Cancer cachexia, from bench to bedside

Cortez Natalia Erika, Kawaoka Shinpei, Penna Fabio

Cancer appearance frequently associates with paraneoplastic syndromes and general poor health condition, nowadays known as cancer cachexia. Cachexia, frequently present at cancer diagnosis, negatively impacts on patient quality of life, clinical management and effectiveness of anti-cancer treatment, eventually leading to premature death. In the last two decades a huge effort has been posed towards understanding the underlying mechanisms of cachexia that are summarized in this review, focusing from the canonical view of cachexia as a muscle wasting condition to the more recent evidence of cachexia as a systemic metabolic disorder. The clarification of the mechanisms behind cancer cachexia produced two main outcomes, the first being the design and testing of prospective therapeutic protocols that include nutritional interventions, anti-cytokine treatments, proteostasis modulators, exercise, and exercise-mimicking drugs, that in the near future will allow to define a multimodal standard of care for cachexia that is still missing. The second being the increased awareness of the clinical relevance of cachexia, with progressive increasing screening among the cancer population and the definition of peculiarities associated to distinct cancer types. In the future, timely diagnosis and treatment of cachexia will likely lead to more effective therapies and to the improvement of the overall management of cancer patients.

Cancer cachexia: an unmet clinical need

Cancer cachexia (CC) is a complex multifactorial syndrome characterized by unintentional weight loss due to progressive depletion of skeletal muscle with or without loss of adipose tissue[1]. Approximately 30-50% of patients suffer from CC at the time of cancer diagnosis, with the incidence varying depending on the type of tumor (most frequent in pancreatic, gastric, hepatic, pulmonary, esophageal and colorectal cancers) and affecting 50-80% of patients with advanced cancer[2,3]. CC advances from pre-cachexia to cachexia, and finally to refractory cachexia[1]. Several factors related to tumor stage, anorexia, malabsorption, sex and age of patients, treatment type and response, plus burdening psychological factors,add to the complexity and progression of CC[4,5]. CC negatively impacts on the efficacy and tolerance of cancer treatments, quality of life, surgical complications, prognosis, and survival[6,7]. Unfortunately, regardless of diagnosis or stage, there are no effective treatments for CC and it remains an unmet clinical need[8]. Therefore, understanding the pathophysiological mechanisms involved in cancer-related cachexia is critical in order to develop therapies for effective prevention or treatment.

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1 Experimental research: from cancer patientsto experimental model systems

The current knowledge of the molecular and pathophysiological mechanisms involved in CC comes mainly from preclinical animal models, where mechanistic studies can be performed before moving to clinical validation[9]. Still, there is a persistent need of novel and more reliable models[10].

Indeed, before using live mammals, cell-based models, such as the C2C12 mouse myoblast cell line, are useful to evaluate agents for their anti-cachectic activity[11) 12)]. Recently, 3D bioprinted muscle models have been proposed as another *in vitro* model for drug screening in cachexia[13)]. *Drosophilafly* models, which are generally used to study cancer metabolism and to explore potential treatment drugs, are also potentially useful for CC research[14)]. The fast rate of reproduction and the economical husbandry are advantages of the fly models, but the inability to reproduce features of human disease is an important limitation[14) 12)].

Moving to the most used mammal models, rodent cancer cells from stabilized lines are implanted subcutaneously, intramuscularly or intraperitoneally into syngeneic immune-competent animals and are allowed to grow until the tumor burden induces cachexia symptoms[10) 15)].The two most well-established murine cancer cachexia models are the C26 (colorectal cancer) and the LLC (Lewis Lung carcinoma), but an ample variety of models exist[10) 16)~18)]. Syngeneic models are widely employed due to their rapid tumor growth, consistent body weight loss and muscle wasting, plus simplicity to use[19)]. Nevertheless, while tumors in humans usually do not grow to more than 1% of body mass, in animals they can reach up to 10% of body weight[7) 20)]. Moreover, cachexia usually occurs within months to years in humans, while in rodents the wasting is much more aggressive and fast, limiting the therapeutic window for testing prospective anti-cachexia agents[19) 20)]. Xenograft models like patient-derived xenografts (PDX) where tumor fragments or cells from patients are transplanted in immunodeficient mice are also used[21)], although the lack of an intact immune system imposes a strong limitation.

Finally, in orthotopic cancer mouse models, either genetically engineered mouse models (GEMMs), transplanted, or chemically induced, the tumor grows in the appropriate anatomical site. When compared to ectopic models, orthotopic tumor models better recapitulate human cancer features such as tumor microenvironment, vascularization, metastasis, and chemotherapy response[10) 20)]. Among the more widely used GEMM to study CC, it is worth mentioning the adenomatous polyposis coli (Apc) Min/+ mouse for intestinal cancer[19)], the KPC ($KRAS^{G12D}P53^{R172H}$ $Pdx\text{-}Cre^{+/+}$) and the KPP ($Kras^{+/G12D}$, $Ptf1a^{+/ER\text{-}Cre}$, $Pten^{f/f}$) mice for pancreatic cancer-associated cachexia[22) 23)]. Major limitations of orthotopic models are that for transplanted models the procedures entail considerable technical skills, and for GEMMS there are elevated costs required to breed and maintain a colony in order to generate a sufficient sample size for experimental analysis[19) 12)].

Several factors impact preclinical findings, such as the model used, the type of tumor, the rate of disease progression, the age of the animals, the presence of metastasis and the use of chemotherapy[9)]. Pre-clinical studies using a variety of models that take into account the previously mentioned factors, such as diverse tumor types and therapeutics, could be beneficial in the design of future clinical trials[24)].

2 Molecular bases of muscle wasting

Several factors contribute to cancer-related muscle wasting (the main hallmark of CC), including anorexia, malnutrition, increased resting energy expenditure and decreased physical activity and/or mobility[25)~27)]. Additionally, cancer treatments can cause dysphagia,dry mouth, mouth ulcers, nausea, vomiting, constipation, diarrhea and/or malabsorp-

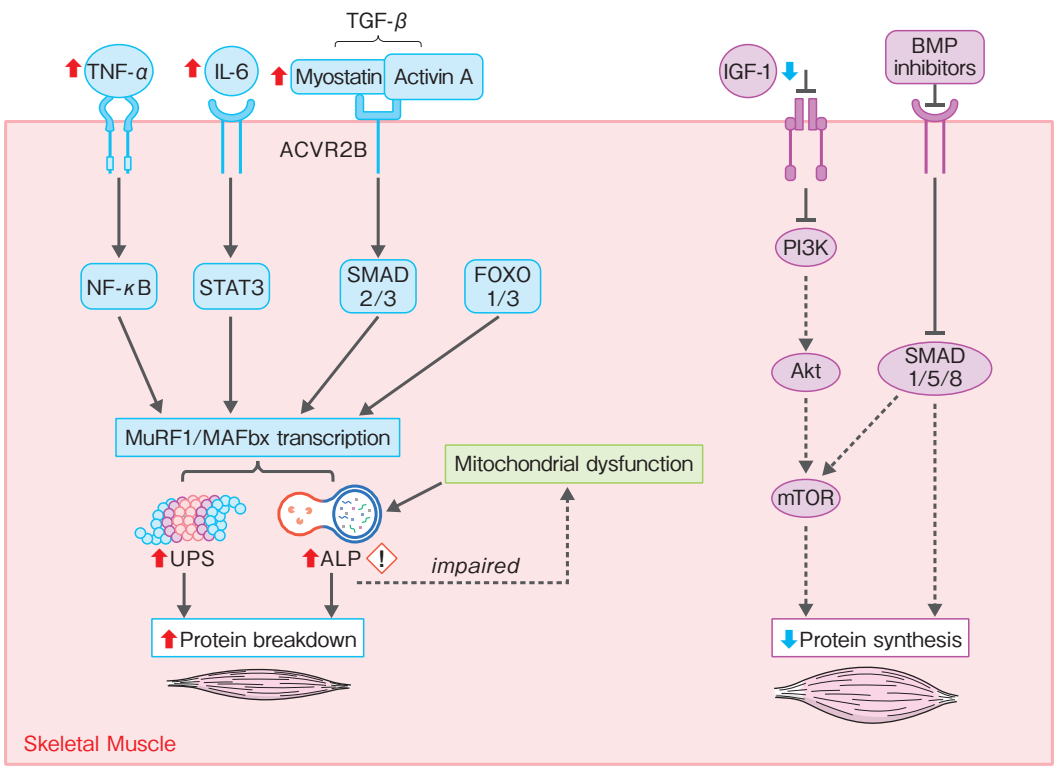

Figure 1. Key molecular bases of muscle wasting in cancer cachexia.
Cytokines, like tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) activate the nuclear factor kappa-light-chain enhancer of B cells (NF-κB) and the signal transducer and activator of transcription 3 (STAT3) respectively. The signaling molecules myostatin and activin A, members of the transforming growth factor β (TGF-β) family, bind to the ActR2B receptor complex and activate the transcription factor Smad2/3. The transcription factors NF-κB, STAT3, Smad2/3 and forkhead (FOXO1/3) induce the activation of two key ligases, muscle RING-finger protein-1 (MuRF1) and muscle atrophy F-box (MAFbx), which in term activate catabolic pathways, primarily the ubiquitin-proteasome system (UPS) and the autophagy/lysosomal pathway (ALP), and induce protein breakdown. Effective mitochondrial disposal via ALP is impaired and contributes to mitochondrial dysfunction. A decrease in protein synthesis occurs due to a decrease in the insulin-like growth factor1 (IGF-1) which inhibits the Akt/ mammalian target of rapamycin (mTOR) in addition to the suppression of the bone morphogenetic protein (BMP)/Smad1/5/8 axis by BMP inhibitors.

tion, exacerbating weight loss and wasting[28) 29)].

Cancer cells can cause a derangement that mobilizes glucose precursors from the muscle to provide fuel to the tumor and to cope with the increased energy need of the host, which in turn affects body composition[30) 31)].

Several cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and IL-1 are considered mediators of CC, since they are increased in tumor hosts and are sufficient to directly increase protein degradation and to decrease protein synthesis[32) ~ 35)]. Altered muscle proteostasis is indeed the major cause of muscle wasting in CC 36. Increased protein degradation is due to the activation of catabolic pathways, primarily the ubiquitin-proteasome system (UPS) and the autophagy/lysosomal pathway (ALP)[37) 38)] . Muscle RING-finger protein-1 (MuRF1) and muscle atrophy F-box (MAFbx)/Atrogin-1, two key ligases that mark muscle proteins to be degraded via UPS and ALP, are induced by the activation of several transcription factors such as nuclear factor-κB (NF-κB), Fork-

head (FOXO1 and FOXO3), SMAD2/3, and STAT3[39)37)40)]. The transcriptional regulation of genes critical to the cachexia-associated catabolism is controlled by cytokine signaling; for example, TNF-α activates NF-κB, while IL-6 activates the JAK/STAT3 pathway[41)~43)]. Beyond the canonical cytokines, myostatin and activin A are members of the transforming growth factor β (TGF-β) family that bind to activin type 2 receptor B (ACVR2B) inducing SMAD2/3 activity[37)]. ALP physiologically removes damaged proteins and organelles including dysfunctional mitochondria (mitophagy), but is upregulated during cancer cachexia largely by FOXO3[37)44)]. The dysregulation of mitochondrial metabolism also plays a critical role in muscle wasting during CC[45)36)32)46)47)]. Interestingly, mitophagy is induced in cachectic skeletal muscle, but effective mitochondrial disposal is impaired, eventually contributing to mitochondrial dysfunction in tumor hosts[48)49)]. Protein synthesis is controlled by anabolic pathways such as the insulin-like growth factor1 (IGF-1)/Akt/ mammalian target of rapamycin (mTOR) and the bone morphogenetic protein (BMP)/Smad1/5/8[37)50)]. In cachexia, IGF-1 decrease suppresses the Akt pathway and inhibits protein synthesis[51)52)26)53)]; consistently, the BMP/Smad1/5/8 axis is suppressed by BMP inhibitors such as Noggin, contributing to wasting[54)]. A graphical summary of the alterations described above can be found in Figure 1.

3 Liver metabolism: an emerging contributor to cachexia

The liver controls systemic energy metabolism, as it regulates the transport, storage, breakdown and use of glucose, lipids and amino acids[55)56)]. Alterations in hepatic function influence energy expenditure in cancer patients, with evidence indicating that hepatic impairment of metabolism and energy imbalance directly contribute to cachexia[55)~58)]. Inter-organ substrate shuttling among liver, skeletal muscle, and tumor contributes to cachexia[59)]. Hepatic futile cycles represent a large proportion of the energy demand of cancer patients[60)]. Tumors can increase the rate of hepatic glycolysis, glycogenolysis, lipolysis, and proteolysis to generate glucose via gluconeogenesis[31)]. Meanwhile, an increase in muscle and tumor glycolysis leads to higher production of lactic acid, which is then driven to the liver to be used in gluconeogenesis as part of the Cori cycle, but in an energy inefficient manner[31)58)]. The hepatic depletion of glycogen stores together with the lactate shuttling between liver and tumor potentially elevates the whole body energy expenditure, thus producing weight loss[61)62)]. Furthermore, the energy inefficiency in the onset and progression of CC may also be influenced by hepatic mitochondrial dysfunction[55)61)63)]. Interestingly, decreased hepatic mitochondrial function in CC has been associated with increased cholesterol synthesis and accumulation in the mitochondrial membrane[55)64)]. Also disrupted hepatic lipid metabolism occurs in CC, with preclinical models showing impaired VLDL secretion and inefficient mobilization of intra-hepatic triglycerides into circulation[65)~67)]. Moreover, bile acid metabolism is altered, which contributes to liver inflammation and CC[16)60)].

The inflammatory response imposed by the tumor and the immune system of the host is exacerbated by the liver[31)]. When pro-inflammatory cytokines are increased systemically they may target the liver to further contribute to CC[27)]. TNF-α and IL-6 in particular induce the acute phase response (APR) gene expression while reducing albumin production[67)]. Contrary to the reduced protein synthesis observed in muscle, the liver increases the protein synthesis as cancer progresses[31)68)69)], mainly due to APR that serves as an indicator of inflammation in cachexia[70)71)]. Moreover, the APR requires amino acids, which are partly obtained from muscle proteolysis and driven to the liver, contributing to muscle atrophy[30)59)60)]. C-reactive protein (CRP), the main acute-phase protein synthesized by the liver, is a marker of sys-

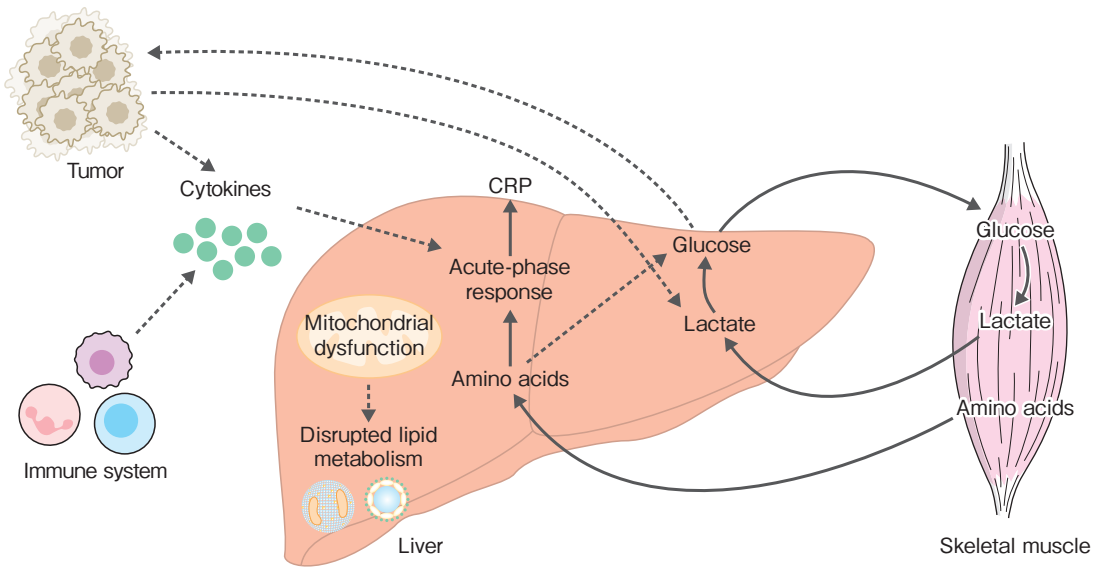

Figure 2. Disrupted liver metabolism contributes to cachexia.
Inter-organ substrate shuttling among liver, skeletal muscle, and tumor contributes to cachexia. Skeletal muscle and tumor glycolysis lead to production of lactate that is driven to the liver to be used in gluconeogenesis. Inflammatory cytokines (in particular TNF-α and IL-6) are increased by the tumor and the immune system of the host and target the liver which in term induces the acute phase response (APR). The APR requires amino acids, which are partly obtained from muscle proteolysis and driven to the liver. C-reactive protein (CRP), the main acute-phase protein synthesized by the liver, is a marker of systemic inflammatory response produced by the APR. Hepatic mitochondrial dysfunction occurs and impacts the disruption of lipid metabolism.

temic inflammatory response and has been directly associated with pain and mortality in patients with advanced CC[72)73)]. These main liver alterations are summarized in Figure 2.

4 Prospective cachexia treatments targeting host metabolism

❶ Nutritional interventions for Cancer Cachexia

Cancer cachexia cannot be fully reversed by conventional nutritional support; however, nutritional status assessment and malnutrition prevention remain a fundamental prerequisite for the management of CC[5)1)].The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines designate oral and enteral nutrition as the first choice for cancer patients, with tube feeding recommended only when oral intake is complicated[74)]. Parenteral nutrition may help patients that are unable to eat, digest or absorb food, but can cause adverse events in those with advanced cancer[75)]. Overall, aggressive nutritional support is not recommended in the refractory cachexia stage[76)].

The aim of nutritional support in patients with CC is to counteract the negative energy balance and the net protein loss, while avoiding to stimulate tumor growth or negatively influence cancer therapies[77)]. The impact of specific diets such as the Mediterranean diet and ketogenic diets on CC has been and is currently under investigation; however a clear conclusion regarding their effectiveness is still missing[78)~81)]. Overall, an individually adjusted protein enriched diet (1.0–1.5 g/kg/day) is recommended for patients with cancer-related cachexia[82)76)]. Nevertheless, evidence on the sufficient and optimal quantity and quality of protein intake is lacking[77)].Amino

acids (AAs) are the building blocks of protein and the main component of skeletal muscle mass; thus, the supplementation of several AAs has been studied as a potential therapeutic strategy for CC[83)~89)]. Although the preclinical results show promise, clinical trials in this direction are scarce[83)].

Supplementation of other specific nutrients has shown amelioration of CC. Omega-3 fatty acids, particularly eicosapentaenoic acid, represents a potential valid supplement to manage CC due to its anti-inflammatory and anti-catabolic actions[90)~94)]. However, clinical evidence for omega-3 supplementation remains inconclusive, although rich food sources can be included in the diet, if tolerated[95)~97)]. Micronutrients like iron, vitamin D and vitamin B3 have also been studied for their potential anti-cachexia properties[98) 99) 69) 100)]. Nevertheless, clinical validation remains insufficient for a recommendation in favor of supplementation for CC treatment[101) 102)]. In general, the use of oral nutritional supplements for cancer patients is advised only when an enriched diet is not effective in reaching nutritional goals[103)].

❷ Physical Therapies for Cancer Cachexia

Physical inactivity contributes to skeletal muscle wasting; nonetheless, it is frequent in cancer patients due to several barriers such as the presence of cancer/treatment-related fatigue and psychological symptoms (depression)[104) 105)]. Exercise has shown promise for the amelioration of CC through diverse mechanisms including the normalization of muscle metabolism, the reduction of inflammation, and improved insulin sensitivity[106) 107)]. Different types of exercise, mainly resistance (anaerobic) training versus endurance (aerobic) training, activate distinct molecular pathways. While resistance stimulates anabolism, endurance exercise activates mitochondrial biogenesis and improves oxidative metabolism[106) 108)~110)]. As a consequence, the combination of resistance and endurance training is considered the most beneficial exercise-based approach to purse in CC[109)]. Still, the type, amount, and timing of exercise may produce different outcomes, which could even be potentially detrimental to cancer patients that are exercise resistant. Thus, the impact of different training protocols in CC requires further elucidation and a more pragmatic and structured approach is needed before being able to prescribe precise exercise-based interventions for CC[111)]. Importantly, exercise appears to be beneficial during the pre-cachexia stage, while benefits are limited or nonexistent during refractory cachexia[112) 113)].

❸ Pharmacological Therapies for Cancer Cachexia

Several studies have investigated potential therapies for CC, yet there is no single agent approved for its treatment[5) 10)]. A non-exhaustive list of molecules tested against CC and divided by mechanism of action follows.

1) Agents targeting anorexia

Progestagens, megestrol acetate and medroxyprogesterone acetate increase appetite and improve body weight mainly by increasing adipose tissue mass and are approved for cachexia treatment in the United States and certain European countries[114)~116) 84)]. Their action is exerted via modulation of glucocorticoid activity, and their ability to downregulate cytokines and increase food intake by neuropeptide Y release[117)]. Anamorelin, a ghrelin receptor agonist that increases appetite and promotes growth hormone (GH) secretion in the pituitary gland, which in term secretes IGF-1 promoting muscle protein synthesis, has been approved in Japan for the treatment of CC[74) 118)]. Cannabis drugs mimic the effect of endocannabinoids and impact appetite by interacting with their receptors (CB1 and CB2), and are used to treat chemotherapy-induced nausea, vomiting and anorexia[119)~121)]. The growth differentiation factor-15 (GDF15) is a cytokine that when bound to its receptor, the glial cell line-derived neurotrophic factor family receptor α-like (GFRAL), causes anorexia and its increase has been associated to CC[122)]. Thus, GDF15-GFRAL axis inhibition has been proposed as a potential therapy for cachexia-associated anorexia[123) 124)].

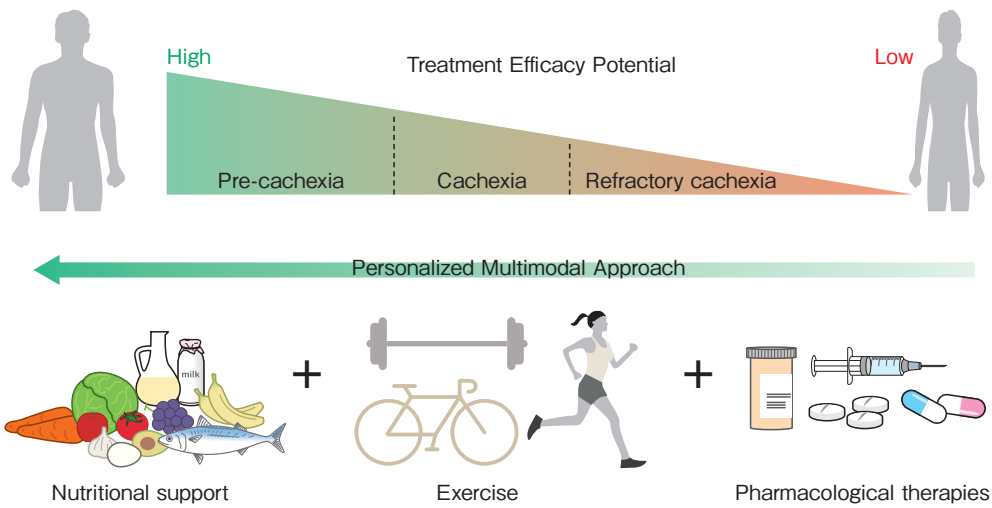

Figure 3. Prospective anti-cachexia treatments.
Early diagnosis followed by individualized multimodal approaches that include nutritional counseling, exercise training and/or exercise-mimicking agents, and pharmacologic treatments may have better probability for success in the prevention and/or treatment of cancer cachexia.

2) Anti-inflammatory agents

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) can moderate inflammation and preliminary studies have demonstrated encouraging results for CC, but there is insufficient evidence to recommend the use of these drugs in clinical practice[125) 126)]. Anti-cytokine therapeutic strategies have been based on either blocking the synthesis or the action of the main cytokines implicated in cachexia and have demonstrated the most prominent clinical benefits in larger phase II or III clinical trials[8) 127)]. Corticosteroids are anti-inflammatory drugs often used with progestogens to treat anorexia in cachexic patients, but they are limited to end-of-life care[74)].

3) Protostasis modulators

Activin receptor type 2 (ACVR2) signaling blockers have shown benefits in a variety of tissues including the prevention of wasting in the muscle and attenuation of protein synthesis in the liver, leading to improved survival[128) 129)]. Androgens and selective androgen receptor modulators, which mimic male sex hormones and promote protein synthesis, have also shown promising results[103) 130)]. Results from large phase III trials are still missing before adopting such molecules routinely for CC.

4) Exercise mimetics

Pharmacological treatments that simulate the beneficial effects of exercise are a potential tool for patients with low training levels or unable to perform exercise that could provide beneficial effects to patients with CC. The three long known classes of exercise mimetics are agonists of 5′ AMP-activated protein kinase (AMPK) or of peroxisome proliferator-activated receptor (PPAR-δ) and activators of silent-information-regulator-two-protein (SIRT)1[110)], while others emerged more recently and have been extensively reviewed elsewhere[131) 132)].

5) Multimodal approaches

Single-agent treatments are so far mostly ineffective as therapies for a complex multiorgan syndrome such as CC, suggesting that multimodal approaches that include nutritional counseling, exercise training and/or exercise-mimicking agents, and pharmacologic treatments may have better probability for success (Figure 3)[49) 117) 133) 134)].

Conclusion

CC is a complex condition that affects multiple organs and distinct pathways, among which the muscle and the liver show the most relevant and potentially targetable alterations. Therapeutic interventions have demonstrated limited effectiveness so far; thus, high-quality research of multi-modal and multi-targeted approaches is needed in order to find adequate treatments to prevent and/or treat cancer-associated cachexia.

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