disorders are thought to be due to the release of large amounts of 5-HT from enterochromaffin cells, which then bind to 5-HT receptors [6]. 5-HT activates various serotonin receptor subtypes in the gastrointestinal tract and ganglia, exerting a range of biological and physiological effects [6]. It has been reported that a significant increase in 5-HT concentrations in the hypothalamus of cisplatin-treated rats [7]. Accumulated findings suggest that serotonin 2C (5-HT2C) receptor subtypes are involved in appetite regulation [8, 9]. The 5-HT2C receptor subtype is expressed in proopiomelanocortin neurons in the hypothalamus, which is the major site of its anorexigenic action [6]. In the present clinical setting, nausea and vomiting can be controlled by administering 5-HT3 receptor antagonists together with anticancer agents [6]. However, 5-HT3 receptor antagonists may not be sufficiently controlled in cisplatin-induced anorexia [6]. Recent studies have reported that cisplatin-induced anorexia is mediated through reduced gastric and hypothalamic ghrelin secretion, and peripheral 5-HT2B and cerebral 5-HT2C receptor activation are responsible for the phenomenon [6, 10, 11]. Facilitating the gastric and hypothalamic ghrelin secretion through 5-HT2C receptor inhibition can be a useful therapeutic approach for cisplatin-induced anorexia.

Cytokines

Cytokines are protein molecules released by lymphocytes and/or monocyte macrophages [5]. They are released into the circulation and transported to the brain through the blood–brain barrier (BBB) and circumventricular organs (i.e., 'leaky' areas in the BBB) [12–17]. Peripheral cytokines may influence the brain via neural pathways or second messengers such as nitric oxide (NO) and prostanoids [5]. Cytokines are also produced by neurons and glial cells within the brain, partly in response to peripheral cytokines [12–17]. Although the site of cytokine synthesis within the brain is dependent on the nature of the stimulus, systemic disease seems to predominantly influence expression in the hypothalamus, the area with the highest densities of receptors [16].

Numerous cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-γ), have been postulated to play a role in the etiology of cancer cachexia [12, 13, 18–21]. It is not certain whether the cytokine production is primarily from tumour or host inflammatory cells. It has been hypothesised that either tumour cell production of proinflammatory cytokines or the host inflammatory cell response to tumour cells is the source of the acute phase protein response (APPR) seen in many malignancies and in cachexia [22].

High serum levels of TNF-α, IL-6, and IL-1 have been found in some cancer patients, and the levels of these cytokines seem to correlate with the progression of some tumors [23–25]. Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and inducing cancer cachexia [18, 23–26]. The role of TNF-α in mediating cancer cachexia is supported by evidence that intraperitoneal injection of a soluble recombinant human TNF-receptor antagonist improved anorexia in tumor-bearing animals [27]. In humans, IL-1 appears to play a significant role in mediating cachexia, as megestrol acetate has been shown to exert its effects via reduced expression of IL-1 by mononuclear cells beyond its influence on hypothalamic NPY concentrations, which shows orexigenic effect [28]. Interestingly, anorexigenic neurons, such as proopiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART) neurons in the arcuate nucleus of the hypothalamus express the type 1 IL-1 receptor, and intracerebroventricular injection of IL-1 increases the frequency of action potentials of POMC/CART neurons and stimulates the release of alpha-melanocyte-stimulating hormone (α-MSH), which shows anorexigenic effect as well [29].

TNF-α, IL-1, IL-6, and IFN-γ have been implicated in the induction of cancer-related muscle wasting [30]. There is growing evidence that the accelerated muscle proteolysis seen during malignant tumor growth is mediated by the activation of the non-lysosomal adenosine triphosphate-dependent (ATP-dependent) ubiquitin proteasome pathway [31, 32]. In addition, inflammatory cytokines influence the expression of functionally relevant enzymes in cardiac cachexia [30]. It has been demonstrated that TNF-α, IFN-γ, and IL-1β are potent activators of inducible nitric oxide synthase (iNOS) expression [30], which in turn produces toxic levels of NO high enough to inhibit the key enzymes of oxidative phosphorylation [30]. It has also been shown in vitro that NO is able to impair the contractile performance of skeletal muscle [33].

More direct evidence of cytokine involvement comes from experiments in which specific neutralization of cytokines can relieve anorexia and cachexia in experimental animal models [18, 24, 25, 34]. Examples of antibodies that have been shown to successfully relieve anorexia and cachexia when administered include the anti-TNF-α, anti-IL-6, anti-IL-1, and anti-IFN-γ antibodies, although no single antibody has been proven to reverse all of the features of wasting seen in cancer cachexia [24]. These studies revealed that cachexia can rarely be attributed to any one cytokine but rather is associated with a set of cytokines and other cachectic factors that work in concert [5]. Recent studies include the use of anti-IL-6 humanized monoclonal antibody, which appears to inhibit cancer cachexia in murine models [35] and may be of clinical significance in cancer patients [35].

The problem with ascribing specific tissue responses to individual cytokines is that considerable overlap and redundancy exists in the cytokine network [14–17, 21]. Administration of either TNF-α or IL-1 will induce the synthesis of a variety of other proinflammatory cytokines such as IL-6 [5]. Thus, studies that use pharmacological administration of recombinant cytokines may not discriminate between biological responses induced directly by the administered cytokine and those induced secondarily by other stimulated cytokines [5]. Systemic disease such as cancer and inflammation may elicit a cytokine cascade in which several cytokines are induced simultaneously [21].

Systemic changes in response to inflammation are denoted the acute phase response [36]. Up to 50 % of patients with solid epithelial cancers may have an elevated APPR [37]. APPR is correlated with elevated resting energy expenditure and reduced energy intake [38]. Other longitudinal studies have found a poorer prognosis in patients displaying this response, independent of weight loss [39].

C-reactive protein

C-reactive protein (CRP) is the most common method used to assess the magnitude of the systemic inflammatory response [36]. The modified Glasgow prognostic score combines CRP and plasma albumin concentrations to create a simple scoring system that serves as a prognostic factor that is independent of stage and treatment and that predicts survival [40, 41] (Table 1).

Raised CRP concentrations at the time of admission to hospital is indicative of an increased risk for all-cause mortality; there is a 22.8-fold increase in cancer mortality in patients with highly elevated CRP concentrations (>80 mg/L) [42]. It has been shown that patients with inoperable non-small cell lung cancer had at least 5 % weight loss and almost 80 % an elevated CRP levels [43]. In patients without weight loss, those who displayed evidence of a systemic inflammatory response reported more fatigue ($P < 0.05$) [43]. In another study of patients with gastroesophageal cancer, the rate of weight loss was also correlated with elevated CRP serum concentrations [44].

Table 1 Modified Glasgow Prognostic Score (mGPS): an inflammation-based prognostic score

Biochemical measure	Score
C-reactive protein ≤10 mg/L + albumin ≥35 g/L	0
C-reactive protein ≤10 mg/L + albumin <35 g/L	0
C-reactive protein >10 mg/L	1
C-reactive protein >10 mg/L + albumin <35 g/L	2

Source: [41]

Negative nitrogen balance

In adults, muscle mass remains fairly constant in the absence of stimuli (e.g., exercise) and thus protein synthesis and degradation generally remain in balance [45]. However, in cachexia, muscle atrophy occurs, which results from a decrease in protein synthesis, an increase in protein degradation, or a combination of both [45]. In recent years, it has become evident that specific regulating molecules are upregulated (e.g., members of the ubiquitin–proteasome system, myostatin, and apoptosis inducing factors), whereas other factors (e.g., insulin-like growth factor 1) are down-regulated in cachexia muscle wasting [30]. A major barrier to the effective management of skeletal muscle wasting is the inadequate understanding of its underlying biological mechanisms [30]. The most evident metabolic explanation for muscle decline is an imbalance between protein catabolism and anabolism [30]. In addition to an increase in catabolism, a reduction in anabolism has been shown to occur in cancer cachexia [30]. Skeletal muscle wasting in cancer cachexia can be mediated by multiple factors derived from tumor and host cells [46].

At least four major proteolytic pathways (lysosomal, Ca^{2+}-dependent, caspase-dependent, and ubiquitin–proteasome-dependent) operate in skeletal muscle and may be altered during muscle cachexia [30]. Aside from these four distinct pathways, the autophagic/lysosomal pathway must also be considered [30]. In this pathway, portions of the cytoplasm and cell organelles are sequestered into autophagosomes, which subsequently fuse with lysosomes, where the proteins are digested [47].

When dissecting the molecular regulation of the ubiquitin–proteasome-dependent system (UPS) and autophagy, it became evident that forkhead box O (FoxO) transcription factors play a central role [30]. FoxO transcription factors, which are normally phosphorylated and inactivated by phosphatidylinositol 3-kinase (PI3K)-Akt/PKB, translocate into the cell nucleus and induce the transcription of the skeletal muscle-specific E3 ubiquitin ligases, muscle RING-finger protein-1 (MuRF1), and atrogin-1/muscle atrophy F-box (MAFbx) [48], as well as autophagy-related genes such as LC3 and Bnip3 [49]. Upstream of PI3K-Akt, several factors including reactive oxygen species (ROS), TNF-α, tumor-released proteolysis-inducing factor (PIF), peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), and IGF-1 have been shown to influence this regulatory system [48, 50–52]. In contrast, protein anabolic factors such as IGF-1 counteract muscle atrophy [30]. Aside from inhibiting autophagy and the UPS, IGF-1 activates protein synthesis via the Akt-mammalian target of rapamycin (mTOR)–p70 S6 kinase (p70S6K) signaling pathway [53, 54].

The UPS is a major intracellular system that regulates skeletal muscle wasting in response to tumor factors and inflammatory cytokines [46]. In cancer cachexia, the decrease in skeletal muscle protein synthesis is partly related to the increased serum levels of PIF [30]. Intravenous administration of PIF to normal mice produced a rapid decrease in body weight that was accompanied by increased mRNA levels of ubiquitin in the gastrocnemius muscle [51]. There were also increased protein levels of the 20 S proteasome core and the 19 S regulatory subunit, suggesting activation of the ATP–ubiquitin-dependent proteolytic pathway [30]. Recent evidence suggests that PIF decreases protein synthesis by inhibiting protein translation initiation through phosphorylation of the eukaryotic initiation factor 2 (eIF2-alpha) [55].

Myostatin

Myostatin is an extracellular cytokine that is mostly expressed in skeletal muscles and is known to play a crucial role in the negative regulation of muscle mass [56]. Upon binding to the activin type IIB receptor, myostatin can initiate several different signaling cascades, resulting in decreased muscle growth and differentiation [56]. Muscle size is regulated via a complex interplay of myostatin signaling with the IGF-1/PI3K/Akt pathway, which is responsible for increased protein synthesis in muscle [56]. Therefore, the regulation of muscle weight is a process in which myostatin plays a central role, but the mechanism of its action and the role of the signaling cascades involved are not fully understood [56]. Myostatin upregulation was observed in the pathogenesis of muscle wasting during cancer cachexia [56].

Data are available that demonstrate a beneficial effect of myostatin inhibition in cancer cachexia [57], but conflicting study results have also been reported [58]. With respect to apoptosis, several reports demonstrated an increase in apoptosis or apoptosis-related proteins in skeletal muscle after the induction of cachexia [30]. The skeletal muscle of cachectic tumor-bearing animals reveals the presence of DNA fragmentation, a hallmark of apoptosis [59]. In addition to DNA fragmentation, a significant up-regulation of caspase-1, -3, -6, -8, and -9 activity was also documented in the gastrocnemius muscles of tumor-bearing mice [60].

Insulin-like growth factor-1

One of the main positive regulators of muscle growth is IGF-1 [56]. Under normal conditions, IGF-1 signaling seems to be dominant and blocks the myostatin pathway [61]. However,
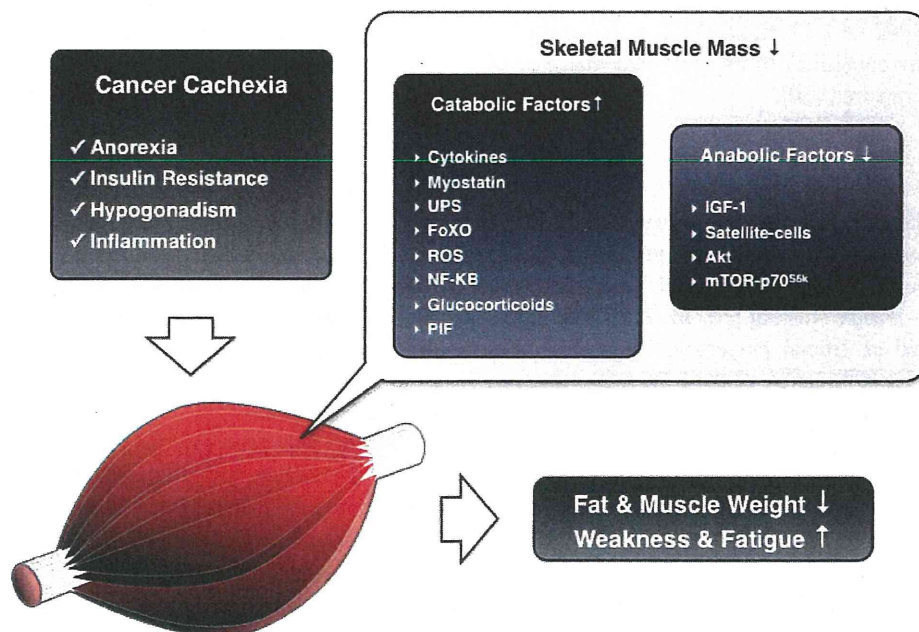

Fig. 2 An abbreviated diagram of skeletal muscle in cancer cachexia. In adults, muscle mass remains fairly constant in the absence of stimuli (e.g., exercise) and thus protein synthesis and degradation generally remain in balance. However, in cachectic situation, the balance of skeletal muscle has been shifted towards protein breakdown, finally leading to the weight loss, weakness, and fatigue that characterize cancer cachexia. In recent years, it has become evident that catabolic factors are up-regulated (e.g., cytokines, myostatin and members of the ubiquitin–proteasome system), whereas anabolic factors (e.g., insulin-like growth factor 1) are down-regulated in cachexia muscle wasting. *IGF-1* Insulin-like growth factor 1, *FoxO* forkhead box O, *UPS* ubiquitin–proteasome system, *ROS* reactive oxygen species, *NF-κBPIF* tumor-released proteolysis-inducing factor, *mTOR* mammalian target of rapamycin, *p70S6K* p70 S6 kinase

an inhibition of IGF-1 can occur when myostatin is overexpressed [62, 63]. IGF-1 can prevent TGF-α family-mediated apoptosis [64], and it was shown that in the absence of IGF-1, the level of apoptosis in C2C12 cells treated with myostatin increased [56]. The mechanism by which IGF-1 regulates myostatin signaling includes the inhibition of transcription factors responsible for the induction of atrogenes via phosphorylation through the PI3K/Akt pathway [56]. Akt plays a significant role in different metabolic processes in the cell, particularly in the hypertrophic response to insulin and IGF-1 [65, 66]. Akt is the 'crossing point' between the IGF-1 and myostatin pathways [56]. It is likely that under conditions of muscle wasting, myostatin can reverse the Akt/mTOR pathway, which is normally responsible for protein synthesis, to inhibit protein synthesis via FoxO, GSK-3β, or other unknown patterns, leading to the loss of muscle mass [56] (Fig. 2).

Another factor that may contribute to decreased anabolism is angiotensin II [30]. In an animal model of continuously administered angiotensin II, markedly reduced plasma IGF-1 levels occurred [67]. Compared with a sham treatment, angiotensin II-infused hypertensive rats lost 18–26 % of their body weight within a week, an effect that was completely reversed by losartan (an angiotensin II receptor type 1 receptor antagonist) [67].

Experimental data suggest that local IGF-1 may act as a regenerative agent, promoting the recruitment of stem cells to sites of muscle injury [68]. Because IGF-1 is reduced in experimental models of cachexia [69], it is reasonable to assume that under conditions of cachexia, the function of satellite cells is impaired [30].

Oxidative stress

There is a wealth of evidence suggesting that oxidative stress is associated with chronic diseases and it is assumed that an increase in ROS directs muscle cells into a catabolic state that leads to muscle wasting [30, 70, 71]. In cachexia, ROS are regarded as crucial players for muscle protein catabolism via their stimulation of the UPS [30]. Reaction products are measured as indirect markers of oxidative stress [30]. In cachexia, malondialdehyde (MDA) is regarded as one such indirect marker [30].

In addition, experimental cancer cachexia appears to be mediated by increased nitrosative stress secondary to increased nitric oxide formation. Indeed, protein tyrosine nitration is markedly increased in the muscles of tumor-bearing rats with advanced cachexia, due to lower levels of antioxidant enzymes [72, 73].

Anabolic hormones

There is a relative deficiency or resistance to anabolic hormones in cachectic states. Up to 50 % of men with metastatic cancer present with low concentrations of testosterone prior to chemotherapy [74]. A reduction in testosterone might lead to reduced bone mass, muscle strength, and sexual function in both men and women [75, 76]. Low concentrations of testosterone and other anabolic hormones are major contributors to cachexia-related wasting of skeletal muscle [77]. However, with respect to a correlation between body composition (including muscle mass) and the concentration of anabolic hormones, conflicting results have been reported in the current literature [30, 74, 78, 79].

Effects on antineoplastic therapy

Catabolic drivers

Antineoplastic therapies such as surgery, radiotherapy, and chemotherapy are known to have a negative impact on a patient's nutritional intake through the development of systemic inflammation, exacerbation of already-reduced energy, and, particularly, on swallowing difficulties and anorexia due to nausea [22, 80]. Additionally, surgical patients may be fasted for prolonged periods perioperatively and both chemotherapy and radiotherapy can induce side-effects such as anorexia, nausea, vomiting, mucositis, taste change, or lethargy [80]. Consequently, antineoplastic therapies interfere with the maintenance of the nutritional state [81] (Tables 2, 3, 4).

Symptoms will depend on the nature and course of the chemotherapeutic drugs being used and the location, volume, and dose of radiotherapy [80]. Some cytotoxic drugs may even generate their own cachexia-like side effects [82]. For example, treatment with antitubulin taxanes reduces body weight in tumor-bearing mice more than healthy mice, even when the agents significantly reduce tumor growth [82]. However, the complex relationship between cancer cachexia and the effects of antineoplastic drugs remains to be fully elucidated [82].

C-reactive protein

A key (but often variable) component of cachexia is hypercatabolism that is directly caused by tumor metabolism, systemic inflammation, or other tumor-mediated effects. The most widely accepted index of systemic inflammation is serum CRP [83]. CRP plasma values are positively correlated with weight loss, the occurence of cachexia, and recurrence in advanced cancer [84]. Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, and gastrointestinal tumors [84, 85].

Recent studies suggest that CRP is much more than a mere marker of the body's inflammatory load [86, 87]. In

Table 2 Nutritional consequences of radical resection of alimentary tract organs

	Nutritional consequences
Tongue or pharynx	Need for nutrition by tube (dysphagia)
Thoracic oesophagus	Gastric stasis (due to vagotomy), malabsorption of fats (due to vagotomy)
Stomach	Dumping syndrome, anaemia, malabsorption of fats, iron, calcium and vitamins
Duodenum	Biliary-pancreatic deficiency
Jejunum (up to 120 cm)	Reduced absorption of glucose, fats, protein, folic acid, vitamin B12, etc.
Ileum (60 cm) or ileocaecal valve	Malabsorption of vitamin B12, biliary salts and fats
Small intestine (75 %)	Malabsorption of fats, glucose, protein, folic acid, vitamin B12, etc., diarrhea
Jejunum and ileum	Complete malabsorption
Colon (subtotal or total resection)	Water and electrolyte loss
Pancreas	Malabsorption and diabetes
Liver	Transient hypoalbuminaemia

Source: [81]

Table 3 Nutritional complications associated with radiotherapy

Region irradiated	Early effects	Late effects
Head and neck	Odynophagia, xerostomia, mucositis, anorexia, dysosmia, hypogeusia	Ulceration, xerostomia, dental caries, osteoradionecrosis, trismus, hypogeusia
Thorax	Dysphagia	Fibrosis, stenosis, fistula
Abdomen and pelvis	Anorexia, nausea, vomiting, diarrhea, acute enteritis, acute colitis	Ulceration, malabsorption, diarrhea, chronic enteritis, chronic colitis

Source: [81]

Table 4 Effects of chemotherapeutic drugs

Drug	Severity and duration
Chemotherapeutic drugs commonly associated with severe nausea and vomiting	
Nitrogen mustard (mustine hydrochloride; mechlorethamine hydrochloride USP)	Occurs in virtually all patients. May be severe, but usually subsides within 24 h
Chloroethyl nitrosoureas, streptozotoci (streptozocin)	Variable, but may be severe. Occurs in nearly all patients. Tolerance improves with each successive dose given on a 5-day schedule
Cis-platinum (cisplatin)	May be very severe. Tolerance improves with intravenous hydration and continuous 5-day infusion. Nausea may persist for several days
Imidazole carboxamide (DTIC; dacarbazine)	Occurs in virtually all patients. Tolerance improves with each successive dose given on a 5-day schedule
Chemotherapeutic drugs commonly associated with mucositis	
Methotrexate	May be quite severe with prolonged infusions or if renal function is compromised. Severity is enhanced by irradiation. May be prevented with administration of adequate citrovorum rescue factor (folinic acid; leucovorin)
5-Fluorouracil (fluorouracil USP)	Severity increase with higher doses, frequency of cycles, and arterial infusions
Actinomycin D (dactinomycin USP)	Very common; may prevent oral alimentation. Severity enhanced by irradiation
Adriamycin (doxorubicin)	May be severe and ulcerative. Increased in presence of liver disease. Severity enhanced by irradiation
Bleomycin	May be severe and ulcerative
Vinblastine	Frequently ulcerative

Source: [81]

cultured human umbilical vein endothelial cells, CRP was shown to activate endothelial cells, which, in turn, express Intracellular Adhesion Molecule-1 (ICAM-1) [86, 88]. CRP also induces other adhesion molecules in endothelial cells such as vascular-cell adhesion molecule-1 (VCAM-1) and E-selectin [86]. These molecules are involved in leukocyte-binding to the endothelial layer. CRP also activates the expression of monocyte chemotactic protein-1 (MCP-1) [87]. In addition, circulating factors, such as lipid-mobilising factors (LMF), and proteolysis-inducing factor (PIF) may play a role in the development of cancer anorexia and cachexia [88]. These are tumor-derived catabolic factors acting directly on adipose tissue and skeletal muscle, without affecting food intake [88].

However cachexia can exist without overt systemic inflammation, and thus indirect indices reflecting the catabolic drive such as responsiveness to chemotherapy and the rate of progression should also be assessed [83]. No consensus was reached about the usefulness of other factors contributing to catabolism [83]. These include insulin resistance, prolonged high-dose corticosteroid therapy, hypogonadism, and increased resting energy expenditure [83].

Increased nuclear factor-κB activity

Nuclear factor-κB (NF-κB), a nuclear transition activator factor, plays a major role in upregulating inflammatory gene expression, including expression of COX-2, nitric oxide synthase, TNF-α, IL-1, and IL-6 [89]. The proinflammatory response occurs particularly with the formation of p65–p50 dimers, which act as the central control to an inflammatory response. NF-κB is one of the principal transcription factors to transduce TNF-a signals into the cells. Moreover, it also activates gene transcription of cytokines, acute-phase response proteins, and cell adhesion molecules [90, 91].

Activation of NF-κB accelerates inflammation, increases cellular proliferation of tumors, and prevents apoptosis [90]. Inhibition of NF-κB therefore is both antineoplastic and can reduce cachexia. Inhibition of NF-κB also sensitizes tumors to chemotherapy and radiation, something that is the subject of multiple research trials [92].

In fact, genetic overexpression of IκB blocks NF-κB-dependent processes. Two studies have shown that glucocorticoid administration induces transcription of IκB gene [93, 94]. Increased levels of IκB gene trap NF-κB in inactive cytoplasmic complexes, hence inhibiting its ability to induce transcription of inflammatory cytokines. Moreover, fumar acid, which blocks the nuclear translocation of NF-κB, has a high anti-inflammatory capacity [93]. More recently, activation of NF-κB by overexpression of a IκB phosphorylating kinase has been shown sufficiently to block myogenesis, thus illustrating the link between NF-κB and cachexia development [94]. However, complete inhibition of NF-κB has proven detrimental; knockout studies targeting the major subunits of NF-κB show severe immunodeficiency in mice, which was lethal in some cases [95]. Resolution of inflammation also requires NF-κB expression and complete inhibition of NF-κB can lead to severe cellular apoptotic damage in critical illness [96].

Managing cancer cachexia

Treatment goals in current standard of care

The European Palliative Care Research Collaboration (EPCRC) has developed evidence-based recommendations for the classification and treatment of cachexia in advanced cancer patients [97]. These treatment guidelines focus on patients with advanced cancer that are likely to suffer from refractory cachexia. Many of these patients are receiving palliative care, and life expectancy often is short. Only little cachexia-specific research has been done on this patient group, and the EPCRC treatment guidelines had to consider whether research results taken from other disease stages could be applicable for patients with advanced and incurable disease with refractory cachexia [97].

Management of cachexia must take into account the patient's prognosis [97], as it may take several weeks for patients to respond to anti-cachectic treatment [97]. For patients with a short life expectancy, treatment options for cachexia may add to the disease burden without offering adequate symptom relief and thus may not be appropriate [97]. Health care professionals should discuss all treatment options with the patient and ensure that they are well-informed about available treatments and expected treatment outcomes [97]. All patients should have equal access to appropriate assessment and management of cachexia, whether they are receiving home care, day care, or are hospital inpatients [97].

The best way to treat cancer cachexia is to cure the cancer, but unfortunately this remains an infrequent achievement among adults with advanced solid tumors [98, 99]. Therefore, the treatment goal for cachexia should be the reversal of the loss of body weight and muscle mass with a variety of pharmacological agents (Fig. 3) [99]. As a minimal goal, body weight should be maintained and further loss prevented [97]. The treatment approach should be multimodal and similar to treatment used in patients with pre-cachexia [97]. This includes detailed assessment and repeated monitoring, vigorous nutritional support, anti-inflammatory treatment, treatment of secondary gastrointestinal symptoms and other causes for decreased oral nutritional intake as well as evaluation of anti-neoplastic

Fig. 3 The potential modalities of pharmacological intervention of cancer anorexia-cachexia syndrome. Agents were classified as those established (first-line) or those unproven/investigational (second-line), depending on their site or mechanism of actions. ①, inhibitors of production/release of cytokines and other factors; ②, gastroprokinetic agents with or without antinausea effect; ③, blockers of Cori cycle; ④ ⑤, blockers of fat and muscle tissue wasting; ⑥, appetite stimulants with or without antinausea effect; and ⑦, anti-anxiety/depressant drugs. These agents should be selected on an individual basis according to the cause of cachexia or the state of the patient. *The precise actions of statins on skeletal muscle still remain controversial. First-line treatments: glucocorticoids ① ⑥, progesterones ① ⑥. Second-line treatments: cannabinoids ⑥, cyproheptadine ⑥, branched-chain amino acids ⑤ ⑥, metoclopramide ② ⑥, eicosapentanoic acid ① ④ ⑤, 5′-deoxy-5-fluorouridine ①, melatonin ①, thalidomide ①, β2-adrenoceptor agonists ⑤, non-steroidal anti-inflammatory drugs ① ⑥, others anabolic steroids ⑤, pentoxifylline ①, hydrazine sulfate ③, statin ① ⑤*, angiotensin-converting-enzyme inhibitor inhibitor ⑤, selective androgen receptor modulator ⑤. Source: [99] with modification
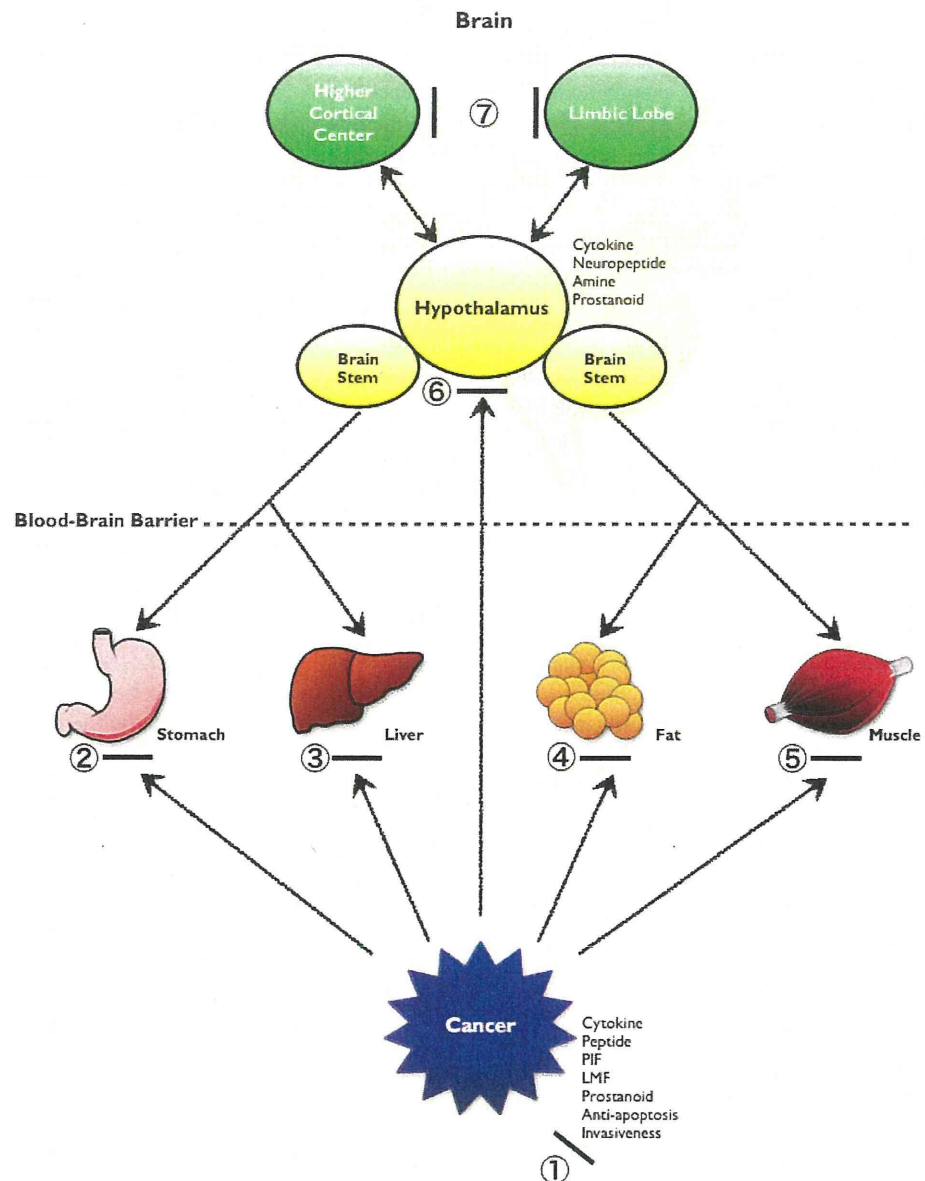
options to reduce the catabolic drive of the cancer [97]. However, for refractory cachexia, the primary treatment goal should not be reversal of weight loss, but the alleviation of cachexia-related symptoms and an overall increase of well-being [97].

Pharmacological treatments

Appetite stimulants

Reversing the effects of cancer cachexia does not appear to be influenced by stimulating the appetite [100]. Thus, the

decision to use an orexigenic drug should be based on tolerance of the side effects, cost effectiveness, and treatment burden [100]. Current studies are investigating an approach of drug combinations to reverse cancer cachexia [101, 102]. A recent study with 332 patients comparing medroxyprogesterone, megestrol acetate, oral supplementation with eicosapentaenoic acid, L-carnitine, and thalidomide found that the combination therapy was superior to any of the other treatment arms with single drug treatment [102]. Combination therapy led to increased lean body mass, decreased resting energy expenditure, and improved appetite [102]. Until an effective intervention for reversing

cancer cachexia is developed, early intervention with nutritional support and prevention of treatment-related morbidities (e.g., nausea, vomiting, diarrhea, dysphagia, pain, or depression) is advised [102, 103].

Progestational drugs, cannabinoids, and cyproheptadine are used in the clinic as appetite stimulatus in the therapy of the cancer-induced anorexia and cachexia syndrome [99]. These drugs have been shown to be partially effective in reversing or maintaining the symptom of body weight loss in patients with chronic illness [99].

Cannabinoids are highly liquid-soluble substances with delta-9-tetrahydrocannabinol (THC) as an active ingredient that work synergistically, additively, or even antagonistically when ingested together (e.g., by smoking marijuana). Appetite stimulation and body weight gain are well-recognized effects of using marijuana and its derivatives [99]. This may have significant implications for the clinical usefulness of marijuana or its individual compounds in treating cachexia.

Dronabinol is the synthetic oral form of THC, which is the active ingredient responsible for the appetite-stimulating effect [99, 104–106]. Dronabinol and marinol (in the United States) and nabilone (in Canada) have been used as antiemetics in cancer, with many studies demonstrating their efficiency in treating chemotherapy-induced nausea and vomiting [99]. Several studies of THC in advanced cancer-associated anorexia have shown some improvement in mood and appetite, with either no or some improvement in body weight [107, 108]. However, randomized, controlled trials are needed to better determine the efficacy and usefulness of THC in cancer cachexia.

The effects of cannabinoids are mediated via specific receptors. Two types of cannabinoid receptors, CB1 and CB2 have been detected. However, the precise mechanism by which cannabinoids exert their effect has yet to be clarified. It has been shown that almost 20 percent of the cancer patients receiving chemotherapy along with dronabinol as an antiemetic experienced side effects, such as euphoria, dizziness, somnolence, and confusion resulting in a dose reduction or less frequently in withdrawal of the treatment [106]. It has been suggested that the drug could be taken at bedtime to avoid some psychotomimetic effects and that it might produce long-lasting appetite stimulation for 24-h period following ingestion [104].

Cyproheptadine is an antiserotoninergic drug with antihistaminic properties that has been shown to have a slight appetite-stimulant effect in a number of human conditions [109]. A randomized, controlled trial found mild appetite stimulation in patients with advanced cancer, although it did not prevent progressive weight loss [110]. Considerable evidence, both in humans and experimental animals, suggests that anorexia may be mediated by increased serotonergic activity in the brain. Its blockade,

therefore, might be beneficial in reducing symptoms [111, 112]. Cyproheptadine also appeared to stimulate appetite and decrease diarrhea in patients with advanced carcinoid tumors [113]. Studies on the effects of cyproheptadine in progressive weight loss in patients with cancer or other causes of cachexia suggest that cyproheptadine has a beneficial effect on appetite stimulation but only slight effects on weight gain [110, 114, 115]. 5-hytroxytryptamine type 3 (5HT3) receptor antagonists, such as ondansetron and granisetron, have entered widespread clinical use as antiemetics for cancer chemotherapy [99].

Progestins

Megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are synthetic, orally active progestational agents. In several randomized controlled studies, these compounds have been found to improve appetite, caloric intake, and nutritional status in patients with non-hormone responsive tumors and cancer anorexia-cachexia syndrome [104–106, 116–122].

MA has demonstrated a dose-related beneficial effect, in a dose range from 160 mg to 1600 mg/day on appetite, caloric intake, body weight gain (mainly fat), and sensation of well-being (with an optimal dosage of 800 mg daily) [118]. Increasing MA dosages from 160 mg to 800 mg/day improves response to a level beyond which no further improvement occurs [118]. It is recommended that a patient is started on the lowest dosage (i.e, 160 mg/day) and that the dose is uptitrated according to clinical response [105, 109].

MPA has similarly been shown to increase appetite and food intake with a stabilization of body weight at a dose of 1000 mg (i.e., 500 mg twice daily) [109]. Although the drug is safe at doses of 500–4000 mg daily, side effects have been shown to increase above oral doses of 1000 mg [104]. At present, there is considerable evidence for the effect of synthetic progestins on appetite and body weight in patients with cancer anorexia and cachexia [123]. However, further issues regarding the optimal treatment duration, the best time to start treatment during the natural history of the disease, and the eventual impact on the overall quality of life need to be clarified [123]. Moreover, optimal dose regimens for MA in different indications, such as appetite improvement, patients' sense of well-being, weight gain, are still to be identified.

The following adverse events have been reported with MPA: thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hyperglycemia, hypertension, adrenal suppression, and adrenal insufficiency if the drug is abruptly discontinued [104–106, 116–120, 124]. Although patients rarely need to stop taking these drugs because of adverse effects, these drugs should not be prescribed in

cases of thromboembolic/thrombotic disease, heart disease, or for patients at risk for serious fluid retention [104].

Although the mechanism of weight gain of progestational drugs in presently uncertain, it might be related to glucocorticoid activity [105]. MA may induce appetite via stimulation of NPY, a potent central appetite stimulant in the hypothalamus, modulation of calcium channels in the ventromedial hypothalamus (VMH)—a well known satiety center [1, 4, 125–133] which reduces the firing tone of VMH neurons. On the other hand, MPA has been shown to inhibit the activity of proinflammatory cytokines such as IL-1, IL-6, and TNF-α [28, 109, 134]. Serum levels of such cytokines were reported to be decreased in cancer patients after MA or MPA treatment [109]. More studies are needed to finally clarify the pharmacologic effects of MA and MPA drugs and to confirm the anti-inflammatory effects.

Several other drugs have been evaluated as agents to ameliorate cancer anorexia-cachexia. Corticosteroids are frequently used in clinical practice for appetite stimulation in patients with advanced malignancies and randomized clinical trials showed that corticosteroid medications may stimulate appetites in patients with advanced cancer [135]. However, these studies were not able to show any substantial non-fluid weight gain in treated patients [135]. Efforts are also ongoing to evaluate both anabolic steroids and hydrazine sulfate as drugs for the treatment of patients with cancer cachexia [135].

Hydrazine is a substance that inhibits the enzyme phosphoenol pyruvate carboxykinase (PEP-CK) and interferes with gluconeogenesis [135]. However, hydrazine and hydrazine sulfate might be a human carcinogen based on evidence for carcinogenicity in animal studies [135, 136]. The preliminary nature of these investigations, however, precludes recommendations for the use of these drugs in routine clinical practice [135].

Other orexigenic agents

The orexigenic mediator ghrelin has been reported as having a key role in increasing appetite and, therefore, food intake. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptors [137, 138]. It is synthesized principally in the stomach and is released in response to fasting [138].

Ghrelin strongly stimulates GH secretion in humans [139–142] and does so more potently than GHRH by several fold under similar circumstances [143]. Furthermore, ghrelin and GHRH synergistically increases GH release [141]. GH regulates IGF-1 levels and increases muscle strength [144, 145], whereas GH enhances lipolysis, IGF-1 stimulates protein synthesis, myoblast differentiation, and muscle growth [143]. Evidence that ghrelin exerts anti-inflammatory actions has been accumulating

[143]. Ghrelin induces the anti-inflammatory cytokine IL-10 [146, 147], suppressing the production of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α both in vitro [148, 149], and in vivo [146, 150, 151]. Additionally, ghrelin inhibits the activation of NF-κB, which controls the production of multiple proinflammatory cytokines during inflammatory insults [147, 149, 150]. Although the molecular mechanisms and cellular targets mediating ghrelin inhibition of NF-κB activation remain to be determined, the vagus nerve may play an important role in the ghrelin-mediated inhibition of proinflammatory cytokine release [150, 152]. MuRF1 and MAFbx are upregulated under cachectic catabolic conditions, and NF-κB activation may regulate skeletal muscle proteasome expression and protein degradation [143]. The elevations in MuRF1 and MAFbx expression seen in skeletal muscle after thermal injury, arthritis, and dexamethasone administration were normalized, attenuated, and prevented, respectively, by ghrelin or GHS administration [153–156]. IGF-1 prevents the expression of MuRF1 and MAFbx by inhibiting FoxO transcription factors via stimulation of the PI3K/Akt pathway [143]. The IGF-1 receptor triggers activation of several intracellular kinases, including PI3K [156]. Thus, the effects of ghrelin on NF-κB activation and IGF-1 synthesis are favorable for minimizing inflammatory responses and skeletal muscle wasting in patients with cachexia [143].

In addition to increasing food intake, an experimental study has shown that repeated administration of ghrelin improves cardiac structure and function, and attenuates the development of cardiac cachexia in chronic heart failure (CHF). These results suggest that ghrelin has cardiovascular effects and regulates energy metabolism through growth hormone-dependent and -independent mechanisms [157]. Thus, administration of ghrelin may be a new therapeutic strategy for the treatment of severe CHF [157].

At present, a phase II randomized, placebo-controlled, double-blind study, using an oral ghrelin mimetic, demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients [158]. Several clinical trials with ghrelin are currently on going.

Herbal medicine; translational aspects, particularly for cancer cachexia

There have been a number of published cases of cancer patients treated with Kampo, a form of Japanese traditional herbal medical practice, who reportedly experienced significant clinical benefits [159]. As an example, *rikkunshito*, a Kampo formula, has been shown to be useful in clinical practice for cachectic cancer patients.

Rikkunshito has been used to treat gastrointestinal tract disorders such as functional dyspepsia [160–164] and

gastroesophageal reflux [165]. A recent study regarding the underlying mechanisms of *rikkunshito* has shown that *rikkunshito* and its component 10-gingerol may inhibit the degradation of acyl-ghrelin by inhibiting the circulating ghrelin degrading enzyme [166]. Another study has shown that administration of *rikkunshito* reversed the decrease in hypothalamic ghrelin secretion and food intake 24 h after cisplatin treatment [6]. A most recent study showed that *rikkunshito* improved anorexia, gastrointestinal dysmotility, muscle wasting, and anxiety-related behavior [10]. In this study, *rikkunshito* in tumor-bearing rats was effective not only against anorexia–cachexia, but also for promoting survival, particularly in combination with chemotherapy [10]. Moreover, median survival of pancreatic cancer patients with ascites who were treated with gemcitabine was significantly prolonged by administration of *rikkunshito* [10]. Active components of *rikkunshito*, *hesperidin* and *atractylodin*, potentiated ghrelin secretion and receptor signaling, respectively, and *atractylodin* prolonged survival in tumor-bearing rats [10]. The physiological functions of endogenous ghrelin are enhanced by the dual actions of rikkunshito; which involve the stimulation of ghrelin secretion and the activation of GHS-R activity, possibly due to allosteric changes in the receptor [10]. These studies suggest that *rikkunshito* may be useful in clinical practice for cachectic cancer patients.

Because Japanese Kampo has long been used, the potential risks and benefits of its use are well recognized despite the relative paucity of the mechanistic insights [159]. Unconventional therapies such as herbs and minerals that have been used in ancient medical traditions have led to the identification of active anticancer agents [159]. Although the working mechanisms of some of the herbs and minerals are unclear and remain to be elucidated, they are worth further studying as newly potential therapy agents for cancer treatment [167].

Non pharmacological treatments

Diet modification

Because cancer cachexia differs from starvation, to date, single modality therapies with traditional nutritional regimens have failed to demonstrate efficacy in improving weight gain, including a gain in lean body mass, in patients diagnosed with cancer cachexia [168]. The average caloric deficit in weight-losing patients with cancer cachexia is approximately 250–400 kcals/day [168]. An average supplementation of 1 calorie/mL has not been shown to improve the nutritional status of patients receiving chemotherapy [169, 170]. However, recent studies using a more calorie- protein-dense supplementation have suggested that weight stabilization can be achieved; however,

improvements in lean body mass has not yet been observed [171].

Patients with cancer cachexia undergoing aggressive re-feeding are at risk for 're-feeding syndrome' during the first 2–3 weeks of treatment [172]. This potentially lethal condition is characterized by severe electrolyte and fluid shifts due to metabolic abnormalities and bears a significant risk for morbidity and mortality [172]. The clinical features include fluid-balance disturbances, abnormal glucose metabolism, hypophosphatemia, hypomagnesiemia, and hypokalemia [173].

Before starting the re-feeding process, electrolyte disorders should be corrected and circulatory volume should be carefully restored. This may delay the administration of complete nutrition but is usually accomplished within 12–24 h. Caloric repletion should be at a slow rate of approximately 20 kcal/kg per day (or 1000 kcal per day) initially. However this rate may not meet the patients' fluid, sodium, potassium, protein, or vitamin requirements unless these are specifically addressed.

Gradual introduction of calories, particularly over the first week of re-feeding, should be prudent until the patient is metabolically stable [174]. Hypophosphatemia has to be treated if the serum level is less than 0.30 mmol/l or the patient is symptomatic. Supplementation of phosphate should be given intravenously at 40–80 mmol/day, together with magnesium (8–16 mmol/day) and potassium (80–120 mmol per day). These dosages should be adjusted according to monitored serum levels [175].

Exercise

Physical exercise may be beneficial in the treatment of cancer cachexia, as it increases insulin sensitivity, protein synthesis rate, and anti-oxidative enzyme activity [97]. It also may lead to a suppression of the inflammatory response and an enhancement of immune function [176]. All of these mechanisms can help to curb the pathophysiological changes underlying cachexia.

There is significant evidence that endurance exercise (e.g., high number of repetitions performed over extended time periods against relatively low resistance) ameliorates cancer-related fatigue [177]. By contrast, resistance exercise (lower number of repetitions against higher resistance) attenuates muscle wasting in different catabolic conditions [97]. Physical therapy is also advised during periods of bed rest, as reduced fitness, strength, and loss of lean body mass may occur [178]. Physical therapy can help to counteract fatigue and depression, as well as maintain strength and range of motion [97].

Although it is increasingly recognized that exercise training seems to be a polypill against the dramatic changes in the skeletal muscle in cachexia, scientific proof is scarce