Cancer-induced muscle wasting: latest findings in prevention and treatment

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Abstract: Cancer cachexia is a severe and disabling clinical condition that frequently accompanies the development of many types of cancer. Muscle wasting is the hallmark of cancer cachexia and is associated with serious clinical consequences such as physical impairment, poor quality of life, reduced tolerance to treatments and shorter survival. Cancer cachexia may evolve through different stages of clinical relevance, namely pre-cachexia, cachexia and refractory cachexia. Given its detrimental clinical consequences, it appears mandatory to prevent and/or delay the progression of cancer cachexia to its refractory stage by implementing the early recognition and treatment of the nutritional and metabolic alterations occurring during cancer. Research on the molecular mechanisms underlying muscle wasting during cancer cachexia has expanded in the last few years, allowing the identification of several potential therapeutic targets and the development of many promising drugs. Several of these agents have already reached the clinical evaluation, but it is becoming increasingly evident that a single therapy may not be completely successful in the treatment of cancer-related muscle wasting, given its multifactorial and complex pathogenesis. This suggests that early and structured multimodal interventions (including targeted nutritional supplementation, physical exercise and pharmacological interventions) are necessary to prevent and/or treat the devastating consequences of this cancer comorbidity, and future research should focus on this approach.

Keywords: muscle wasting, cancer, cachexia, nutritional intervention, exercise, multimodal treatment

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Introduction

Muscle wasting (with or without fat loss) is a pivotal feature of cancer cachexia, a multifactorial condition that negatively impacts patients' prognosis and quality of life.1,2 The severity and phenotypic presentation of cancer cachexia may vary, and often muscle wasting may be an occult condition.3 Regardless of body mass index (BMI), skeletal muscle depletion is considered a meaningful prognostic factor during cancer4 and has been associated with higher incidence of chemotherapy toxicity, shorter time to tumor progression, poorer surgical outcome, physical impairment and shorter survival.4–8

Cancer cachexia may result from reduced nutrient intake and/or availability (secondary to anorexia, malabsorption or mechanical obstruction) and metabolic abnormalities, triggered by a complex network of cytokines, hormones and other tumor- and host-derived humoral factors. Apart from the consequences of cancer per se, the adverse effects of anti-neoplastic therapies may also contribute to exacerbation of this condition.3,9,10

The molecular mechanisms underlying cancer-related muscle wasting have not been fully elucidated. Available evidence suggests that a prominent role is played by increased muscle protein degradation, although impaired muscle protein synthesis and defective myogenesis may contribute as well. In addition, alterations in energy metabolism involving mitochondrial dysfunction have been implicated in the wasting...
The prevalence of muscle loss has been reported as between 20% and 70%, depending on the type of tumor and the criteria used for assessment. In advanced cancer patients, the prevalence of muscle loss was found to be variable and dependent upon tumor type, stage, and assessment tool. In early cancer patients undergoing curative treatment, prevalence of muscle loss ranged from 16% in breast, to 33% in cholangiocarcinoma and to 40.3% in hepatocellular carcinoma patients. Loss of strength secondary to muscle loss is also frequent in cancer patients. Chemotherapy may induce fatigue and a severe decrease in muscle strength, especially in striated muscles, which may be further aggravated by reduced physical activity. In patients not training and receiving chemotherapy for lymphoma, a decrease of up to 14.6% in muscle strength was reported. The loss of contractile strength and function associated to muscle wasting and the onset of chronic fatigue may result in reduced physical activity, which in turn can further exacerbate muscle loss by instigating a vicious cycle.

Although muscle mass depletion is a common feature of experimental and human cancer cachexia, discrepancies in the mechanisms underlying cancer-related muscle wasting have been reported between different experimental models as well as in patients with different tumor types, data available in human cancer cachexia still being scanty. These diversities challenge the development of effective therapeutic strategies and underscore the need to implement research on patients and to design pre-clinical systems which as much as possible model the clinical scenario, in order to identify the categories of patients who are more likely to respond to drugs targeting specific intracellular pathways. Further, the development of effective treatments has been hampered by the high variability in clinical study design, including different patient selection criteria, clinical endpoints, analysis plans and definition of best supportive care. Time of therapy administration is also critical: to date, most clinical trials on cancer cachexia have been conducted in patients very advanced in their disease trajectory, and experts have speculated that this could be a reason why many drugs, deemed effective at the pre-clinical phase, failed to show any benefits at the clinical evaluation. Indeed, according to an international panel of experts, cancer cachexia may evolve in three stages of clinical relevance: pre-cachexia, cachexia and refractory cachexia. Although not all patients necessarily experience all of these stages, treatments should begin early in order to prevent or delay the progression to refractory cachexia.

Despite these obstacles, several promising agents acting on specific molecular targets are currently under investigation. Results obtained so far suggest that a single therapy may be insufficient to counteract cancer cachexia and that early multimodal interventions (including targeted nutritional supplementation, physical exercise and pharmacological interventions) should be considered the best modality to manage the multifaceted aspects of this cancer comorbidity.

The present article aims at reviewing the latest findings in the prevention and treatment of cancer-related muscle wasting that may represent the basis for the development of future cachexia therapies.

**Options for prevention and treatment**

**The role of nutritional support**

Nutritional interventions should be an essential part of the multimodal approach to cancer cachexia, as in the absence of an adequate energy and nutrient supply it is unlikely that muscle mass and body weight will be increased or stabilized. Since the reduction in food intake is an important yet reversible pathogenic mechanism accounting for cancer-related muscle wasting, the nutritional and metabolic support should be started early rather than delayed until there is an advanced degree of body weight loss. This implies that when the diagnosis of cancer is made, any single patient should be nutritionally monitored in parallel with the oncologist by a clinical nutrition unit.

During this ‘parallel pathway’ continuous nutritional and metabolic support should be provided, which, according to patients’ needs, may include nutritional counseling, administration of oral supplements, nutraceuticals and artificial nutrition.

**Overcoming anabolic resistance: is it a clinical issue?** A defining feature of cancer cachexia is that it cannot be fully reversed by conventional nutritional support. Cancer cachexia, indeed, is different from simple starvation since, conceptually, both inflammation and metabolic abnormalities may alter the anabolic response of the skeletal muscle after meal ingestion. Recent evidence, however, suggests that cancer patients have an exploitable anabolic potential prior to reaching the
refractory phase of cachexia, thus creating a strong rationale for early nutritional interventions.\textsuperscript{23,28,29} In this respect, a euglycemic, hyperinsulinemic clamp study in stage III and IV non-small cell lung cancer (NSCLC) patients showed a blunted whole-body anabolic response in conditions of iso-aminoacidemia, but a normal whole-body anabolic response to hyperaminoacidemia, suggesting that a significant protein intake is necessary to induce whole-body anabolism during cancer.\textsuperscript{30} Consistently, another study reported that a high-protein formula containing high leucine levels, specific oligosaccharides and fish oil was able to stimulate muscle protein anabolism in advanced cancer patients compared to a conventional nutritional supplement.\textsuperscript{31} In further support of a preserved anabolic potential, a recent study reported that the intake of 14 g of essential amino acids determined a high whole-body anabolic response in patients with stage III/IV NSCLC. Such effect was comparable to that observed in healthy matched controls and independent of recent weight loss, muscle mass, mild-to-moderate systemic inflammation and survival.\textsuperscript{32} A comparable positive net balance during oral sip feeding of a commercially available formula was also observed in cachectic pancreatic cancer patients and controls, although with a different protein kinetic: indeed, while in cachectic patients only protein breakdown was reduced; in control patients both protein breakdown and synthesis were modulated.\textsuperscript{33}

On the whole, these studies suggest that the failing anabolic response associated with cancer cachexia, if present, may be at least in part circumvented by providing an adequate nutritional support. Additional, \textit{in vivo}, clinical investigations, however, are needed to determine to what extent in the long term cancer-related muscle wasting can be attenuated and reversed by an early and appropriate nutritional intervention, and to establish the optimal dose, timing and composition of the nutritional support.

\textit{Can nutrients act as metabolic modulators in cancer cachexia?} Besides providing energy and protein requirements, the nutritional intervention could also represent a potential strategy to counteract inflammation and interfere with molecular mechanisms involved in the pathogenesis of cancer cachexia through the use of specific nutrients/nutraceuticals.\textsuperscript{34}

Many studies examined the effects of fish oil-derived fatty acids [either eicosapentaenoic acid (EPA) or docosahexaenoic acid] in the prevention and treatment of cancer cachexia, given their potential ability to modulate pro-inflammatory cytokines and increase insulin sensitivity.\textsuperscript{35} As recently reviewed, although not all studies in the past reported a benefit of fish oil supplementation on cancer cachexia, promising results were obtained in recent trials.\textsuperscript{36,37} Since it has been suggested that possible reasons for such inconsistencies among trials could be the variability in study design, compliance with the supplement, contamination between study arms and different methodologies used to evaluate body composition,\textsuperscript{36} future well-designed trials are needed to clarify the therapeutic potential of n-3 fatty acids for cancer-related muscle wasting.

Branch chain amino acids (BCAAs) have been shown to attenuate muscle wasting in experimental cancer cachexia, possibly by stimulating protein synthesis and attenuating protein degradation.\textsuperscript{38} Besides their proposed role in ameliorating cancer anorexia,\textsuperscript{39} a few clinical studies seem to support the hypothesis that BCAAs can ameliorate muscle protein metabolism, but larger randomized, blind, placebo-controlled trials are needed to confirm the beneficial effects of BCAAs in cancer patients and indicate the optimal dosage.\textsuperscript{26,28,40}

Beta-hydroxy-beta-methylbutyrate (HMB) is a metabolite of the BCAA leucine that, according to previous experimental studies, may attenuate muscle wasting during cancer cachexia by inhibiting protein degradation and/or stimulating protein synthesis.\textsuperscript{41–43} The therapeutic role of HMB in human cancer cachexia, however, is still uncertain and deserves further investigation, as was noted in a recent systematic review on this topic.\textsuperscript{44}

L-carnitine is an amino acid derivative involved in fatty acids metabolism and in energy production processes.\textsuperscript{45,46} Carnitine supplementation has been proven beneficial in experimental cancer cachexia,\textsuperscript{47,48} as well as in clinical trials on cancer patients, where it has been tested alone\textsuperscript{49} or in combination with other drugs;\textsuperscript{50} additional investigations are needed to clarify its therapeutic potential for cancer-related muscle wasting.

\textit{The role of physical exercise}

In addition to nutritional interventions, physical exercise has been proposed as another crucial component of the multimodal approach to cancer
cachexia. Indeed, physical activity may modulate inflammation and skeletal muscle metabolism, with substantial differences in relation to the exercise modality. In particular, while endurance training stimulates oxidative metabolic adaptations (with little effect on muscle mass), resistance training exerts an anabolic action resulting in muscle hypertrophy. Moreover, exercise improves insulin sensitivity, regulates cellular homeostasis by stimulating proteins and organelles turnover and promotes myogenesis. Particularly relevant, in this regard, is the ability of exercise to induce autophagy and mitophagy, enhancing the disposal of damaged/aged mitochondria, thus improving muscle energy balance.

Experimental studies have shown that treadmill exercise training attenuates the initiation and progression of cancer cachexia in mice and that both endurance and resistance exercise can modulate the inflammatory response in tumor-bearing rats. In addition, it has been recently reported that voluntary wheel running may prevent cachexia and increase survival in tumor-bearing mice, and also alleviate cisplatin-induced muscle wasting in mice undergoing chemotherapy.

Is physical exercise feasible in cancer patients? During cancer, exercise programs are frequently difficult to implement and factors limiting the exercise capacity (such as chronic fatigue, anemia, cardiac dysfunction and other comorbidities) should be carefully considered. Indeed, in a recent experimental study, 2 weeks of low-intensity endurance exercise did not improve, and even worsened, muscle wasting in mice bearing the C26 carcinoma (an experimental model of cancer cachexia associated with anemia and cardiac dysfunction). Conversely, erythropoietin (EPO) treatment in combination with exercise normalized hematocrit rescued atrophy of oxidative myofibers, prevented the oxidative to glycolytic shift of muscle fibers and induced the expression of the peroxisome proliferator activated receptor (PPAR)-γ coactivator-1α (PGC-1α), a factor involved in mitochondrial biogenesis and function. These results suggest that exercise could be an effective tool to be included in the multimodal approach to cancer cachexia, provided the exercise programs are adapted to the individual needs and that comorbidities such as anemia are promptly detected and appropriately treated.

Exercise and nutrition: a strategic interaction? Nutrient and energy availability play an important role in the modulation of acute and chronic adaptations to both endurance and resistance training, suggesting that an adequate nutritional support should be provided to patients in order to preserve the potential benefits of exercise. Vice versa, unloading blunts the amino acid-induced increase in myofibrillar protein synthesis, further supporting the concept that nutrition and exercise may have potential additive effects, although this aspect deserves further investigation in cancer cachexia. It is important to investigate which nutrients/nutraceuticals could boost the effect of exercise in cancer-related muscle wasting. In this respect, EPA in combination with endurance exercise has been shown to improve muscle mass and strength in mice bearing the Lewis lung carcinoma (LLC). Unfortunately, data in humans with cancer are not available.

Is exercise cost-effective? Available evidence suggests that physical exercise may have beneficial effects on cancer patients during and after active treatment, such as improving quality of life and reducing fatigue. According to a recent systematic review, both aerobic and resistance exercise, or a combination, may contribute to improving muscle strength in cancer patients more than usual care, while muscle mass would seem to be more favorably affected by resistance exercise, although supporting evidence in this respect is still insufficient. Moreover, many of the studies included in this systematic review were conducted in patients with early-stage cancer (the majority with breast and prostate cancer, and only a few with other solid tumors) and conclusions cannot be extended to patients with advanced diseases. Of note, a recent Cochrane review pointed out that evidences from randomized controlled trials proving the safety and effectiveness of exercise in patients with cancer cachexia are still lacking. Indeed, available data do not allow establishing whether cancer patients included in studies testing the effect of exercise were affected by pre-cachexia or cachexia. Ongoing clinical trials, however, are exploring the potential benefits of exercise for cancer cachexia within a multimodal approach.

In summary, considering the heterogeneity of cancer cachexia and the possible presence of comorbidities limiting exercise capacity, additional investigation would be necessary to test the effects of personalized exercise programs, possibly designed according to the principles of...
training, in order to optimize the safety and effectiveness of exercise prescriptions within the multimodal approach to cancer cachexia.

The role of pharmacologic treatments

The development of pharmacologic therapies for muscle wasting effects of cancer cachexia have been focused on improving appetite, modulating inflammation and interfering with anabolic and catabolic pathways involved in the modulation of skeletal muscle. In addition, novel suitable therapeutic targets are continuously emerging at the experimental level. No single agent, however, has yet been proven to be completely effective, underscoring the need to integrate pharmacologic therapies into a multimodal approach able to cope with the complex pathogenesis of cancer cachexia.

Appetite stimulants. Several potential appetite stimulants have been tested to counteract cancer anorexia. A recent Cochrane review analyzed data on megestrol acetate, and concluded that it improves appetite and body weight in cancer patients, although it is associated with adverse events. In addition, weight gain is mostly due to an increase in fat and water rather than in lean body mass (LBM), although data in experimental cancer cachexia suggest a possible effect on skeletal muscle.

Cannabinoids have also been evaluated. In this regard, a phase III trial on advanced cancer patients did not show any significant difference on appetite with respect to placebo, while a pilot study suggested some potential beneficial effects that should be tested in larger trials.

Agents targeting inflammation. Since inflammation is a major driver of cancer-related muscle wasting, many anti-inflammatory agents have been evaluated in the last few years.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been tested alone or in combination, and a recent systematic review concluded that they may improve body weight or LBM, although the evidence to recommend NSAIDs outside clinical trials is still insufficient and deserves further investigations. Interestingly, NSAIDs are currently being studied within a multimodal approach for cancer cachexia that includes exercise and nutrition. Preliminary results (presented as abstract) of a multi-center, randomized phase II trial (pre-MENAC [ClinicalTrials.gov identifier: NCT01419145]) suggest that a multimodal cachexia intervention (including exercise, NSAID, energy-dense nutritional supplements combined with dietary advice) may improve weight in patients with incurable lung or pancreatic cancer versus standard of care. Based on these findings, a phase III trial called MENAC [ClinicalTrials.gov identifier: NCT02330926] is currently enrolling patients.

Corticosteroids are potent anti-inflammatory drugs frequently used in cancer patients; results obtained in two randomized, placebo-controlled trials suggest that in the short term they may improve fatigue and appetite. Extended therapy with corticosteroids, however, is not recommended since they may cause side-effects including muscle wasting.

Thalidomide, an agent with immunomodulatory and anti-inflammatory properties, has also been tested in the last few years, despite its serious side-effects, but evidence is still insufficient to recommend this agent for the clinical management of cancer cachexia.

A more selective anti-inflammatory approach has been attempted using monoclonal antibodies targeting cytokines, but inconsistent results have been reported from different studies. Such discrepancies could be due, at least in part, to the variety and heterogeneity of the cytokines involved in different types of cancer and patients. Despite these limitations, targeting cytokines may have some potential therapeutic effects on cancer cachexia, as suggested by recent trials using new biological agents such as MABp1 (a first-in-class true-human monoclonal antibody targeting IL-1α). Further clinical investigation would therefore be necessary to clarify the role of anti-cytokine blockade in cancer-related muscle wasting within a multimodal approach.

Agents targeting muscle catabolic pathways. Much attention in the last few years has been given to the development of agents targeting myostatin and the activin type II B receptor (ActRIIB) pathway, a negative regulator of muscle mass, which is activated upon binding of myostatin as well as other transforming growth factor-β (TGF-β) family members, including Activin A and growth differentiation factor 11 (GDF-11). Modulation of myostatin signaling was described in both cancer-bearing animals and
Beta2-agonists have also been evaluated as a potential target for muscle wasting in cancer. Although some encouraging results were reported for those completing the 8-week course, further investigations in larger and controlled randomized trials are necessary to better assess this treatment in cancer cachexia.

Inhibition of proteolytic pathways (such as the ubiquitin proteasome system) has also been investigated as a possible therapeutic strategy. However, the administration of bortezomib, a potent reversible and selective proteasome and NF-κB inhibitor, has not so far showed a beneficial effect on cancer-related muscle wasting. By contrast, MG132, a different proteasome inhibitor, improved body and muscle weight loss in tumor-bearing mice, possibly due to a different mechanism of action of this drug compared to bortezomib. However, it should be recognized that in human muscle, evidence of increased ubiquitin-mediated proteolysis during cancer cachexia is not as robust as that seen in animal models – this is particularly true for NSCLC. Moreover, it has been observed in gastrointestinal cancer that the well-documented upregulation of markers of ubiquitin proteasome system activity may occur for only a small window during the progression of cachexia. This could in part be responsible for why proteasome inhibitors have largely failed in clinical trials. Taken together, the available evidence suggests that further studies are needed before the ubiquitin proteasome system may be definitely identified as a possible therapeutic target for muscle wasting in cancer.

Beta2-agonists have also been evaluated as a potential anti-catabolic therapy for cancer cachexia, although their possible cardiovascular effects have limited their application. Researchers focused in particular on formoterol, a β2-agonist with a high degree of selectivity for skeletal muscle β2-receptors and a relatively low toxicity. In experimental cancer cachexia, formoterol has been shown to ameliorate muscle wasting, without negatively altering heart function. Formoterol fumarate has been tested also in combination with megestrol acetate in a single-arm, uncontrolled pilot study on a small cohort of advanced cachectic cancer patients. Although some encouraging results were reported for this combination, further investigations are required.

Agents targeting muscle anabolic pathways. Extensive efforts during the last few years have been directed toward the study of anamorelin, an oral selective agonist of the ghrelin receptor GHSR-1a (growth hormone secretagogue receptor) with orexigenic and anabolic effects. Ghrelin induces the release of growth hormone (GH), stimulates appetite, regulates energy homeostasis and decreases inflammation. Based on the promising results obtained in several phase II studies, anamorelin was recently tested in two large double-blind, phase III trials (ROMANA 1, n = 484; ROMANA 2, n = 495). In these trials, patients with incurable stage III/IV NSCLC and cachexia were randomized 2:1 to receive anamorelin 100 mg or placebo over 12 weeks. In both studies, anamorelin significantly improved LBM, body weight and anorexia-cachexia-related symptoms, but failed to significantly improve handgrip strength, a co-primary endpoint of the study. In this regard, the lack of effect of anamorelin on muscle strength in face of improved LBM might reflect the not necessarily linear relationship between skeletal muscle mass and strength, the latter also depending on myofiber quality. Moreover, in these studies food intake was not recorded and it is not known whether the improvement in anorexia translated into an adequate nutritional intake, which is likely to be important to support (and maybe enhance) the anabolic action of anamorelin.

Patients who completed ROMANA 1 or ROMANA 2 trials had the option to continue their assigned treatment for another 12 weeks to further evaluate efficacy and safety of anamorelin. In this extension study, anamorelin treatment over 24 weeks was well tolerated and the incidence of adverse events was similar in both anamorelin- and placebo-treated patients.

Besides anamorelin, other novel ghrelin agonists (such as macimorelin) are currently under investigation.
Other emerging anabolic agents for the prevention and treatment of cancer-related muscle wasting are the selective androgen receptor modulators (SARM), a new class of non-steroidal, tissue-specific, anabolic drugs that can increase muscle mass and ameliorate physical function without the side-effects commonly associated with testosterone or other nonselective, synthetic anabolic steroids. In particular, Enobosarm, an orally bioavailable SARM, was recently tested in a double-blind, randomized, controlled phase II trial on cancer patients who had at least 2% weight loss in the previous 6 months. Results obtained showed a significant increase, compared with baseline, in total LBM and in mean stair-climb power among patients who received enobosarm 1 mg and 3 mg, while no significant changes were observed for handgrip strength. The 3 mg dose of enobosarm was next evaluated in two placebo-controlled, double-blind, phase III clinical trials, named POWER 1 and POWER 2 [ClinicalTrials.gov identifiers: NCT01355484, NCT01355497], in which stage III or IV NSCLC have been randomized to receive for 5 months an oral daily dose of enobosarm 3 mg or placebo at the initiation of first-line chemotherapy (platinum + taxane in POWER 1; platinum + non-taxane in POWER 2). Preliminary results reported that enobosarm treatment was associated with an increase in LBM and stair-climb power (co-primary endpoints) in the POWER 1 trial, while in the POWER 2 trial there was only a significant increase in LBM.

Many drugs, however, may affect both anabolism and catabolism. Espindolol (MT-102), for example, may decrease catabolism (through nonselective β-blockade), reduce fatigue and thermogenesis (through central 5-HT1a antagonism) and increase anabolism (through partial β2-receptor agonism). The ACT-ONE phase II trial in stage III/IV NSCLC or colorectal cancer patients showed that espindolol 10 mg twice daily improved body weight, LBM and handgrip strength.

New scenarios in pharmacological treatment. Insights into the molecular basis of cancer cachexia suggest that counteracting intracellular kinases such as the mitogen-activated protein kinase (MEK), the extracellular signal protein kinase (ERK) and the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, could represent a promising approach. In experimental cancer cachexia, administration of PD98059, a MEK inhibitor able to block ERK activation, has been shown to restore myogenesis and attenuate muscle depletion and weakness. Consistently, selumetinib, an MEK inhibitor with tumor-suppressive activity and inhibitory effects on IL-6 production, in a phase II trial induced gain of skeletal muscle in cholangiocarcinoma patients. Pharmacologic or genetic inhibition of the JAK/STAT3 pathways has been reported to reduce muscle wasting in experimental cancer cachexia. Ruxolitinib is an oral, potent and selective JAK1/2 inhibitor; use in a clinical trial on patients with myelofibrosis has been associated with an increase in body weight. Currently, an open-label phase II trial [ClinicalTrials.gov identifier: NCT02072057] is investigating the safety and efficacy of ruxolitinib for the treatment of cachexia in patients with tumor-associated chronic wasting diseases. Sunitinib, a tyrosine kinase inhibitor used for the treatment of renal cell carcinoma, has been shown to prevent experimental cancer cachexia by inhibiting STAT3 activation and muscle RING Finger 1 protein (MuRF1) upregulation in the skeletal muscle. More controversial results are available for sorafenib, a multi-kinase inhibitor that has been proven effective in attenuating experimental cancer cachexia by inhibiting both STAT3 and ERK activity in the skeletal muscle, but shown to cause muscle wasting in patients with advanced renal cell carcinoma.

Targeting the alterations in fat and energy metabolism underlying cancer cachexia is also gaining attention as a potential therapeutic strategy. Recently, pharmacological inhibition of fatty acid oxidation by etoxomir (a specific inhibitor of carnitine palmitoyltransferase-1) has been shown to rescue muscle wasting in experimental cancer cachexia. Inhibition of white adipose tissue browning, a process involved in increasing energy expenditure and thermogenesis, has also been shown to ameliorate experimental cancer cachexia. Consistently, treatment with an antibody neutralizing the parathyroid-hormone-related protein (PTHR) is also gaining attention as a potential therapeutic strategy. Besides the aforementioned approaches, targeting mitochondrial dysfunction is emerging as another potential therapeutic opportunity to...
normalize energy metabolism in catabolic conditions, but available data are still scanty.136

Exercise is an important regulator of mitochondrial dynamics and skeletal muscle metabolism, but training programs are not always easy to implement, therefore scientists are working on the development of exercise mimetics.137 In this regard, the administration of the exercise mimic 5-aminimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR), an adenosine monophosphate-activated protein kinase (AMPK) activator, has been shown to counteract cachexia and restore the autophagic flux in the skeletal muscle of C-26 bearing mice, similarly to rapamycin (an mTOR inhibitor able to trigger autophagy) and voluntary wheel running.60

Other novel agents targeting different molecular mechanisms are also currently under investigation in experimental cancer cachexia, and very promising results were recently reported for the administration of the histone deacetylase (HDAC) inhibitor AR-42138 and the antibodies targeting the fibroblast growth factor-inducible 14 (Fn-14), a member of the TNF family.139 Both treatments indeed prevented cancer cachexia and prolonged survival in tumor-bearing mice. It should be noted, however, that not all HDAC inhibitors share the same ability to treat cancer cachexia,138,140 suggesting that AR-42 beneficial effects are presumably mediated by specific effects intrinsic to this drug, which at the moment are only partially understood.

Finally, modulation of gut microbiota has been recently proposed as a potential therapeutic opportunity to counteract cancer-related muscle wasting, but data available are still scarce and more insights on the mechanisms linking skeletal muscle homeostasis to gut microbiota are necessary to ascertain whether this could represent a suitable therapeutic target.141

Overall, experimental studies seem to indicate a vast array of promising therapeutic opportunities for cancer-related muscle wasting, but additional investigations are needed to better understand the therapeutic potential of all these new pharmacological approaches.

Conclusions and perspectives
No effective therapy against cancer cachexia is available at present. For this reason, it is mandatory to implement strategies aimed at preventing or at least delaying this condition. In this regard, the increasing knowledge about the molecular mechanisms underlying cancer-related muscle wasting has allowed the identification of several potential therapeutic targets and the development of many promising drugs, some of which reached the clinical trial phase. At the same time, however, it is becoming clear that a multimodal approach is mandatory to successfully manage patients with cancer cachexia. Another crucial point is the early recognition and treatment of the nutritional and metabolic alterations occurring during cancer. Several evidences, indeed, suggest that cancer patients have an exploitable anabolic potential. For this reason, adequate nutritional support should be provided to slow the wasting process. Along this line, exercise training, compatible with the exercise capacity of cancer patients, could represent another important tool to boost the anabolic effects of the nutritional support and to prevent the detrimental consequences of physical inactivity on muscle mass and function.

Additional clinical trials are therefore necessary in the next few years to optimize multimodal interventions to counteract cancer cachexia and deliver the best of care to patients.

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