

# Cancer cachexia: impact, mechanisms and emerging treatments

Vanessa C. Vaughan · Peter Martin ·  
Paul A. Lewandowski

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**Abstract** Many forms of cancer present with a complex metabolic profile characterised by loss of lean body mass known as cancer cachexia. The physical impact of cachexia contributes to decreased patient quality of life, treatment success and survival due to gross alterations in protein metabolism, increased oxidative stress and systemic inflammation. The psychological impact also contributes to decreased quality of life for both patients and their families. Combination therapies that target multiple pathways, such as eicosapentaenoic acid administered in combination with exercise, appetite stimulants, antioxidants or anti-inflammatories, have potential in the treatment of this complex syndrome and require further development.

**Keywords** Cancer cachexia · Oxidative stress · Antioxidant · Eicosapentaenoic acid · Oxypurinol

## 1 Introduction

Cancer cachexia is a complex condition of tissue wasting which develops as a secondary disorder in cancer patients and leads to progressive functional impairment. Cancer cachexia is characterised by systemic inflammation, negative protein and energy balance and involuntary loss of lean body mass, with or without wasting of adipose tissue [1]. Clinically, cachexia is represented by significant weight loss

in adults and failure to thrive in children [2], accompanied by alterations in body composition and disturbed balance of biological systems [3–5]. Whilst the loss of skeletal muscle mass is the most obvious symptom of cancer cachexia, cardiac muscle is also depleted, though other visceral organs tend to be preserved [3].

Cachexia has been recognised as a serious condition for some time; however, due to the complex nature of the condition, guidelines for its definition and diagnosis have only recently begun to emerge [1, 2]. Even so, there is great variation in definitions, which present problems when comparing studies and informing clinical diagnoses [6, 7]. This in turn may affect the ability to identify cachectic patients and appropriate treatment, for which there is no globally recognised ‘gold standard’. Current therapies focus on palliation of symptoms and reduction of distress of patients and families rather than a cure [8]. As such, cachexia remains a largely underestimated and untreated condition [2, 9]. Approximately half of all patients with cancer experience cachexia [10, 11], with the prevalence rising as high as 86 % in the last 1–2 weeks of life [12], and 45 % of patients losing more than 10 % of their original body weight over disease progression [13]. Death usually occurs once weight loss has reached 30 % of the patient’s historic stable body weight [3], with cachexia being directly attributable for 20 % of cancer deaths [14]. Whilst cachexia is seen in several other diseases, such as HIV/AIDS, sepsis, chronic obstructive pulmonary disease and congestive heart failure, the loss of muscle mass has been shown to occur most rapidly in cancer patients [15].

Due to the unique mechanisms involved in each disease, it is likely that factors influencing the onset of skeletal muscle cachexia vary between conditions [16], despite sharing several common pathways [7]. The progression of the disease also varies between cancer types, with cachexia being more prevalent within pancreatic, colon or non-small

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V. C. Vaughan · P. Martin · P. A. Lewandowski (✉)  
School of Medicine, Deakin University,  
75 Pigdons Road,  
Waurn Ponds, Victoria 3216, Australia  
e-mail: paul.lewandowski@deakin.edu.au

P. Martin  
Palliative Care Program, Barwon Health,  
Geelong, Victoria, Australia

cell lung malignancies [1]. Whilst loss of adipose tissue often occurs prior to wasting of lean mass [17], unlike anorexia, where adipose tissue is depleted in response to nutritional deficit, cachexia degenerates both adipose tissue and skeletal muscle indiscriminately [16]. It is a profound atrophic response that cannot be directly attributed to lowered calorific or nutrient intake nor fully reversed by increased nutritional support [6, 16]. Cachexia is also considered distinct from conditions of starvation, age-related sarcopenia, malabsorption and other similar pathological states [2, 7].

Currently, most definitions of cachexia focus on weight loss alone. Cachexia is generally defined as being involuntary weight loss of >5 % from historical weight, a body mass index (BMI) <20 kg/m<sup>2</sup> with any degree of weight loss >2 % or a skeletal muscle index consistent with sarcopenia with any degree of weight loss >2 % [1]. However, these defining characteristics have yet to be validated in a cancer-specific cachectic population and fail to consider other widely accepted and characterised hallmarks of the condition, such as inflammation, altered body composition, accelerated protein degradation, increased treatment toxicity, fatigue and reduced quality of life [9]. They also do not take into account the severity of the disease, which may be compounded by factors such as weight loss from an already low BMI, where a small change may have a much larger impact than the same loss in someone of higher BMI [1].

These developing definitions should not only describe established cachexia, but provide criteria for the identification of ‘at-risk’ populations. Historically, classification or staging of cachexia has been poorly represented, with most studies focusing on the mid-to-late stages of the disease. Therefore, an improved three-step classification of cachexia has been proposed following international collaboration and development [1]. These steps now include:

1. Pre-cachexia—when a patient has weight loss <5 %, but has not yet developed serious complications.
2. Cachexia—where the syndrome is progressing, with weight loss exceeding the above-mentioned parameters, but still potentially able to be treated.
3. Refractory cachexia—the point at which the disease is no longer responsive to treatment or when treatment benefits are outweighed by burden and risk.

Often, the refractory stage is dictated by the overall stage of underlying illness and condition of the patient, rather than cachexia alone [1], and reflects periods of palliation, where the focus of treatment moves from cure and control to maintenance of quality of life [12]. This type of grading system allows for greater tailoring of treatment to patients in various stages of disease progression and would enable targeted research and therapies to be developed for each stage.

## 2 Impact

### 2.1 Quality of life

Cancer cachexia has been shown to impact on patient outcomes, quality of life and survival when compared to weight-stable patients. Cancer cachectic patients experience numerous complications including, but not limited to, reduced effectiveness of chemotherapy, reduced mobility and reduced functionality of muscle-dependent systems, such as the respiratory and cardiovascular systems, leading to decreased quality of life and survival [18–20].

Research by Ravasco et al. [21] indicated that self-rated quality of life scores in patients with cancer were more often determined by issues relating to weight loss and nutritional status (50 %), compared to cancer location, disease duration or cancer stage (30, 3 and 1 %, respectively). Studies using self-assessment questionnaires also tend to show higher prevalence of symptoms than those reported during a standardised review [12]. In particular, quality of life in patients with advanced cancer is most significantly affected by symptoms associated with pain, fatigue and reduced appetite, in particular toward refractory cachexia [22]. Patients may feel they have more time and/or feel free to indicate the presence of symptoms less often mentioned in interview, and as such, questionnaires may identify symptoms not considered important by the patient and thus not addressed [12]. Cachectic patients are also more likely to score lower than their weight-stable counterparts in standard quality of life measures [19]. Decreased quality of life scores have been shown to be accompanied by significant decreases in physical activity and exercise capacity, which is strongly related to weight loss [23].

Cachexia negatively impacts on surgical risk and response to chemotherapy and radiotherapy and ultimately results in decreased quality of life [24]. Cancer patients experiencing weight loss leading up to and during chemotherapy receive a lower initial dose and experience more frequent and severe dose-limiting toxicity when compared to weight-stable patients [25, 26], consequently receiving significantly less treatment [27]. These patients also experienced decreased quality of life, performance status and survival intervals and lowered response to treatment. Importantly, these negative outcomes appear to occur due to decreased treatment and increased toxicity, rather than alterations in the effectiveness of the therapy itself. Cancer patients without weight loss have demonstrated a better chance of survival and a greater response to cancer therapy than their cachectic counterparts [18]. This indicates that an effective treatment for cachexia would result in more positive outcomes for these patients. A reduction in the occurrence or progression of cancer cachexia would have several flow-on effects in terms of health economic outcomes, for

example, reduced hospital admissions for adverse effects of cachexia, shorter hospital stays due to greater capacity to regain health sooner or maintain health longer and reduced attendance to emergency departments for cachexia-related complications. The complex interplay of systemic inflammation, metabolic disruption and the presence of numerous factors that are now thought to play an important role in the development and progression of cachexia make it unlikely that a single therapy will have the ability to combat the condition as a whole. Rather, a multi-targeted approach should be considered when developing treatment plans for cachectic patients [28]. This is supported by numerous single modality studies that, whilst showing theoretical merit or some minor improvement, do not produce a substantial change in either quality of life or patient outcomes [3, 4, 24, 29, 30].

## 2.2 Social and psychological

Cancer cachexia has a significant psychological impact on both patients and their families, being identified as one of the top 2 most frequent and devastating problems in advanced cancer [31]. However, in the past, these concerns have taken a back seat to biomedical aspects of research. There is a high prevalence of depression in cancer patients (10–30 %) compared to the general population (5–10 %), with depression leading to reductions in drug compliance and effectiveness [32, 33]. Clinical depression in cachexia appears under-recognised and undertreated, perhaps due to the difficulty in distinguishing between reactive demoralisation and clinical depression or due to overlapping symptoms of illness and depression [34]. However, the increased expression of shared inflammatory cytokine pathways ([32]; see also Section 5) may lead to increased prevalence of clinical depression in a cachectic patient population. As such, treatments that address pro-inflammatory cytokine activity in cachexia may also contribute toward the alleviation of clinical depression in susceptible patients.

Further to clinical (inflammatory) depression, high psychologic distress occurs in response to reduced appetite and food intake, increases in fatigue and significant alterations in appearance [35], which contribute to a cascade of losses experienced by both the patient and their family. Families often rationalise that, if food intake is increased, weight will be regained and survival increased, with a failure to increase intake being equated with expedition of death [36]. This stems partially from a lack of communication with families about the nature and causes of wasting in cachexia, as atrophy is caused by factors independent of nutritional or calorific intake [36, 37], and also from the need to take an active role in treatment, with food preparation being highly symbolic of this need to nurture [36, 38]. This often leads to conflict between the patient and their family, as the patient's refusal of food is interpreted as a rejection of care and

support, increasing anxieties over food and ultimately contributing to a decreased quality of life [35, 36, 38]. Patients, on the other hand, more often associate their weight loss with their decline during disease progression, recognising that increased intake is futile and, as such, view weight loss as inescapable, with pain being of much more immediate concern [39]. It has been noted that many patients, despite an absence of appetite, often retain the motivation to eat, whether to avoid confrontation or to maintain some aspect of normalcy about food [40].

Alterations in body image also have a significant impact on patients, with loss of weight often perceived as undermining identity and self-esteem and alienation from themselves, i.e. 'not recognising the person in the mirror' [31, 37]. Given that the severe physical decline of cachexia is quite evident to sufferers and those they engage with, the social consequences of weight loss are also a major source of distress. Self-consciousness acts as a barrier to social engagement, with patients often choosing to isolate themselves from previous social circles rather than be 'besieged by attention' [37], with negative reactions highly stigmatising and positive engagement often regarded as a reminder of their illness [31, 37]. Given that conflicts often arise from reduced food intake, patients may further increase social isolation to avoid confrontation with family [36, 41]. The appearance of refractory-stage cachectic patients is often likened to that of death camp victims during World War II, indicating the associations by family and friends that this is a neglect-linked disease that if left untreated will ultimately end in death [37].

It is important to recognise that cachexia is a condition that has profound psychological as well as physiological implications for patients and their families. Better communication from researchers and healthcare professionals with patients and their carers is of great importance to not only reduce the burden of disease but also provide better understanding and support during disease progression.

## 3 Anorexia and appetite in cachexia

Unlike many other forms of weight loss, cachexia is not the result of reduced calorific or nutrient intake alone. The term 'malnutrition' is often misused with regard to cachexia, as this incorrectly implies that the underlying cause of wasting is associated with diet and nutrition and that increasing intake or absorption of nutrients and calories will solve the problem [40]. Whilst malnutrition is often present for various reasons [21], unlike forms of weight loss such as anorexia nervosa where wasting is caused by decreased energy consumption, it is not the underlying cause in cachexia [2]. It has previously been shown that increasing calorie intake does not replenish the loss of skeletal muscle mass but rather

increases total body weight through water retention and replenishment of fat stores, with some steroidal treatments in fact having a negative impact on muscle retention [42–45]. Other studies have shown that, whilst nutritional counselling may improve calorific intake, it did not assist to increase weight, anthropometrics, therapeutic response, quality of life or survival [46–49] and that there is little observed benefit from parenteral nutritional support [50–52]. However, as previously discussed, nutritional counselling and a subsequent increase in calorie intake may help relieve ‘caregivers anxiety’, prevent further decline in nutritional status and even improve patient outcomes during radiotherapy [53, 54], with nutritional counselling increasingly promoted as part of a multimodal approach to therapy [55, 56]. These results indicate that, whilst malnutrition may play an important role in cachexia, it is not the major factor in the development and, although increased intake of nutrients and calories may be considered for the treatment of cachexia, it should not be the only consideration.

Chemosensory alterations in cancer and during cancer therapy are well documented [57–62], with alterations in taste and smell often contributing to the development of food aversion and reduced hedonic response. This in turn may lead to the development of anorexia and acceleration of the disease. Zinc has been shown to play an important role in taste perception, with deficiency linked to a diminished sense of taste among cancer patients undergoing radiation therapy, in particular irradiation of the head and neck [59, 63]. It has been proposed that zinc acts as a cofactor for receptors in the apical pore of taste bud membrane, and therefore, changes in the availability of zinc causes conformational changes to these pores [59]. This in turn reduces the amount of taste stimuli that may pass through the pore, reducing taste response. There has been some argument as to whether this response is linked to low serum zinc levels [59, 63–65]; however, whilst supplementation does not preserve taste perception in those undergoing radiation therapy [65, 66], it does reduce symptom severity and may improve recovery of acuity and response to taste stimuli [59, 65].

Decreased appetite and early satiety have a high prevalence in the late stages of disease, with decreased appetite described in more than 50 % [14] and early satiety in 23–51 % of patients [12, 67]. These changes suggest a disruption of central and peripheral signalling for regulation of eating behaviour [48, 68] and, together with metabolic abnormalities generated by the disease, drive the negative protein and energy balance thought to be the key contributor of cachexia.

#### 4 Futile cycling and resting energy expenditure

The condition of cachexia is associated with metabolic disruption from various causes, all of which lead to the

eventual increases in energy expenditure, systemic stress and disruption of normal cellular function. The balance of protein synthesis and degradation is one of the most obvious aspects of metabolism disruption in cancer cachexia. It has been widely observed that the rate of muscle protein catabolism increases in cachexia, whilst anabolism of new proteins decreases, resulting in net protein breakdown [15, 69–71]. This increase in protein turnover is higher in cancer cachexia compared to weight loss associated with other diseases and leads to increased energy demand of approximately 100 kcal/day [72–74].

Resting energy expenditure (REE) is also increased in the cachectic state, with futile metabolic cycling accounting for much of this increase. One example of futile cycling is the glucose–pyruvate–lactate transformation seen in the Cori cycle. Lactic acid production from the tumour drives the conversion of lactate to pyruvate and then into glucose in the liver, a process that has high energy expenditure. This glucose is then moved into the circulation and back to the tumour, where it is again transformed into lactate, and the cycle continues [75]. Glucose from this cycle may also serve to feed the tumour, causing it to grow, produce more lactic acid and further drive the cycle. In cachexia patients, the Cori cycle has been described as accounting for 50 % of total glucose turnover, compared to 20 % in cancer patients that are weight stable [75]. Uncoupling proteins (UCPs), related to the regulation of mitochondrial proton gradients and production of reactive oxygen species (ROS) in skeletal muscle and adipose tissue, may also play a role in the increased REE observed in cachexia [15]. In particular, the expression of UCP2 and UCP3, associated with energy expenditure and metabolism in skeletal muscle, are up-regulated in the cachectic state, indicating the involvement of these mechanisms [15].

Increased mass and proportion of high metabolic tissue such as the liver occurs in cachexia and has been shown to contribute significantly to this increase in energy expenditure [76]. Cachectic patients also show an increase in the oxidation of branched-chain amino acids from muscle proteins for use in gluconeogenesis [77], which may be triggered by this increase in energy expenditure, and would ultimately contribute to muscular degeneration in cancer cachexia. However, the traditionally accepted view that increased REE and hypermetabolism are essential factors in the pathogenesis of the disease has been disputed, with a heterogeneous picture of REE emerging that range from 60 to 150 % of the norm [78–81]. Further, whilst REE may be increased, total energy expenditure may be decreased due to reduced physical activity [81, 82]. Assessments of metabolic alteration in cachectic rodents has described a progressive hypermetabolic state in pre-cachexia and early cachexia, passing through a stable metabolic phase and finally progressing to a pre-terminal hypometabolic phase [83]. These

differences in metabolic pathology may be attributed to tumour-specific factors, a view which has been supported by preliminary studies in a human cohort [84].

### 5 Inflammation and circulating factors

Systemic inflammation is another symptom seen in cancer cachexia, indicated by the production of acute-phase response (APR) proteins such as C-reactive protein (CRP) and fibrinogen. CRP is considered an accurate measure of pro-inflammatory cytokine activity [85] that has been implicated in muscle wasting by its binding to exposed ligands in damaged cells and has been shown to aggravate tissue damage in ischemia–reperfusion injury [86]. The APR has been related to the inflammation seen in cachexia [87, 88] and the reduced quality of life and shortened survival in these patients [89–92], causing increased muscle catabolism and diversion of amino acids from muscle anabolism to feed the amino acid pool required for APR protein anabolism (see Fig. 1) [93, 94]. Whilst these mechanisms are designed for host defence and tissue repair, short-term gain may be outweighed by long-term loss of lean body mass. Increases in CRP have been shown to correlate with increased weight loss in cachectic patients [85], indicating that there is an increase in pro-inflammatory cytokine activity during the progression of the disease [95, 96], with eicosanoid-driven inflammation also implicated [97–99].

The presence and severity of cachexia correlates poorly with tumour size [100], and therefore, metabolic alterations are more likely the result of mediators produced by the tumour or by the body in response to the tumour. Several pro-inflammatory cytokines are elevated in patients with cachexia, including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1) and interleukin-6 (IL-6), all of which have been shown to induce cachexia-like effects when administered in the absence of tumours [11]. TNF- $\alpha$  is a circulatory factor which increases gluconeogenesis, lipolysis and proteolysis, whilst causing decreases in protein, lipid and glycogen synthesis, induces the formation of IL-1 [11] and has been demonstrated to stimulate the expression of UCP2 and UCP3 in cachectic skeletal muscle [15]. However, whilst it may induce symptoms of cachexia, the inhibition of TNF- $\alpha$  has been shown to neither stop nor reverse cancer cachexia [100]. This indicates that TNF- $\alpha$  may be involved in the development of cachexia, but is not solely responsible for the effects seen in cachectic patients. IL-1 induces anorexia in cachectic patients as it causes an increase in plasma concentrations of tryptophan, which in turn increases serotonin levels, causing early satiety and suppressing hunger [11]. IL-1 also induces the production of IL-6, an immune-linked cytokine that increases lipolysis and contributes to weight loss. Levels of IL-6 were observed to be lower in weight-stable patients than those with cachexia; however, whilst IL-6 is thought to be important in

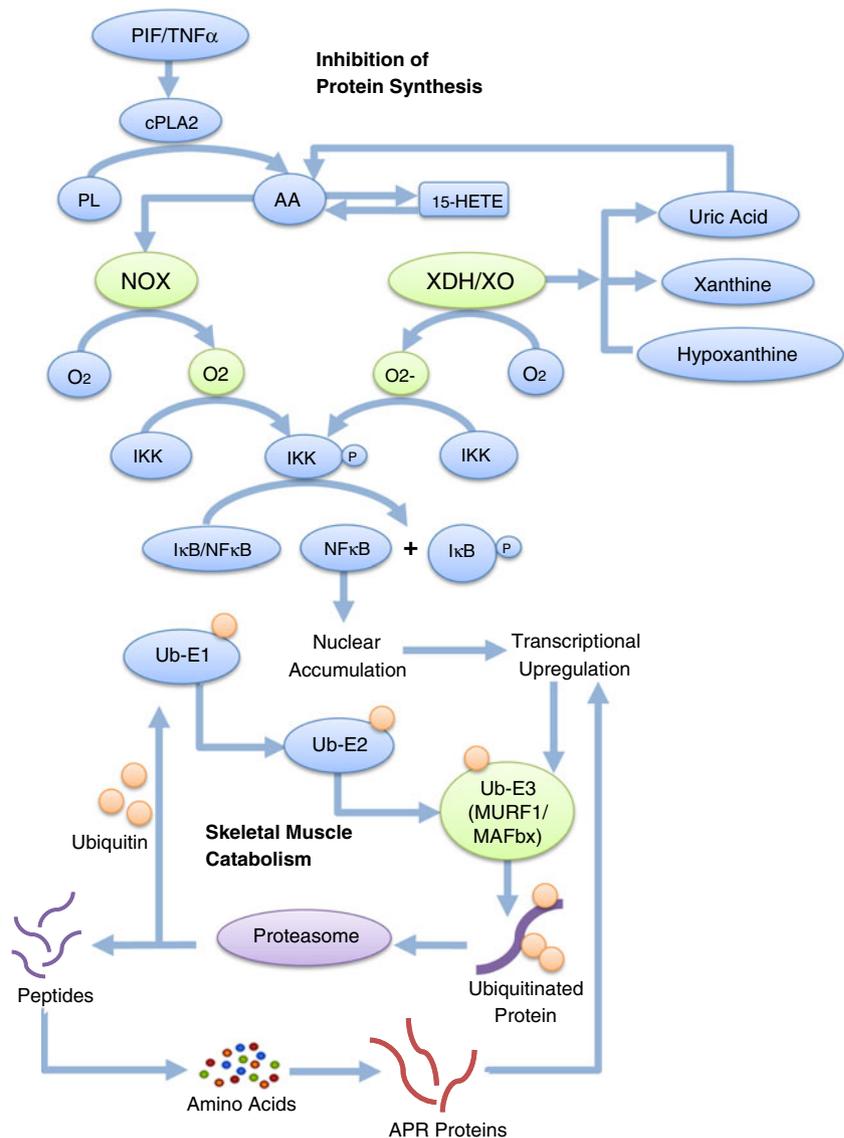
the development of cachexia, it has been shown not to be solely responsible and works through indirect action [11]. As such, it is likely that a complex interplay of these factors is responsible for cachexia, rather than each working in isolation [101]. However, there is limited variation in circulating cytokines [102], and cytokine production by isolated peripheral mononuclear cells suggests that local production in affected tissues is more important and relevant to cachexia than systemic circulation of these factors [82].

Proteolysis-inducing factor (PIF) is a circulatory factor produced by some tumours and is present in some cohorts of cancer patients with cachexia, but absent in cancer patients without active weight loss or weight-losing patients with benign disease [70, 103–105]. Patients with circulating PIF experience a significant decline in body weight, mainly of lean body mass, accounted for by a 50 % reduction in protein synthesis and a 50 % increase in protein catabolism [106]. PIF has been shown to increase the expression of ubiquitin proteolytic pathway (UPP) elements (see Fig. 1) [103, 106–108], induce the accumulation of ubiquitin-conjugated proteins [15] and play a role in the increased production of the cytokines IL-6 and IL-8, indicating that PIF acts as part of an inflammatory response pathway in the cachectic state [109]. However, there has been some debate over the existence of PIF, with several studies unable to identify the factor outside of the murine adenocarcinoma 16 model and having difficulty in identifying a human homologue through conventional methods, casting doubt as to the relevance of a PIF homologue in a clinical setting [110–112]. Lipid-mobilising factor/zinc- $\alpha$ 2-glycoprotein (ZAG) has been demonstrated to play an important role in the lipid depletion that occurs in cachexia and other catabolic states. Whilst ZAG is expressed in normal tissues such as the liver and adipose tissue [113], it is also over-expressed in patients with several types of tumour [114, 115] and acts as a local factor in catabolic states, mobilising lipids from adipose by increased lipolysis for gluconeogenesis [116]. However, whilst there is a strong relationship between adipose ZAG release and nutritional status, it has been indicated that there is no relationship between release of ZAG and BMI or relative fat mass nor circulating levels of ZAG and nutritional status [116]. Whilst stimulating adipose depletion utilising  $\beta$ -adrenoreceptors, ZAG has also been shown to stimulate skeletal muscle hypertrophy via the cAMP-mediated pathway and decreased proteasome activity [117]. Therefore, ZAG may in fact play a protective role in fat-free mass and may explain why depletion of adipose stores often precedes the loss to skeletal muscle protein seen in cachexia [17, 117].

### 6 Oxidative stress

ROS are oxygen-derived molecules that have an odd number of valence electrons. As a result, these molecules are highly

**Fig. 1** An example pathway for the induction of the ubiquitin proteasome pathway. Tumour factors and pro-inflammatory mediators initiate a complex signalling cascade that eventuates in increased skeletal muscle catabolism. *PL* phospholipids, *AA* arachidonic acid. Adapted from [118]



reactive and, if not neutralised by antioxidant enzymes, may cause damage to DNA, proteins and lipids within the cellular environment [119]. ROS such as superoxide (O<sub>2</sub><sup>-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and hydroxyl radicals are normal products of cellular metabolism, commonly utilized in cellular signalling cascades (see Fig. 1); however, increased levels caused by environmental stress, metabolic imbalance or reduced antioxidant activity may lead to a state of oxidative stress, resulting in extensive oxidative damage [119]. Oxidative stress has been uncovered as one of the key players in the development of cachexia, contributing to muscle wasting both directly, through oxidative damage, and indirectly, through redox signalling in degradation pathways [120]. Oxidative damage, ROS levels and mRNA levels for ROS-producing enzymes have all been shown to be elevated in the cachectic state [121, 122], whilst the production and activity of antioxidant enzymes have been shown to decrease [123, 124], indicating a reduced capacity for the conversion of excess ROS into less toxic molecules.

The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) is an enzyme system that catalyses the production of O<sub>2</sub><sup>-</sup> from NADPH and oxygen and has been implicated as a major contributor of ROS in cancer cachexia [125]. NOX was first described in phagocytes as an immune response against microbial pathogens [126]; however, NOX is now known to function in many non-phagocytic cells and plays a role in cellular signalling [127], in particular with the formation of O<sub>2</sub><sup>-</sup>. The NOX enzyme is made up of several subunits, and an up-regulation of any one of these components may, therefore, potentially increase enzyme activity in cachexia. The ROS produced by NOX are associated with several negative effects within cells, such as apoptosis and inflammation, which ultimately contribute to the onset and progression of several diseases [128]. NOX also acts as a downstream regulator of several redox signalling pathways, in which the ROS it produces act as steps in a signalling cascade [122] that eventually result

in the alteration of expression of target genes (see Fig. 1). In addition, an excess of NOX activity, when coupled with uncompensated antioxidant activity in cancer cachexia, can contribute to oxidative stress and associated damage.

Whilst some of the pathways involved in the excess production of ROS have been studied at length in cancer cachexia, there are others that have been implicated to induce oxidative insult in other diseases, whose roles have yet to be studied in cancer cachexia. Xanthine oxidoreductase (XOR) is an enzyme with two distinct forms that are responsible for catalysing the conversion of hypoxanthine to xanthine and xanthine to uric acid [129]. Xanthine dehydrogenase (XDH) is expressed *in vivo* and uses NAD<sup>+</sup> as an electron acceptor for the reduction reaction, forming NADH. In the presence of pro-inflammatory mediators, XDH readily cleaves into xanthine oxidase (XO), which instead uses molecular oxygen for the conversion of hypoxanthine to xanthine and xanthine to uric acid, producing the highly reactive O<sub>2</sub><sup>•-</sup> or H<sub>2</sub>O<sub>2</sub> [129]. Uric acid has also been shown to act as an inflammatory agent, stimulating an inflammatory response to cell death in multiple tissues [130], and has been found in high levels in the serum of cachectic patients whose primary disease is not cancer [131, 132]. Whilst XO is not usually present in high levels in skeletal muscle, elevated levels are commonly seen in muscle tissue damage and ischemia–reperfusion injury [133]. High levels of XO have also been observed in the blood of cancer patients compared to patients without cancer [134], though this has yet to be documented in cachectic skeletal muscle. The abundance of pro-inflammatory factors present in cachexia may lead to an increase in the cleavage of XDH to the XO form, explaining higher circulating levels of XO, consequently contributing to increased O<sub>2</sub><sup>•-</sup> and uric acid levels. The inhibition of XO has recently been shown to improve skeletal muscle dysfunction associated with oxidative stress in a model of sarcopenia in aging rodents [135] and, though preliminary, suggests that it may effectively dampen ROS production that contributes to muscle wasting, an application that may lend itself to the treatment of muscle wasting associated with cachexia. XO has also been suggested to play a role in secondary inflammation in skeletal muscle after eccentric exercise [136], a further possible role for this enzyme in cachexia.

The body has a finely balanced and highly structured antioxidant defence system, which provides protection from ROS-induced damage. If this balance is shifted away from antioxidants by a decrease in antioxidant activity or an increase in ROS production, a state of oxidative stress is observed [119, 120]. Oxidative stress has a detrimental effect on the cellular environment and may be one of the key factors in the development of cachexia [120]. Superoxide dismutase (SOD) is an enzyme responsible for the dismutation of O<sub>2</sub><sup>•-</sup> into H<sub>2</sub>O<sub>2</sub> and oxygen. In some cachexia

studies, the activity of SOD in skeletal muscle is decreased, contributing to oxidative stress and cellular damage [124, 125], whilst others have shown no change in the activity of SOD [121]. Catalase is another antioxidant enzyme, which breaks down H<sub>2</sub>O<sub>2</sub> into oxygen and water. Whilst not as reactive as O<sub>2</sub><sup>•-</sup>, in high levels, H<sub>2</sub>O<sub>2</sub> can also cause damage to cells and disrupt metabolism. A decrease in catalase activity has been observed in cachexia studies [123], indicating that the system would contribute to an increase in oxidative stress. Glutathione peroxidase (GPx) also plays an important role in the metabolism of ROS, utilising glutathione as a reducing substrate to reduce hydroperoxidases. Studies of cachectic tissue have shown no change in the activity of GPx [123, 137]. Collectively, these studies suggest not only the reduced antioxidant capacity of these systems but also their inability to respond to increased oxidative conditions and, therefore, an inability to protect the cell from oxidative stress in the cachectic state, a malfunction that may be the major contributor to the state of oxidative stress observed in cancer cachexia.

## 7 Skeletal muscle in cachexia

The loss of lean body mass, in particular skeletal muscle, is the most prevalent and obvious symptom of cancer cachexia, contributing significantly to negative patient outcomes and quality of life, as previously discussed. Muscle atrophy in cachexia results from a combination of increased catabolism by cytokine-dependent hyperactivation of various pathways and reduced protein anabolism [138–142]. Interestingly, muscle protein synthesis may at times be elevated in cachexia due to increased availability of amino acids from accelerated muscle catabolism [1]; however, this is not sufficient to outweigh the net protein loss. There has been some debate as to whether certain muscular elements, such as the myosin heavy chain, are selectively targeted for degradation or whether general, untargeted wasting occurs [71, 143, 144]. As yet, no consensus has been reached and may be dependent upon other factors, such as tumour type or levels of particular circulating factors. Decreased muscle strength has been shown to be a strong predictor of morbidity and mortality in cancer patients [145, 146] and has been linked to fatigue [147–149]. The loss of skeletal muscle mass in cachexia is not restricted to those patients that appear thin, with low muscularity in obese patients recognised as an independent prognostic indicator [1, 150].

### 7.1 Pathways to protein degradation

The progressive catabolism of muscle in cancer cachexia suggests a pivotal role in systems of protein degradation, such as the UPP, which has been found to be up-regulated

both in experimental models and patients with cancer cachexia [151–154]. Components of the UPP also increase in patients with pre-cachexia, suggesting that not only does the system contribute to muscle atrophy in cachectic patients but also indicates a causative role early in disease development [151, 155]. Before proteins can be degraded by the UPP, they must first be targeted by conjugation to multiple molecules of ubiquitin. In order for this conjugation to occur, ubiquitin must first be activated by an ubiquitin-activating enzyme (E1) and then transferred to the active site of an ubiquitin carrier protein (E2). The bound E2 recognises ubiquitin-conjugating enzymes (E3 or E3 protein ligase), which allow conjugation reactions to take place, forming a chain of ubiquitins linked to each other and the protein substrate. Only when ubiquitin is targeted to a selected protein can it then be recognized by the proteasome and processed into smaller peptides [15, 156]. In particular, three E3 protein ligases have been shown to be active during proteolysis in muscle atrophy, namely, E3 $\alpha$ , muscle-specific F-box (MAFbx)/atrogin-1 and muscle-specific ring finger 1 (MuRF1) [143, 157–162]. Oxidative stress is thought to play a key role in the induction of this system (see Fig. 1) due to the increased redox activation of the transcription factor NF- $\kappa$ B, which in turn increases proteasome expression [154], indicating that excess ROS production plays an important part in increased activity on the UPP and, therefore, muscle degradation. NF- $\kappa$ B, cytokine and proteasome inhibitors such as bortezomib and infliximab initially demonstrated potential to ameliorate cachexia-associated weight loss, however did not impress in trials. These proteasome inhibitors have been deemed ineffective as individual treatments for cachexia and may in fact have a negative effect on patient outcomes [163–165].

Further studies suggest that the UPP may not play a role in the early stages of muscle wasting, where patients with <10 % weight loss showing no increase in UPP mRNA [166, 167] or activity levels [168] compared to control patients. Pre-cachectic patients also had no increase in NF- $\kappa$ B-mediated inflammation in muscle, despite the presence of circulating/systemic inflammatory markers, and may suggest that a transition from systemic to local inflammation is required for the UPP to become active in these patients [168]. In contrast, calpain-dependent proteolysis has been implicated in gastric cancer patients with little or no weight loss, with increased mRNA levels and activity of components of this system [166]. However, the activity of the UPP and calpain systems have not yet been looked at in parallel, and longitudinal studies would be beneficial in determining if these patients developed further weight loss and if the UPP was activated in later stages.

TNF receptor adaptor protein 6 (TRAF6) has also been indicated as a major upstream regulator of muscular atrophy, with its role as an E3 ligase in the ubiquitination of proteins, leading to the induction of autophagy [169]. The autophagy–

lysosomal pathway is involved in myofibril degradation through the activation of NF- $\kappa$ B [170], the activity of which is reduced when TRAF6 is knocked out in the skeletal muscle of mice [169]. The inhibition of TRAF6 also resulted in the attenuation of wasting in cachectic mice, with decreased expression of the E3 MuRF1 and the autophagy-related genes LC3B and Beclin1 [169]. TRAF6, therefore, presents another key target for treatment, with inhibition potentially attenuating downstream cytokine signalling cascades leading to UPP and autophagy-mediated wasting.

## 8 Treatments

It is generally accepted that the only way to treat cachexia is to cure the cancer [52]. However, this is not always viable, and even after resection, weight loss may continue for as long as 12 months [20]. Due to the complex nature of cancer cachexia and the vast array of contributors to muscle wasting involved, there is as yet no globally effective or accepted treatment for this condition. It has also been recognised that patients may exhibit different catabolic mechanisms, dependent upon various factors, and therefore, it may be appropriate to discriminate between patients in order for the best form of treatment to be applied [99].

Previously, the main focus of treatment development has been in the maintenance and recovery of lean body mass, in particular upstream intervention of cytokine signalling. Whilst interfering with these systems was considered promising, there was limited efficacy in trials [29, 30]. As such, focus has now shifted toward a downstream approach, with inhibition of the UPP of particular interest [158, 171, 172]. Stimulation of anabolism has also been targeted, with testosterone-related hormone therapy shown to increase the expression of skeletal muscle androgen receptors, thereby increasing utilisation of amino acids derived from protein degradation and stimulating muscle synthesis [160]. Non-steroidal anti-inflammatories such as indomethacin and ibuprofen have been trialled and shown to reduce inflammation and lower levels of acute-phase proteins, IL-6 and cortisol [173–177], whilst antioxidant supplementation such as combination  $\alpha$ -lipoic acid, carbocysteine lysine salt and vitamins E, A and C also had some success in multimodal phase II trials [178, 179].

Combination trials are becoming increasingly prevalent as better understanding of the mechanisms and pathophysiology of cachexia emerges, with simultaneous, multi-target therapies more likely to elicit desirable outcomes than single agents [9, 180]. This view has been confirmed by a large five-arm study, in which patients were prescribed oral antioxidant supplementation, plus medroxyprogesterone acetate or megestrol acetate, eicosapentaenoic acid (EPA)-enriched nutritional supplement, carnitine or thalidomide [180]. The combination therapy showed improved response over each

in isolation, in terms of primary end points (LBM, REE and fatigue) as well as inflammation, suggestive of a compound or synergistic effect when given simultaneously. A combination therapy of this sort, where the intervention is largely diet- or nutrition-based, with the addition of low-cost drugs, may assist with compliance [180]. However, in a population where polypharmacy, in terms of the number of drugs and inappropriate drug use (duplication, underuse, interaction, etc.), is prevalent, the introduction of multiple new therapies increases the risk of adverse interactions [181]. Increased polypharmacy also places a greater burden on patients, both medically and financially, and may lead to non-adherence [181]. A further study from the Mantovani group has highlighted this issue in cachexia, where the individually promising treatments carnitine (amino acid involved in cell energy metabolism), celecoxib (anti-inflammatory, COX2 inhibitor) and megestrol acetate (appetite stimulant) were trialled in combination [182]. The study indicated that carnitine and celecoxib without megestrol acetate was non-inferior to the three in combination, and therefore, the two-drug combination may be more feasible in this instance.

Combination interventions that target cachexia-related pathways in multiple locations, whilst also augmenting treatment of other aspects of patient disease, may assist in reducing the polypharmacy implemented for symptom management. Whilst the search for effective therapy combinations for the treatment of cachexia continues, we propose EPA and oxypurinol as examples of how a combined therapy with common targets may be utilised as part of a broader treatment strategy here.

### 8.1 Eicosapentaenoic acid

EPA is an omega-3 fatty acid which has received much attention in recent years due to the emergence of studies reporting its effects as a broad-spectrum health-promoting agent. EPA supplementation at clinically relevant doses is generally well tolerated in capsule and liquid form, with high doses above clinical relevance having mild side effects of loose bowel movements, bloating and fishy aftertaste, where dose is limited by low-purity fish oils, and sensations of ‘fullness’ rather than toxicity [183, 184]. Along with this high tolerability, EPA’s intersection with multiple pathways involved in cancer cachexia makes it an ideal candidate as a treatment for the condition.

EPA has exhibited anti-tumour properties, inhibiting cancer growth during tumourigenesis and early stages of development through a variety of mechanisms, such as apoptosis, cell signalling and gene expression. The anti-tumour properties of EPA continue with disease progression, improving the efficacy of chemotherapy by protecting non-target tissues and improving its effect on tumour tissue, and may be responsible for stabilisation in dose-limiting toxicity, seen with the addition of EPA supplementation [99, 185].

In recent years, EPA has been trialled as a treatment for cancer cachexia due to its upstream regulation of the expression and activity of the UPP. EPA may alter the balance of eicosanoids toward the production of less inflammatory compounds than those produced by omega-6 fatty acids such as arachidonic acid [186, 187]. EPA replaces arachidonic acid in phospholipid membranes when consumed at high levels [188] and has also been shown to inhibit the production of the eicosanoid 15-HETE from arachidonic acid, which has been implicated in UPP regulation in murine models of cachexia [191]. The administration of EPA attenuates the activation of NF- $\kappa$ B by upstream stabilisation of the I $\kappa$ B/NF- $\kappa$ B complex [98, 189, 190] and reducing nuclear accumulation, which in turn reduces transcriptional activation of proteasome subunits involved in protein degradation [191]. EPA is the only nutritional supplement known to interfere with the UPP [24, 192], but results from trials investigating its anti-cachectic effects are contradictory and often suffer from high attrition [194].

Recent research has shown that EPA can act as an agonist of SOD, with supplementation leading to increased SOD activity in mice treated with chemotherapeutics [195], and has been hypothesised to preserve adipose tissue though interference in glucocorticoid signalling in the regulation of ZAG [196].

Animal trials of EPA have been largely successful [192], as has its combination with other therapeutic approaches, such as leucine supplementation and a high protein diet [77], and in conjunction to other drugs as detailed previously [180]. Several small-scale human trials have demonstrated EPA to significantly reduce the production of cytokines and concentration of CRP and PIF, improve overall weight and functional status and increase appetite in refractory cancer cachexia patients, and in contrast to megestrol acetate, improved lean body mass [184, 186, 187, 193, 197–199]. Jatoi and colleagues demonstrated that EPA scored well against megestrol acetate in areas of overall weight gain, increased survival and improved quality of life, although the proportion of patients gaining <10 % of the body weight was lower in the EPA group [194]. It has further been confirmed that EPA-associated weight gain or stabilisation in cachectic patients is not due to water retention [186, 193]. EPA’s amelioration of cachexia has been shown to be particularly effective in the presence of a targeted exercise regime [77, 200, 201], supporting the inclusion of physical activity in multimodality treatments.

### 8.2 Oxypurinol

Oxypurinol is a non-competitive, irreversible inhibitor of XO, considered more potent than allopurinol, of which it is a metabolite [202]. Currently, oxypurinol is used as a treatment for conditions where XO is a contributor and has been shown to decrease tissue wasting and increase cardiac function in

cachectic animals [203]; however, its specific action in cachexia is yet to be elucidated. Oxypurinol indirectly inhibits XOR through feedback inhibition of amidophosphoribosyltransferase, the first step in purine synthesis, caused by products of increased salvage of hypoxanthine and xanthine [204]. A decrease in purine production and associated metabolism requirements may prompt the reduction of XDH expression and, therefore, downstream activity of this enzyme. Uric acid, produced by XO, increases the conversion of arachidonic acid into its biologically active metabolites (see Fig. 1) [205]. This in turn increases the activation of NOX, perpetuating the signaling cascade that results in the activation of increased transcription of the components of the muscle degradation systems. A combination of the well-documented effect of EPA on attenuation of this pathway, with further inhibition of XO, may have the potential to compound this effect and presents itself as a possible candidate for multimodal treatment of cancer cachexia in conjunction with nutritional support, targeted exercise and further pharmacological intervention.

## 9 Conclusion

Our understanding of cancer cachexia has improved dramatically in the past 10–15 years, as the mechanisms involved in the development and progression of the condition continue to be elucidated. However, there still exists a gap in the clinical management of cachexia due to the complex nature of the condition. As pathways continue to be identified, the development of multimodal therapies becomes more effective, with potential for the treatment of muscle wasting not only in cancer patients but also in other pathologies, such as sarcopenia, sepsis, HIV/AIDS and ischemia–reperfusion injury. EPA continues to display promise for inclusion, in particular as part of a broad approach including targeted exercise, nutritional counselling, social support and pharmaceutical intervention.

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