

# The scientific rationale for optimizing nutritional support in cancer

Richard J.E. Skipworth and Kenneth C.H. Fearon

**Cancer patients lose weight as a result of the anorexia-cachexia syndrome, and this weight loss is associated with significant morbidity and mortality. Thus, nutritional support to arrest or reverse weight loss is of paramount importance in the management of Cachexia cancer patients. Persistent tumour-induced metabolic changes result, however, in a suboptimal response to such support, making nutritional maintenance or improvement difficult targets to achieve. Mechanisms involved in the blockade to anabolism in cancer cachexia include alterations in skeletal muscle and hepatic protein metabolism, and reduced physical activity. Mediators underlying these mechanisms of weight loss include proinflammatory cytokines, tumour-specific cachectic factors, and neuroendocrine mediators of muscle catabolism. The complex mix of different mediators renders unimodal nutritional intervention a strategy that is unlikely to succeed completely.**

## Introduction

Cancer patients lose weight as a result of reduced food intake (secondary to anorexia), abnormal metabolism, or a combination of the two. For patients whose weight loss is predominantly due to anorexia, artificial nutritional support can be very successful. In this situation, the only real problem arises in balancing the use of invasive techniques against the preservation of quality of life, in an individual whose lifespan is quite limited. This is not the situation, however, in most cancer patients. The majority of weight-losing cancer patients probably have a mixture of anorexia and abnormal metabolism, and this situation is more challenging to treat. In these patients, it is clear that nutrition alone is not the answer. For reasons that are not completely understood, nutrition as a unimodal therapy is unable to completely reverse the wasting associated with cancer [1]. Suggested reasons include the promotional effect of nutrition on tumour growth, the action of the tumour as a 'nitrogen trap', and the persistence of complex metabolic and catabolic processes involved in cancer cachexia. Understanding the mechanisms behind the anabolic blockade in cancer cachexia should provide new therapeutic pathways to improve patient outcome and complement the use of nutritional support alone.

## What is the response to nutritional support in weight-losing cancer patients?

It is now more than 25 years since Nixon and co-workers observed a suboptimal response to nutritional support in

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cancer patients [1]. In this study, weight-losing cancer patients who were treated with enteral nutritional support demonstrated significantly less improvement in body weight, serum albumin level, creatinine/height ratio, and midarm muscle area, compared with weight-losing noncancer controls. Thus, there appeared to be a partial blockade to the accretion of lean tissue in advanced cancer patients. In contrast, gain in fat mass was the same in the wasted cancer and noncancer patients (Fig. 1). These findings demonstrate that, although the negative energy balance in cancer cachexia can be overcome by artificial nutritional support, it appears to be much more difficult to prevent or reverse the loss of lean body mass (LBM).

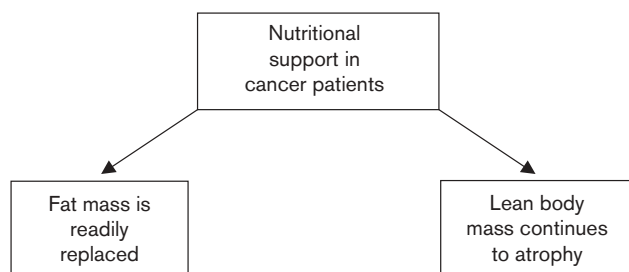
The aim of this article is to examine in detail the scientific basis for the blockade to anabolism in cancer cachexia, and to suggest potential avenues to overcome this problem.

## Mechanisms behind the suboptimal response to nutritional support in cancer patients

### Nutrition as a stimulant for tumour growth

Overnutrition is known to be a significant risk factor in carcinogenesis [2]. Dietary energy restriction has therefore been proposed as a method of inhibiting tumour development and subsequent progression [3–5]. This concept obviously runs contradictory to the idea of nutritional supplementation for cancer patients. Support for this concept, however, has come from work in several

Fig. 1



The effect of nutritional support in wasted cancer patients.

different types of cancer, including bladder transitional cell [6], breast [7], prostate [5] and mononuclear cell leukaemia. The beneficial effect of dietary energy restriction appears to be a result of enhanced DNA repair, reduced oxidative DNA damage, altered adrenal metabolism, altered insulin metabolism, changes in growth-signalling pathways [e.g. insulin-like growth factor-1 (IGF-1)], and various changes in expression of oncogenes (e.g. Ras, c-erbB-2) and oncosuppressors (e.g. p53) [8].

Human studies have also suggested that tumour metabolism may be stimulated by nutritional supplementation. Following preoperative intravenous nutrition administration of conventional mixtures (0.2 g of N and 103 nonprotein kJ/kg body weight) or mixtures enriched with the branched-chain amino acids (BCAAs) leucine, isoleucine and valine (0.2 g of N with 30% from BCAAs and 103 nonprotein kJ/kg body weight), rates of protein synthesis were measured (by the incorporation of L-[1-<sup>13</sup>C] leucine) in muscle tissue and colorectal tumours removed at surgery from cancer patients [9]. Both forms of intravenous nutrition resulted in a significant stimulation of the rate of protein synthesis in muscle tissue and tumour tissue compared with intravenous saline controls. The nutritional supplement enriched with BCAA, however, was less stimulatory than the conventional supplement [9]. The tumour expression levels of proliferating cell nuclear antigen also showed changes with intravenous feeding of the two different amino acid mixtures that correlated significantly with the changes in protein synthesis levels. Although this study, however, demonstrated an increase in protein synthesis in response to nutritional support, it only examined the very short-term effects of total parenteral nutrition, and it may be that over time the changes observed would have been less significant. Moreover, the balance of clinical evidence is not in favour of a significant stimulation of tumour growth by either enteral or parenteral nutritional support.

#### Metabolic competition theory

Metabolic competition theory states that the rapidly dividing neoplastic cells compete with host tissues for

amino acids, thereby acting as a 'nitrogen trap' [10]. This mechanism may be important in experimental animal models in which neoplastic tissue accounts for a high proportion of carcass mass, but is unlikely to be the case in human cancers. Most human tumours weigh only a few grams and constitute a very small percentage of total patient mass. Similarly, patients with large abdominal masses may sometimes exhibit otherwise reasonable nutritional status.

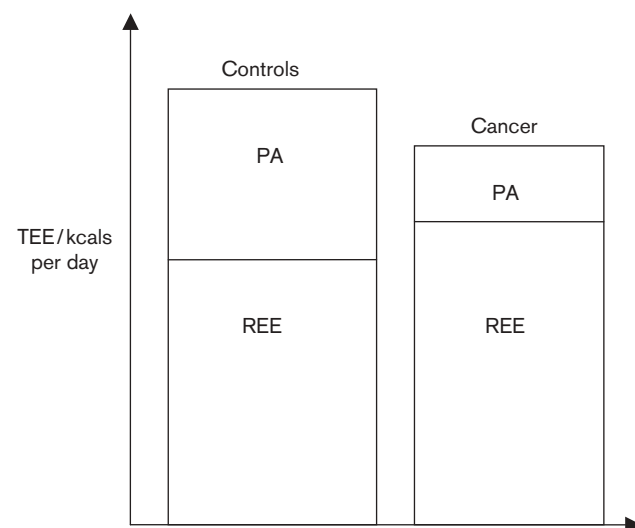
#### Persistent metabolic change driving ongoing catabolism

##### Energy balance

Cancer patients may lose weight despite a normal food intake, suggesting that resting energy requirements are increased. In practice, however, measured resting energy expenditure (REE) levels have been variable. Indeed, increased [11], normal [12] and reduced REE [13] have all been described in cancer patients. It has been suggested that different tumour types (and stage of disease) may be associated with different effects on REE; lung and pancreatic cancer inducing an increased REE [14,15], whereas gastric and colorectal cancer having little effect [16]. Although REE may be increased in some wasted cancer patients, however, total energy expenditure (TEE) may actually fall owing to reduced physical activity (PA) [17] (Fig. 2). PA is a significant and variable component of daily energy expenditure in free-living individuals and its reduction can more than compensate for any elevated REE.

The natural consequence of such compensation is that the patient is able to do less and this reduction in PA

Fig. 2



Although resting energy expenditure (REE) may be increased in cancer patients, total energy expenditure (TEE) may be reduced owing to a decrease in physical activity (PA).

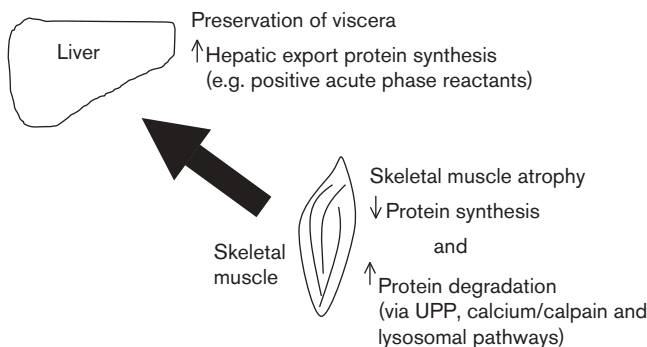
directly affects quality of life. It has been estimated that the net energy deficit in cachectic patients is of the order of 200–300 kcal/day. Filling this energy gap is an essential objective of nutritional support in advanced cancer patients.

**Protein metabolism**

A key feature of the altered body composition in patients with cancer cachexia is a severe and specific loss of skeletal muscle mass with relative preservation of the visceral protein mass (Fig. 3). These gross changes are a reflection of a complex array of metabolic changes in both the skeletal muscle and the liver. Understanding the mechanisms underlying this reprioritization of protein metabolism away from the peripheral tissues and towards the liver is thought to be vital in understanding both the cachectic process and the molecular targets for its reversal.

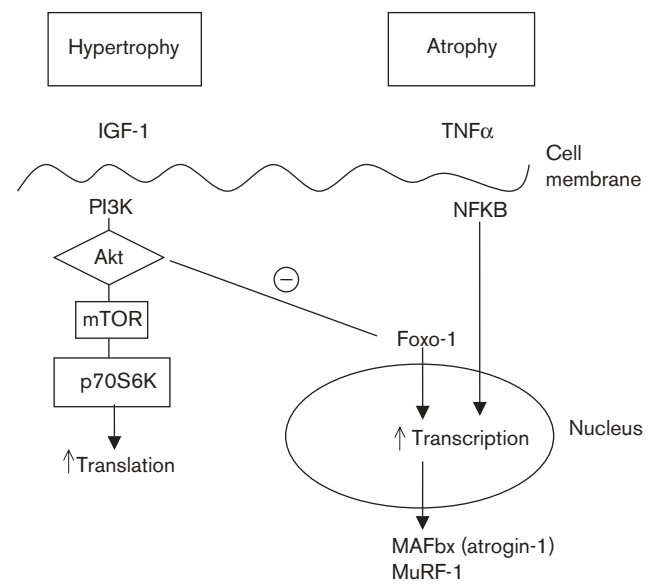
*Muscle protein metabolism* In cancer cachexia, muscle protein synthesis rates tend to be decreased (or unchanged) whereas protein breakdown rates are increased [18] (or unchanged). These observations result in the overall net loss of skeletal muscle/LBM seen in cancer patients [19]. The proteolytic pathways leading to the degradation of skeletal muscle are various and complex (Fig. 4). The predominant mechanisms appear to be the increased gene expression and activity of the calcium/calpain and ubiquitin–proteasome pathways (UPP) [20], in addition to the classical proteolytic mechanisms of the lysosomal cathepsins B, H, D and L [21]. The calcium/calpain-regulated release of microfilaments is an early (and perhaps rate-limiting) component of the catabolic response in muscle. Released microfilaments are then tagged for degradation by the attachment of a poly-ubiquitin chain, which is recognized by the 26S proteasome, a large multisubunit catalytic complex. This process is regulated by the ubiquitin-conjugating enzyme E2<sub>14k</sub> and the specific ubiquitin E3 ligases MuRF-1 and

**Fig. 3**



The reprioritization of protein metabolism in cancer cachexia.

**Fig. 4**



Molecular mechanisms of skeletal muscle hypertrophy and atrophy.

atrogin-1/MAFbx [22,23]. Recent evidence has suggested that cancer cachexia is driven by a specific targeted loss of myosin heavy chains by the UPP and other pathways [24].

The E3 ligases are strongly regulated by the transcription factor nuclear factor-κB (NF-κB) [25]. The pivotal involvement of NF-κB in many other pathways allows for a great deal of molecular cross talk. For example, Akt, a key serine-threonine kinase within the phosphatidylinositol 3-kinase (PI3K) pathway, stimulates NF-κB-dependent transcription by stimulating the transactivation domain 1 of the p65 subunit (in an IκB-kinase-dependent pathway) [26]. This observation suggests a possible mechanism by which derangements of anabolic neuroendocrine (e.g. IGF) pathways (see later) may exert their influence on skeletal muscle mass. Cytokine-induced activation of NF-κB has also been shown to inhibit skeletal muscle differentiation and function, by the down-regulation of Myo-D mRNA [27], an essential regulator of skeletal muscle differentiation and repair.

In addition to NF-κB, the forkhead box, class O (Foxo) family of gene transcription factors has also recently been shown to regulate expression of the E3 ligases in various models of skeletal muscle atrophy [28]. In particular, Foxo-3 upregulates atrogin-1, resulting in decreased muscle fibre size, whereas Foxo-1 is specifically induced in atrophying muscle [28]. These transcription factors are also inhibited by the IGF/Akt/PI3K pathway [29].

Recently, other specific mechanisms have been suggested as important in the regulation of skeletal muscle atrophy

in cancer cachexia. Aberrant glycosylation of the dystrophin glycoprotein complex, a multiprotein structure associated with myofibre membranes, in conjunction with reduced dystrophin expression, appears to be a possible regulatory link between cancer cachexia and muscular dystrophy [30].

Certain tumour-specific cachectic factors are also important in skeletal muscle protein degradation (Fig. 5). Proteolysis inducing factor (PIF) is a sulphated glycoprotein of  $M_r$  24 000 that was first identified as a glycosylated polypeptide using an antibody cloned from splenocytes of mice transplanted with the MAC16 adenocarcinoma [31]. PIF is capable of inducing skeletal muscle breakdown [31] (via activation of the UPP [21]) and apoptosis (via stimulation of caspase activity [32]). PIF has since been detected in the urine of weight-losing patients with carcinoma of the pancreas, breast, ovary, lung, colon, rectum and liver [33]. Patients with pancreatic cancer excreting PIF in the urine have a significantly greater total weight loss and rate of weight loss than patients whose urine does not contain PIF [34].

**Hepatic protein metabolism** It has been suggested that the increased acute phase protein production by the liver represents a sink for amino acids that, in the face of inadequate dietary protein intake (owing to anorexia), contributes to the overall loss of skeletal muscle [35] (see Fig. 3). Recent studies in weight-losing patients with pancreatic cancer have shown that not only are synthesis rates of hepatic export proteins elevated in the fasted state, but that they rise even higher during enteral feeding. Thus, in terms of altered hepatic protein metabolism, enteral feeding appears to accelerate one of the basic mechanisms that may be contributing to loss of lean tissue. This mechanism may also contribute to the relative lack of efficacy of conventional nutritional support in reversing loss of lean tissue in such patients.

## Mediators of metabolic change in cancer cachexia

### Proinflammatory cytokines

Strong evidence from many studies suggests that a variety of proinflammatory cytokines have a role in the genesis of

cancer cachexia [36,37]. It can be shown that human cancer cell lines produce proinflammatory cytokines, and that these cytokines consequently induce the hepatic acute phase protein response (APPR) [36–38]. Systemic inflammation has been found in association with the majority of solid epithelial malignancies, and up to 50% of patients may have an APPR at the time of diagnosis [39]. The presence of this response is now recognized as an independent adverse prognostic factor in these patients [39,40]. C-reactive protein (CRP) is the prototypical positive acute phase reactant, and elevated CRP levels have been identified in patients with lung [41], melanoma [42], multiple myeloma [43], lymphoma [44], ovarian [45], renal [46], pancreatic [39], gastro-oesophageal [47] and colorectal tumours [40]. Within these disease conditions, serum CRP concentration has positively correlated with weight loss [48], the presence of hypermetabolism and anorexia [49], the extent of disease [40], and reduced survival [39,40]. The induction of the APPR appears to occur primarily through an interleukin (IL)-6-dependent mechanism [38], although other molecules such as tumour necrosis factor (TNF), IL-2, IL-8, interferon (IFN)- $\gamma$  and parathyroid hormone-related peptide (PTHrP) [50] are also important. Indeed, polymorphisms of the human IL-1 $\beta$  gene [51], IL-1 receptor antagonist gene [52] and the human IFN- $\gamma$  gene [53] have all been associated with the reduced survival of patients with certain cancers.

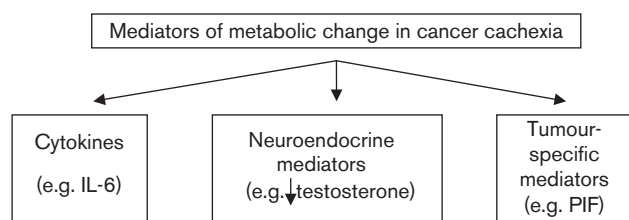
Cytokines released by tumour cells are generally not detectable in the circulation and probably act only locally to promote inflammation and activate host inflammatory cells passing through the tumour. These activated host cells then release their own cytokine cascade, which initiates the APPR. In cancer cases when serum levels of cytokines (e.g. TNF- $\alpha$ ) are elevated, these levels generally correlate with the stage of the disease, reflecting tumour size and metastasis [54].

Some cytokines may be potential repressors of cachexia. IL-4, IL-10 and IL-13 all demonstrate anti-inflammatory, and presumably anticachectic, activity. IL-15, for example, is reported to have anabolic effects on skeletal muscle through the direct inhibition of muscle proteolysis [55]. The final wasting status of the cachectic patient presumably depends on the balance between procachectic and anticachectic cytokines.

### Neuroendocrine mediators of muscle catabolism and anabolism

The precise role of activation of the neuroendocrine stress response in relation to the development of cancer cachexia in general, and muscle wasting in particular, is little researched. It seems clear, however, that muscular atrophy in cancer cachexia is a result of inadequate anabolic activity and/or excess catabolic activity. Media-

Fig. 5



Mediators of metabolic change in cancer cachexia.

tors involved in the anabolism of skeletal muscle include insulin, growth hormone (GH) and testosterone, whereas catabolic mediators include cortisol and myostatin. Weight-losing cancer patients frequently exhibit insulin resistance [56], GH resistance [57], hypogonadism [58], elevated serum cortisol and significantly increased cortisol:insulin ratio [56]. Insulin resistance is associated with increased concentrations of IL-6 in the same patients [56].

Testosterone is a major determinant of skeletal muscle mass [59]. Decreased levels of testosterone are a common finding in cachectic male patients with advanced pancreatic cancer, and the presence of hypogonadism correlates positively with weight loss, and negatively with survival (unpublished results).

Recently, major research interest has focused on the importance of reduced IGF-1 and increased myostatin in cachexia. As part of the GH/IGF-1 axis, IGF-1 is able to inhibit atrogen-1 through the Akt/PI3K/Foxo pathway [29]. The downregulation of IGF-1 therefore results in an increase in skeletal muscle atrophy via the E3 ligase. The concept of increasing IGF-1 levels, however, as a possible treatment for cachexia is complicated by the possible associated side-effects of increased carcinogenesis and/or disease progression. Myostatin, a member of the transforming growth factor (TGF)- $\beta$ , plays a pivotal role in the negative regulation of skeletal muscle growth. Myostatin overexpression has been found in a wide range of disease states including cachexia, disuse atrophy and ageing sarcopenia [60]. Loss of myostatin activity in cattle [61], mouse [62] and human [63] has subsequently led to skeletal muscle hypertrophy and increased muscle function.

#### **Role of reduced physical activity in the anabolic blockade in cancer cachexia**

It has been shown that weight-losing cancer patients have markedly reduced levels of PA [17]. In hypermetabolic, weight-losing pancreatic cancer patients TEE was significantly reduced owing to a lower physical activity level (PAL: ratio of TEE to REE) [17]. Measured PAL [mean 1.24 (SD 0.04)] was much lower than that recorded in healthy adults of similar age [mean 1.62 (SD 0.28)] [64], and it is entirely plausible that levels of activity as low as this may exacerbate the muscle wasting seen in cachexia [65]. These levels are comparable to those observed in spinal cord injury patients living at home [66] or in patients with cerebral palsy [67].

In experimental postprandial states, muscle inactivity has been shown to impair the amino-acid-mediated stimulation of protein synthesis [68]. The ability of combined insulin and glucose infusion to decrease whole-body proteolysis, however, is not affected [68]. Thus, an

impaired ability of protein/amino acid feeding to stimulate body protein synthesis may be the major catabolic mechanism for the effect of bed rest/physical inactivity on protein metabolism. This suggests that a protein intake level greater than normal may be required during nutritional supplementation of cachectic cancer patients to achieve the same postprandial anabolic effect during muscle inactivity. It is worth noting that in weight-losing pancreatic cancer patients, it was possible to increase TEE and PAL with a specialized nutritional supplement containing eicosapentaenoic acid (an omega-3 fatty acid with anti-inflammatory properties) administered over an 8-week period, but not with an isocaloric, isonitrogenous control supplement [17].

#### **Conclusion**

Although nutrition is of paramount importance in the management of cancer patients, persistent tumour-induced metabolic changes result in a suboptimal response. A complex mix of different mediators renders unimodal nutritional intervention a strategy that is unlikely to succeed completely. Further issues that must also be overcome when administering oral nutritional therapy include the high prevalence of primary anorexia/early satiety in cancer patients (ranges from 15 to 40% at diagnosis [69], and increases with disease progression). Cytokines [including IL-1 $\beta$ , IL-6, TNF and macrophage inhibitory cytokine (MIC)-1], central neurotransmitters (e.g. serotonin), feeding-stimulating neuropeptide systems [e.g. neuropeptide Y (NPY)], anorexigenic neurone systems [e.g. pro-opiomelanocortin (POMC)], hormones (e.g. leptin and ghrelin) and tumour-derived compounds have all been implicated in this process [69]. Despite these difficulties, however, clinical trials using combination therapies or immunonutrition have shown promise for the future. For example, oral nutritional supplements containing eicosapentaenoic acid have resulted in net weight gain and improvements in LBM in patients with pancreatic cancer cachexia [70]. Combination studies using cyclo-oxygenase inhibitors, erythropoietin therapy and specialized nutrition-focused patient care (either oral nutritional support or home total parenteral nutrition) have demonstrated improved patient survival, improved energy balance and higher maximum exercise capacity [71]. Continued improved understanding of the specific molecular pathways involved in cancer cachexia will offer additional potential therapeutic targets for multimodal therapy in the future.

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