process and may be connected to muscle wasting. Therefore, cachexia can be considered to be a multi-organ syndrome.

From this point of view, brain mediators are involved in the control of food

intake — appetite, satiation, taste and smell of food — and, consequently, are partially responsible for the anorexia of the cancer patient, making the brain an important organ involved in the altered energy balance in cancer patients[79] (FIG. 4). Tumour burden may influence not only the amount but also the quality of the ingested food. From this point of view, cancer patients experience changes in the perception of food — both smell and taste[80], which may contribute to a change of diet. However, both orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) brain pathways are profoundly altered[81]. The inflammatory response seems to be responsible for an activation of anorexigenic pathways and the inhibition of the orexigenic ones that leads to a decrease in neuropeptide Y (NPY) production and, therefore, a decrease in food intake[82]. Additional factors contributing to the anorexia observed in cancer patients are: therapy-induced side effects[83], depressed motor activity, possible obstruction in the gastrointestinal tract induced by a tumour and, of course, psychological factors[84]. In addition to anorexia, the hypothalamus, through the melanocortin system, may participate in muscle wasting, as suggested by different animal studies. Thus, in a mouse model of chronic kidney disease[85], and in a colon-26 tumour mouse model[86], administration of melanocortin receptor antagonist (the so-called Agouti-related peptide) ameliorated muscle wasting.

Concerning the gastrointestinal tract, in addition to the gut barrier dysfunction syndrome mentioned above, recent studies support a role for gut microbiota in cancer cachexia. Indeed, decreased levels of bacteria (*Lactobacillus* spp.) with immunomodulating properties are found in a mouse model of leukaemia[87]. The existence of a gut-microbiota–skeletal muscle axis has been proposed[88]; gut microbiota generates metabolites that can reach skeletal muscle and influence energy expenditure in the muscle cells[89]. The gastrointestinal tract may also be related to muscle wasting through ghrelin. This peptide, which is produced mainly in the stomach, increases appetite. Interestingly, ghrelin levels are elevated in cancer cachectic patients with neuroendocrine[90], gastric[91,92] and lung[93] tumours. These elevated levels could represent a counter-regulatory mechanism to fight anorexia that is associated with tumour growth, but it seems more likely that they represent an endocrine response to the so-called 'ghrelin resistance' that is found in cancer patients. In addition to its orexigenic properties, ghrelin has also been shown to have direct effects on muscle cells by inhibiting the increased protein degradation that is promoted by catabolic cytokines[94,95]. Moreover, a recent study demonstrates that ghrelin can inhibit apoptosis that is induced by doxorubicin (an antitumoural agent) in skeletal muscle cells[96].

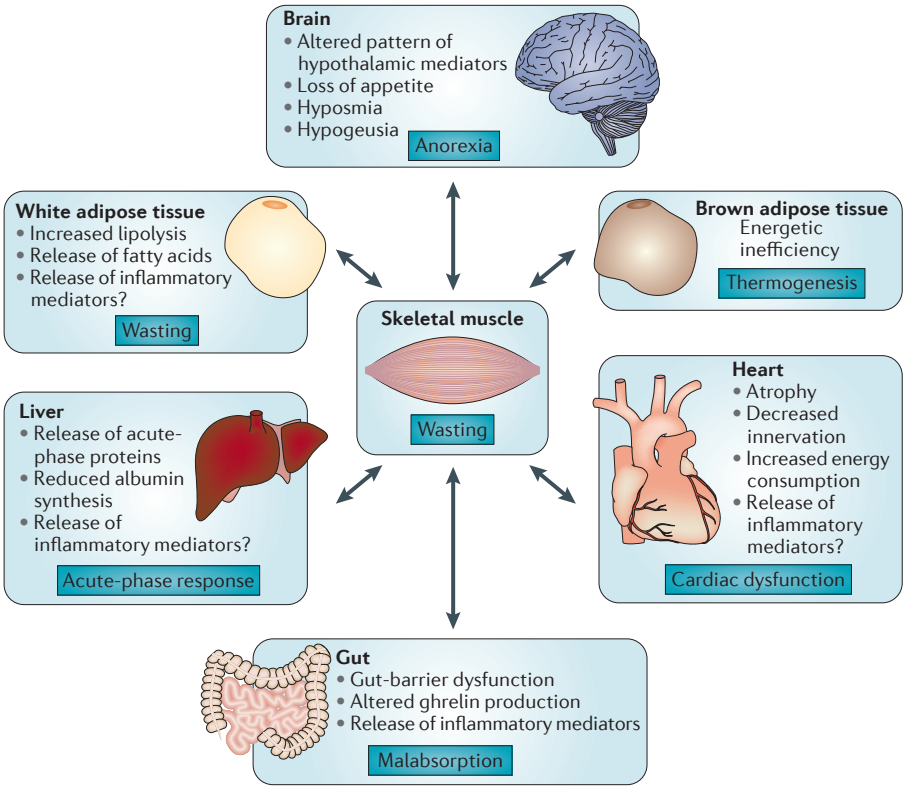



Figure 4 | **Cachexia as a multi-organ syndrome.** In addition to skeletal muscle and adipose tissue, other organs are affected by the cachectic process. In fact, the wasting that takes place in muscle could well be dependent on alterations in other organs or tissues, such as white adipose tissue (see the main text). Abnormalities in heart function, alterations in liver protein synthesis, changes in hypothalamic mediators and activation of brown adipose tissue are also involved in the cachectic syndrome.

During cancer, an important flow of amino acids from skeletal muscle to the liver takes place and serves for both gluconeogenesis and acute-phase protein synthesis (FIG. 1). Indeed, in many types of human cancer, C-reactive protein (the main acute-phase protein that is synthesized by the liver) seems to be a very important prognostic parameter[97,98]. The liver may also participate in generating energy inefficiency. On these lines, Dumas *et al.*[99] reported that the efficiency of oxidative phosphorylation in liver mitochondria was decreased in a rat model of peritoneal carcinosis, suggesting that the liver could also contribute to hypermetabolism in cancer.

Heart alterations are very often present in both human[100] and rodent cancer. Indeed, tumour-bearing rats experience a decrease of the heart weight[101], accompanied by functional cardiac changes that are similar to those found in congestive heart failure. In the mouse colon-26 cancer cachexia model, Tian *et al.*[102] reported that cardiac alterations include marked fibrosis, disrupted myocardial ultrastructure and altered composition of contractile proteins, such as troponin I and myosin heavy chain. Cardiac atrophy in experimental cancer cachexia seems to be associated with growth inhibition by activation of the ACTRIIB following stimulation by a subset of TGFβ family ligands, including myostatin, activin, growth/differentiation factor 11 (GDF11) and others. Pharmacological blockade of this receptor is able to reverse cancer-induced atrophy of the heart[76]. In addition to cardiac atrophy, Drott and Lundholm[103], using an experimental rodent model of cancer (methylcholanthrene-induced sarcoma), reported an increase in heart oxygen consumption — most likely related

to the anaemia that is very often present in cancer patients. Moreover, ultrastructural changes, such as decreased myofibrillar volume, increased sarcoplasmic volume and increased volume of lipid droplets, similar to those observed during cardiac failure, were also observed[104]. The increased oxygen consumption is linked with increased energy expenditure, therefore involving the heart as an additional organ that generates energetic inefficiency. Thus, heart rate seems to be elevated in cancer patients[105] and this parameter is an indicator of cancer death risk. However, the mechanisms underlying the association between heart rate and cancer mortality are unclear; the increase in heart rate could be a marker of chronic stress and anxiety, both of which are natural consequences of the disease.

## Conclusions and perspectives

As in many research areas, molecular knowledge of a pathological state (that is, cachexia) is mainly derived from animal models, which are used to extrapolate this to human beings. Unfortunately, many of the tumour models that are used with experimental animals grow faster than tumours found in humans; in addition, very few experiments are carried out using orthotopic inoculation and therefore may not reflect the behaviour of a tumour in the correct anatomical location. Although our understanding of the biology and molecular mechanisms of cancer cachexia has considerably expanded over the past 10 years, little is known about effective biomarkers, particularly in blood or urine. A method for early detection of the syndrome would increase the possibilities of treatment, as late-stage cachexia, as found in terminally ill cancer patients, is completely refractory to treatment. Knowledge of the molecular mechanisms underlying cancer cachexia may also allow for the design of distinctive therapeutic approaches that ameliorate or even successfully cure the syndrome. From this point of view, among oncologists, the traditional treatments, which are ineffective in the long term, involving either megestrol acetate (a progestogen that stimulates appetite) or glucocorticoids (used as anti-inflammatory agents), should be replaced by newer treatments that incorporate the molecular knowledge developed.

There are a couple of considerations concerning treatment. First, as cachexia is a multifactorial syndrome, a multimodal approach is needed. A single drug is unlikely to be very effective. The ideal therapeutic approach should therefore contemplate nutritional advising, nutritional supplements incorporating nutraceutics[106] and drugs. Particular emphasis should be placed on ghrelin agonists[107] and selective androgen receptor modulators (SARMs)[108]. Second, the multimodal therapy should incorporate a double strategy, both anticatabolic and anabolic. Indeed, blocking the catabolic drive that is linked with cachexia seems absolutely essential. For example, effective inhibition of muscle proteolysis, as well as prevention of lipid loss, should obviously be taken into consideration. However, as the demand of the tumour for amino acids is very high, the therapeutic approach also has to incorporate an anabolic agent that potentiates muscle protein synthesis. Furthermore, future treatments should be started right from the moment of cancer diagnosis and should be adapted to the stage of cancer cachexia[11]. Cachexia treatment for a terminal patient is primarily palliative and has to be different from that of a patient who has earlier stage cancer; from this point of view, staging of cachectic patients is absolutely essential for the application of therapy and should be accompanied by clinical guidelines.

## Glossary

**Adipokines**
Cytokines that are released by adipose tissue cells.

**Asthenia**
From the Greek, *a stenos*, meaning 'without force'; loss of muscle force.

**Brown adipose tissue**
(BAT; also known as brown fat). One of two types of fat or adipose tissue (the other being white adipose tissue (also known as white fat)) found in mammals. Its primary function is to generate body heat, being responsible for the so-called non-shivering thermogenesis.

**Calcium release units**
Specialized junctional domains of the sarcoplasmic reticulum that bear calcium release channels, also known as ryanoidine receptors.

**Glycaemia**
Blood glucose levels.

**Ghrelin resistance**
Reduced effects of ghrelin, in spite of high circulating levels of the molecule.

**Myokines**
Cytokines that are released by skeletal muscle.

**Sarcomere**
From the Greek *sarx* (flesh) and *meros* (part), it represents the basic muscle. Sarcomeres are composed of long, fibrous proteins that slide past each other when the muscles contract and relax.

**Total parenteral nutrition**
Intravenous artificial nutrition without oral ingestion.

**White adipose tissue**
(WAT; also known as white fat). WAT is used as a store of energy in the form of triacylglycerols. It may account for up to 25% of body weight in healthy humans.

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