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Immunosenescence in skeletal muscle: The role-play in cancer cachexia chessboard

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ABSTRACT

With the increase in life expectancy, age-related conditions and diseases have become a widespread and relevant social burden. Among these, immunosenescence and cancer cachexia play a significant often intertwined role. Immunosenescence is the progressive aging decline of both the innate and adaptive immune systems leading to increased infection susceptibility, poor vaccination efficacy, autoimmune disease, and malignancies. Cancer cachexia affects elderly patients with cancer causing severe weight loss, muscle wasting, inflammation, and reduced response to therapies. Whereas the connections between immunosenescence and cancer cachexia have been raising attention, the molecular mechanisms still need to be completely elucidated. This review aims at providing the current knowledge about the interplay between immunosenescence, skeletal muscle, and cancer cachexia, analyzing the molecular pathways known so far to be involved. Finally, we highlight potential therapeutic strategies suited for elderly population aimed to block immunosenescence and to preserve muscle mass in cachexia, also presenting the analysis of the current state-of-the-art of related clinical trials.

1. Introduction

Aging is gradually increasing more and more its social impact indeed and, according to the World Health Organization, by 2030 one in 6 people worldwide will be aged 60 years or older, with the number expected to reach 2.1 billion by 2050. Aging is a complex and variable biological process with detrimental effects encompassing the functional and structural impairment of multiple organs and systems in the body. During the aging progress, the accumulation of cellular and molecular damages, leads to physical changes, cognitive decline and health risks (i.e., chronic disease, cardiovascular disease, diabetes and cancer).

Skeletal muscle is the biggest organ in the body and one of the most affected by aging. The age-dependent deterioration of skeletal muscle leads to sarcopenia that may eventually result in cachexia, with a chronic weight loss unmanageable with life-style intervention. Cachexia is usually observed as a consequence of cancer and is mainly related to malignancy and the key role played by the immune response in initiating and accelerating it has been extensively studied [1,2]. In the last decades it has been shown that also the immune system may undergo deleterious senescence state in a process called immunosenescence and that this may be connected with sarcopenia during aging. Our understanding of immune system aging involvement in skeletal muscle mass regulation is just emerging as it represents the links between this process and that involved in cancer cachexia. Understanding how immunosenescence occurs and the mechanisms of it has a strong social impact as this process affects not only individual health outcomes but also public health strategies aimed at managing population aging.

In this review we provide an updated overview of aging-and cancer-related muscle wasting integrated with the role of the immune system, focusing on the immunosenescence development. In addition, we describe the potential therapeutic strategies to counteract age-related degenerative processes affecting both skeletal muscle and immune system highlighting the recent ongoing and finished clinical trials.

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2. Muscle wasting as common feature in aging and cancer

2.1. Age-related muscle wasting

Muscle tissue is one of the tissues mainly affected by the aging process. Beginning at age 30, the body naturally starts losing 3–5 % of muscle mass per decade worsening with age, such that, typically after 50 s, it can advance to a condition called sarcopenia characterized by low muscle mass, muscle force, and physical performance with increased risk of falls, decreased mobility, and reduced quality of life as the major hallmarks. While a natural part of the aging process [3] sarcopenia can be accelerated by sedentary lifestyle, malnutrition, and illnesses [4]. Sarcopenia has a high variability in initiation and progression such that a common clinical definition classifying sarcopenic patients is difficult to achieve [5]. Cachexia shows several traits similar to sarcopenia, since both are forms of muscle atrophy arising from an increased protein breakdown in the presence of reduced protein synthesis and organelle biogenesis. Mechanistically, TGFβ family ligands, through activin receptors (ActRs) and SMAD2/3 as second messengers, regulate such protein turnover in favor of catabolism while the BMP pathway, repressing the atrophy-associated E3 ubiquitin ligases, operates in opposition fostering muscle mass growth [6–9]. In sarcopenia, fat mass may remain stable or even increase (i.e., visceral fat) mainly because of changes in metabolism and decreased physical activity [10]; muscle and fat mass are instead both affected negatively in cachexia due to an aberrant activity of the immune system [11]. Another relevant difference between cachexia and sarcopenia is the presence of chronic inflammation in cachexia, particularly in the advanced stages. Despite the two syndromes have different traits and pathogenic causes they can also co-exist in the elderly especially as comorbidities in pathological condition, namely chronic kidney disease, chronic obstructive pulmonary disease (COPD), advanced HIV/AIDS, and of course cancer [12], one of the most frequent illnesses associated with aging, leading to cachexia in 50 % and 70 % of the cases.

2.2. Cancer cachexia

Clinical data indicate that increased inflammation and altered immune system response in cancer cachexia play a critical role in the development and progression of patients' symptoms [13–16]. Muscle wasting in cachexia occurs regardless of an adequate nutritional intake, impairing the correct muscle function. Along with muscle wasting, fat loss is a common outcome leading to the severe weight loss that appears in cachectic patients [17]. Unfortunately, this progressive pathological condition is only partially fixable with dietary intervention because it is the consequence of a multifactorial combination leading to an overall metabolic imbalance [18]. Therefore, cancer cachexia is challenging to tackle as it occurs as a complex etiologic illness and the exact mechanisms of which are not fully understood.

In cancer patients, a systemic inflammation can be considered one of the main drivers of malignant progression and is determined by the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), and interferon-γ (IFN-γ) [19]. Chronic production of these cytokines promotes catabolic pathways that induce lipolysis and alter protein homeostasis by protein breakdown. These cytokines can be released by either cancer or tumor-microenvironment cells with a concomitant downregulation of anti-inflammatory cytokines, such as IL-10 [20]. IL-6 is deemed as a key cachectic factor released by tumor cells; its role has been implicated in various murine cancer models and patient-derived tumor xenograft systems [21–26]. Clinical data and mouse models show that tumor tissues highly expressing and releasing IL-6 are more aggressive leading to a shorter survival time [27]. Cancer patients may have chronically elevated IL-6 levels secreted by the tumor cells, acting as pro-inflammatory agent and fueling cachexia [28]. Additionally, critical metabolism shifts occur from oxidative phosphorylation to unnecessary anaerobic glycolysis in the presence of oxygen; this causes a serious imbalance leading to an excessive energy consumption in a hypermetabolic status which favors both tumor growth and muscle loss. Impaired metabolism is further exacerbated by an altered mitochondrial activity which has been reported in cachectic patients. Increased stressors, such as reactive oxygen species (ROS), reduced availability of endogenous antioxidants, and defective mitochondrial biogenesis are common features of cancer cachexia [29]. This switch of metabolism is often accompanied by the production of catabolic and stress factors, such as TNF-α and glucocorticoids [30], which further promote the loss of muscle mass and block muscle regeneration [31].

Cancer cachexia is indeed a heterogeneous multidimensional clinical syndrome for which linear strategies, such as simple nutritional supplementation, are likely to fail unless accompanied by a multimodal approach. The complexity of cancer cachexia calls therefore for standardized disease assessment procedures followed by a personalized disease management plan for cachectic patients. Accordingly, it is crucial to conduct a regular "parameters panel" assessment including cognitive and physical performance tests, weight loss and body composition measurements, as well as nutritional evaluations. Indeed, early intervention is critical to prevent the progression of muscle loss and improve outcomes. Ideally, the combination of non-pharmacological intervention, such as physical exercise, food intake, and nutritional supplement (e.g., fish oil or eicosapentanoic acid), with pharmacological strategies (e.g., corticosteroids, progestational agents/progestins, cannabinoids, antipsychotics, androgens, and beta blockers) is mandatory to successfully manage the myriad of critical aspects involved in cachectic patients [32,33].

3. Immunosenescence in skeletal muscle homeostasis and tumor progression

Immunosenescence was first described in 1960s by Roy Walford (Professor of Pathology at UCLA) to define the concept of "immune aging": the normal process of aging in humans and in all animals is pathogenetically related to faulty immune processes [34]. This prophetic paradigm emerged in the last decades as a key player on host fitness [35,36]. Immunosenescence process changes the immune cells' surface marker expression, reducing the production of anti-inflammatory over pro-inflammatory cytokines. All these events induce the activation of inflammatory signals that might be used as aging and fragility biomarkers [37]. There is now a general consensus that immunosenescence-dependent functional reshape of leukocytes promotes chronic inflammation, tissue damage, autoimmune disorders thus increasing the likelihood of developing age-related diseases [38]. Accordingly, the immune system aging has been described as a risk factor for cancer onset, despite the specific mechanisms are still elusive as the immune system plays a paradoxical role in cancer either counteracting or promoting tumor development.

3.1. Mechanisms of immunosenescence

Different molecular alterations contribute to the aging of both circulating/infiltrating immune cells and lymphoid organs affecting both the innate and adaptive arms of the immune system [39]. Senescent innate immune system displays a decline in antigen processing and presentation abilities. Furthermore, chronic antigen stress contributes to the exhaustion of macrophages activity with poor antigen response eventually fueling the cells' shift toward senescence. Aged adaptive immune system exhibits age-related changes resulting in functional impairment. In general, aging leads to the variation of the relative abundance of immune cell subsets, with a decline of naïve T-cell and an increase in the number of memory T-cells [40], accompanied by a loss of T-cell receptors' (TCR) variability leading to a decline of immunological memory formation [41,42]. This, may be in part explained by age-related thymic involution that causes the decrease of naïve T-cells

triggering the imbalance of global T-cell proportion toward memory type proliferation although not completely explaining the reduced TCR diversity [43,44]. The number of memory CD8 + T-cells gradually rises during aging, changing the naïve/memory ratio and negatively impacting on immunological homeostasis [45]. Other age-related alterations observed in senescent T-cells, are the downregulation of the costimulatory molecule CD28 and the increased expression of immune checkpoint-related molecules, such as Tim-3, Tight, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), also increase during T-cell aging [46]. Another hallmark of T-cells immunosenescence is telomere shortening, which is due to the continuous T-cells turnover and the downregulation of the human telomerase RNA components [47].

T-cell immunosenescence is a state of non-responsiveness molecularly distinct from T-cell exhaustion, typical of human chronic viral infections, such as human HIV, HBV, HCV, as well as cancer [48–50]. T-cell exhaustion mainly occurs following chronic exposure to an antigen which overstimulates TCR finally inducing the physical elimination of antigen-specific T-cell subpopulation. Exhausted T-cells have specific surface markers [51–53] and downregulate IL-2 and TNF production that alters their proliferative abilities, metabolic fitness, and the antigen-independent memory T-cell responsiveness that may lead to apoptosis [54–56].

Recent studies have demonstrated that the cytotoxic activity of senescent immune cells decreases, and the expression of functional cytotoxic factors, such as IFN-γ, granzyme B, and perforin, is also impaired [57,58]. In parallel, immune system aging witnesses an increased presence of mature myeloid cells compared to lymphoid lineage [59].

Immunosenescence is closely linked to inflammaging, a chronic, low-level inflammation that occurs with aging. This process is driven by persistent infections, cellular damage, and the acquisition by senescent cells of a distinctive senescence-associated secretory phenotype (SASP) leading to the release of a combination of inflammatory soluble factors [60]. Inflammaging contributes to many age-related diseases such as cardiovascular disease, neurodegeneration, and cancer through a positive feedback regulatory circuit impacting immune surveillance, cellular catabolism, redox homeostasis, and fueling immunosenescence [61]. Novel immunosenescence biomarkers are constantly updated including T-cell-specific circular RNAs and microRNAs [62].

3.2. *Immune system, aging, and skeletal muscle crosstalk*

Muscle tissue is increasingly recognized as an endocrine organ able to release myokines, a group of cytokines and other soluble signaling molecules acting on various tissues and organs, including brain, liver, adipose tissue, and immune system. Myokines play a major role in whole-body homeostasis maintenance, influencing body weight, insulin sensitivity, tumor growth, and cognitive function also modulating processes such as inflammation, energy metabolism, and tissue regeneration [63,64]. Skeletal muscle homeostasis is finely linked to immune system in a bidirectional fashion: on the one hand chronic inflammation induces muscle wasting by activating muscle catabolism; on the other skeletal muscle is responsible for the release of age-dependent myokine and soluble factors that paracrinally affects immune cells activation and inflammatory events [65–67] (Fig. 1).

The release of myokines is finely regulated in response to exercise and physical activity [68]. Among the most impacting and investigated ones is IL-6, a myokine released by skeletal muscles involved in the metabolic response to exercise, inflammation and muscle regeneration; it is also an important regulator of cancer-induced muscle wasting [2]. Enhanced circulating IL-6 levels have been associated with an acute bout of exercise since contracting skeletal muscle triggers its synthesis and release. Such a peak of release promotes muscle recovery, insulin sensitivity, fatty acids oxidation (FAO) [69], along with anti-inflammatory effects [70]. Beside IL-6, Fibroblast Growth Factor 21 (FGF21) is a hormone-like myokine also regulating glucose and lipid metabolism by improving insulin sensitivity and promoting FAO. FGF21 has also a major role in mitochondrial function by promoting energy expenditure during physical activity [71]. Myostatin (GDF-8) instead, is a negative regulator of muscle growth inhibiting muscle cell differentiation and proliferation. An excessive level of myostatin can contribute to muscle wasting in conditions such as sarcopenia and cachexia [72]. Conversely, interleukin-15 (IL-15) promotes muscle hypertrophy showing anabolic effects. IL-15 also reduces fat mass by influencing fat metabolism and signaling in adipose tissue and its presence is essential in resistance exercise-induced muscle growth [73]. Another key myokine is the Brain-Derived Neurotrophic Factor (BDNF), usually associated with the nervous tissue but also produced and released by skeletal

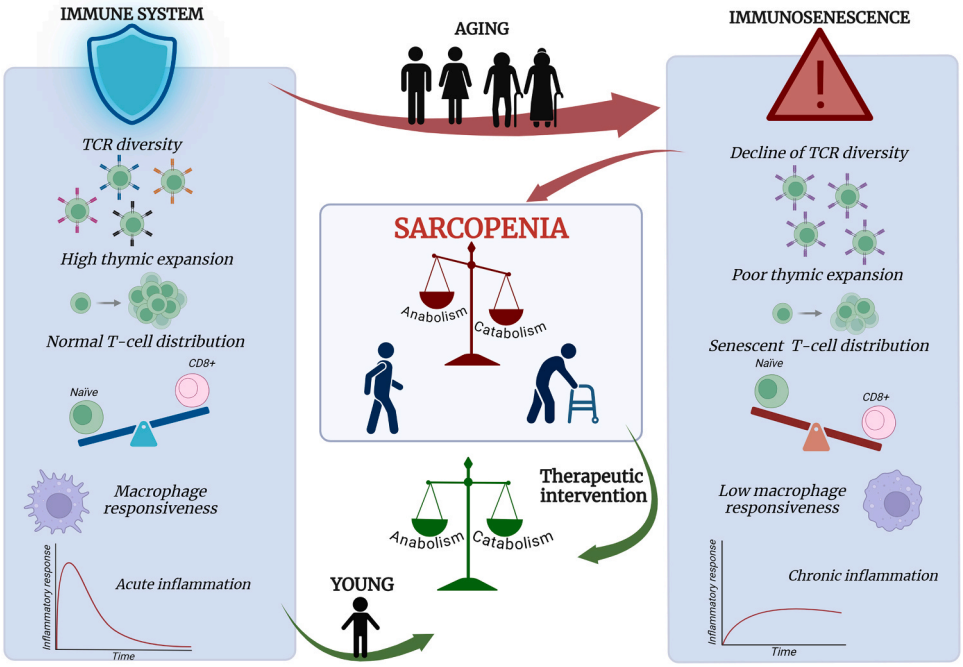

Fig. 1. Immune system aging leads to immunosenescence impairing skeletal muscle tissue and triggering sarcopenia in elderly.

muscles during exercise. Indeed, it plays an important role in neuroplasticity and cognitive function and enhances fat oxidation and improves metabolic efficiency [74].

Muscle regenerative potential, upon injury or tissue turnover, depends on the crosstalk between myofibers and immune cells that can infiltrate skeletal muscle to remove necrotic cells and promote staminal satellite cells (SCs) proliferation and differentiation [75]. Muscle regeneration occurs concurrently with inflammation, with macrophages and neutrophils being the first immune cells reaching the site of muscle injury where they can shift their function as the healing process evolves. The pro-inflammatory (M1) macrophages are present in the early stages of muscle injury; they release pro-inflammatory cytokines, such as TNF-α, IL-1 α, IL-1 β, IL-13, and IL-6, which help damaged muscle fibers clearance and recruit other immune cells to the injury site [76–78]. This inflammatory response is required to initiate the regeneration process. Later, the M1 macrophages transition into anti-inflammatory M2 type promotes tissue repair and regeneration by releasing growth factors like transforming growth factor-beta (TGF-β) and insulin-like growth factor 1 (IGF-1). These growth factors stimulate also the proliferation of SCs and facilitate muscle fiber repair [79]. In addition, neutrophils clear skeletal muscle damaged tissue from debris and dead cells also releasing ROS, which in chronic uncontrolled condition exacerbate tissue damage. Even though typically known for their role in immune defense, T-cells are also involved in muscle repair by avoiding an excessive immune response that is detrimental for regenerating muscle tissue; likewise, eosinophils can help SCs activation, thus promoting new muscle fibers formation through the release of IL-4 [80]. Aging affects the crosstalk between SCs and inflammation leading to a diminished macrophage responses/polarization potential observed in older individuals, likely contributing to a decreased regenerative effectiveness and prolonged recovery from muscle damage [81,82]. Recently, Munoz-Canoves and colleagues investigated the senescence and SASP blueprint within skeletal muscle niche by deeper transcriptome, chromatin and pathway analyses [83]. In whole-tissue analysis, many secreted SASP proteins were commonly upregulated in injured young muscles as well as in aged muscles, indicating a shared inflammatory secretome upon injury (that leads to SCs activation) and in aging (in parallel with an inflammaging process). Functional profiling of SASP transcription factors indicated the involvement of NF-κB, STAT1/3 and SMAD3/4 pathways. SASP acquired by senescent cells (mainly macrophages) may provoke either proliferative arrest or paracrine senescence in SCs, via the inhibition of cell-cycle and proliferative pathways (MAPK and AKT signaling), eventually restraining muscle regeneration while favoring inflammation and fibrosis.

3.3. Immunosenescence involvement in cancer

The immune system has a dual role in cancer, as it exerts constitutive immune surveillance in the antitumor response but is also correlated with the initiation and progression of neoplasms [84]. The accumulation of age-related DNA mutations gradually drives cells senescence and can contribute to tumorigenesis [85]. Immunosenescence weakens the body's ability to detect and eliminate transformed cells, leading to a higher risk of developing cancers in old age. Accordingly, several features of immunosenescence such as SASP, epigenetic modifications and mitochondrial dysfunction are associated with increased morbidity and mortality rates by tumors in elderly. Moreover, aging is frequently associated with more aggressive tumor behavior and disease outcome, possibly because an aged immune system may have a direct role on tumor development boosting the presence of tumor-associated macrophages and regulatory T-cells in the tumor microenvironment [86–88]. The tumor microenvironment can change the behavior of T-cells inducing a metabolic shift toward glycolysis and mitochondrial dysfunction/ROS generation involving stress signal pathways such as NFkB, C/EBP beta, and cGAS-STING, finally driving T-cells to senescence [89]. Within the tumor microenvironment, pro-inflammatory cytokines produced by tumor cells may trigger the activation of cancer-associated fibroblasts (CAFs), an abundant and heterogeneous stromal cell population derived from local fibroblasts able to promote an immunosuppressive environment normally associated with poor prognosis [90–92]. CAFs can also be recruited by tumor stimuli from remotely circulating cell populations such as bone marrow mesenchymal stem cells, transdifferentiated endothelial cells, epithelial cells, adipocytes, and pericytes [93–95]. CAFs themselves can acquire a senescent state and subsequently release SASP-related factors, such as IL-6, CXC chemokine ligands and TGFβ, that in turn promote monocyte differentiation into pro-inflammatory M1 macrophages, finally driving PD-L1 expression in tumor cells [96,97]. In addition, the ability of cancer cells to evade the immune response and their progression toward malignancy might be further promoted by immune cells aging. The abnormal phenotype of senescent T-cell, with the downregulation of CD27, CD28 and the upregulation of CD57, killer cell lectin-like receptor subfamily G, and Tim-3, is indeed tightly associated with malignant progression of tumors [46]. Several studies have also indicated that endogenous cyclic adenosine monophosphate (cAMP) produced by tumor cells induces T-cell senescence by inhibiting tumor-specific effector T-cells in hypoxic microenvironment [46] and by inducing DNA damage through the stimulation of the cAMP-dependent pathways of PKA-CREB and P38 [98].

4. The role of immunosenescence in cancer cachexia

Immune system senescence, inflammaging and related disorders can be considered primary drivers of cachexia [99]. In elderly people affected by cachexia, pathologic traits linked to individual aging, such as muscle wasting (due to impaired skeletal muscle repair capacity and lower SCs number) and chronic diseases (also potentially triggered by immunosenescence), must be integrated in a comprehensive framework to allow suitable therapeutic interventions [100].

In cancer cachexia, immunosenescence fuels muscle inflammation and impairment (Fig. 2). Cachexia leads to alterations of physiological regulatory networks between immune cells and other muscle-resident cell types involved in the regulation of myofiber size and plasticity, including satellite cells, fibroblast, and endothelial cells [101]. Mechanistically, cachexia drives general muscle mass loss disrupting the protein synthesis/breakdown balance normally regulated by nutrient availability, hormones, mechanical loading, and metabolic stress [102]. Deficits in the myogenic regeneration potential have been reported in skeletal muscle from preclinical cachexia models and cancer patients. In particular, the dysregulation of the SCs mastergene Pax7 in cachectic muscle, driven by aberrant NF-kB signaling, compromised SCs differentiation and the regenerative process [103,104]. Transcriptomic analysis of colorectal cancer tumors (both cachectic and pre-cachectic) from the C26 mouse model showed a downregulation of immune pathways related to a depletion of NK cells, CD3 + T-cells, CD8 + T-cells, and CD4 +Foxp3 T-cells, triggering inflammatory cytokines abnormalities and potentially immunosenescence [26,105,106].

Cancer cachexia and related chemotherapies interfere with muscle fibers' regulatory nexus deregulating Akt-mTORC1 axis, AMPK signaling, autophagy, and the ubiquitin proteasome system (UPS), finally disrupting muscle's proteins synthesis/breakdown balance [107–111]. Such pathologic impairment of skeletal muscle homeostasis triggers a reshape of muscle-immune cell balance resulting in a stress-induced release of myokines from muscle fibers that promote immunosenescence of infiltrated immune cells [112].

As mentioned above, immune system aging promotes the shift from lymphoid to myeloid lineage; this leads to the increase of circulating macrophages and the induction of pro-inflammatory factors namely IL-6, IL-8, TNFα, TGFβ, C-reactive protein, serum amyloid A, and members of the IL-1 family, collectively contributing to frailty in cancer-cachexia [113,114]. In addition, activated macrophages produce IL-1alpha and IL-1beta accelerating skeletal muscle proteolysis and fat loss and

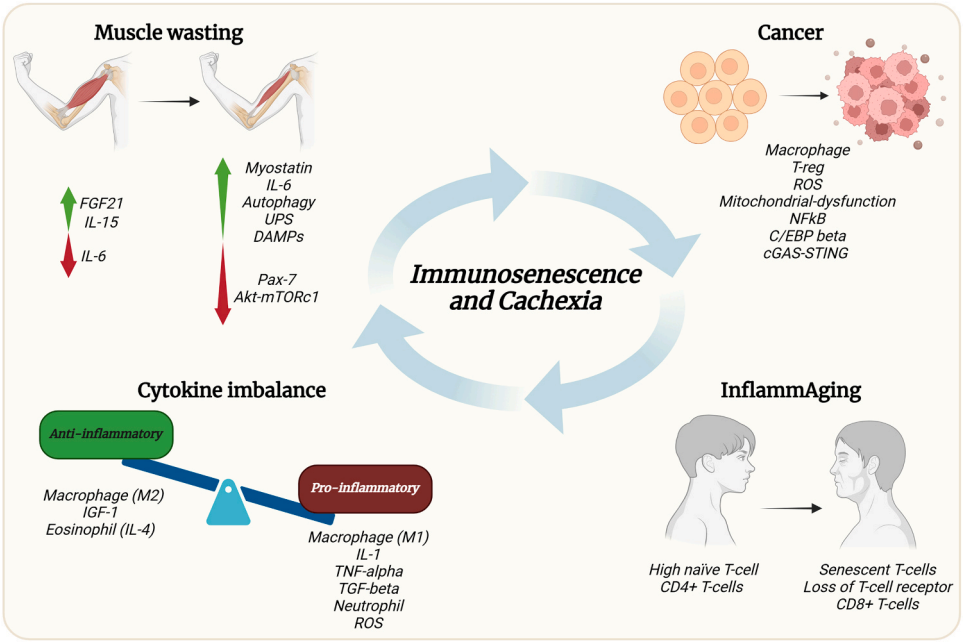

Fig. 2. Immunosenescence and cachexia are involved in cancer and inflammation processes leading to muscle wasting and immune system deregulation (UPS: Ubiquitin-Proteasome System; DAMPs: Damage-Associated Molecular Patterns; ROS: Reactive Oxigen Species).

reinforcing muscle atrophy [115]. In cachectic muscles, the release of danger-associated molecular patterns (DAMPs) represents a hallmark of tissue injury [116]. DAMPs include molecules such as high mobility group Box 1 (HMGB1), DNA, RNA, mitochondrial DNA (mtDNA), and heat shock proteins, overall factors that may activate the immune cells. The chronic release of DAMPs associated with cancer cachexia in the bloodstream can directly interact with Toll-like receptors expressed by immune cells, such as TLR4, resulting in systemic inflammation and indirectly stimulating muscle proteolysis [117].

The tight connection between senescent immune cells and muscle wasting pathologies, is clearly shown in the involvement of immunosenescence in muscular dystrophy degeneration. Using a Duchenne Muscular Dystrophy disease (DMD) mouse model, Mu and coworkers revealed a senescence-like phenotype of infiltrating macrophages expressing the SASP release pattern as well as senescence-related markers (such as p16, β-gal, C12FDG) eventually fueling the exhaustion of satellite cell pool in dystrophic muscle [118].

Although the link between immune activation/inflammation and cancer cachexia is well established, it is still unclear how the host response to cachexia-related muscle wasting is regulated. Patients bearing the same tumor type and with comparable disease stage may present different degrees of cachexia, suggesting that individual factors (gender, age, genotype, environment and lifestyle) might play a role. It seems that cachexia is not solely caused by cytokine rearrangement but rather by a response to combined immune and metabolic disturbance, which is part of a more intricate coordinated reaction. Notwithstanding the identification of different inflammatory mediators in cachexia process, how these signaling pathways interact or overlap with other physiological signaling within the muscle microenvironment to regulate muscle catabolism, cancer, and immunosenescence remains puzzling. Indeed, the interplay between immunosenescence and cancer cachexia forms a vicious cycle in which chronic inflammation and immune dysfunction promote tumor progression and muscle wasting, while cachexia compromises immune competence further. Targeting these common mechanisms could offer therapeutic strategies to mitigate both conditions [119].

5. Strategies to counteract immunosenescence in cancer cachexia

Considering the complexity of cancer cachexia, involving both immune and muscle cells alterations in different metabolic pathways, the identification of effective therapeutic targets is challenging also because of the limited response of cachectic patients to therapies [120]. Cachexia-related clinical data are scarce for various reason, including the fact that this morbidity occurs in late-stage cancer with difficult management, and the reduced patient turnout to cachexia-related clinical trials. Therefore, to date no medications have achieved US Food and Drug Administration approval and there are still obstacles to the implementation of therapeutic interventions targeting specific signaling cascades to preserve skeletal muscle mass in cachectic patients [121]. Although extensive preclinical data indicate that tumor-induced immune disorder and aging drive the development of cancer cachexia, there is still a lack of evidence demonstrating that immune modulation can ameliorate cachectic symptoms.

A combinatorial strategy of nutritional intervention, which alone is not resolutive, pharmacological approaches and daily exercise programs seems to be the more promising. Among pharmacological approaches aimed at counteracting muscle wasting, there are anabolic agents, catabolic/inflammatory cytokines inhibitors and inhibitors of muscle-specific ubiquitination and autophagy [122].

In this section we provide an overview of potential therapeutic strategies addressing many aspects of cachexia pathological findings, including pharmacologic agents regulating immune system and acting on cellular senescence and inflammation. Besides, we explore if/how alternative approaches and other factors, such as exercise, lifestyle, and nutrition can counteract cachexia symptoms and prognosis. Finally, we explore the relatively limited backdrop about current/recent clinical trial data pointed to immunosenescence and cancer cachexia morbidities.

5.1. *Pharmacological intervention with senolytics*

The development of senolytics to eliminate senescent cells is one of the most effective strategies used to treat age-related diseases. In the context of cancer cachexia, elimination of senescent immune cells has

been proposed to improve the immune system activities, as positive effects were witnessed in other tissues [123–125]. The approach with senolytics is aimed at either inhibiting or activating proteins which regulate Senescent Cell Anti-Apoptotic Pathways (SCAPs), such as those involving BCL2 and BCL-XL, that confer apoptosis resistance to senescent cells while preserving quiescent and proliferating cell [126,127]. Most of the senolytic drugs have been identified by repurposing compounds capable of eliminating senescent cells by reducing inflammation and improving immune function [128]. Among senolityc agents effective *in vivo* we can find BCL-2 family proteins, HSP90 and p53/MDM2 inhibitors, galactose modifies prodrugs, and antioxidants [129]. It has been found that the treatment with an IKK/NF-κB inhibitor, SR12343, lowers markers of cellular senescence and inflammation in liver, skeletal muscle, and blood that are elevated in response to chemotherapy. SR12343 effectively attenuates chemotherapy-induced skeletal muscle wasting and dysfunction [130]. This evidence demonstrates the therapeutic potential of senomorphic interventions (i.e., drugs that target the biological activity, but do not induce the death of senescent cells) to counter biological mediators and clinical features of cachexia. In this context, some drugs commonly used in clinical practice and several over-the-counter pharmaceuticals have been investigated in clinical trials, thanks to their pro-longevity effects in different experimental models. Among them, metformin, the first-line medication to treat type 2 diabetes mellitus, has been shown to slow down the aging process and to exert protective effects on skeletal muscle and physical capacity. Diabetic patients treated with metformin have shown lower rates of frailty syndrome and better performance in balance and muscle strength tests than the ones on other medications [131]. Metformin might act by inhibiting T-cell senescence in terms of cell number, effector function, telomerase content and gene expression in middle-aged individuals, thus representing a promising approach for age-related diseases and for treating cancer therapy-related frailty [132]. In skeletal muscle, metformin promotes the activation of AMPK and increases the expression of PGC-1α [133] and also improve myofiber atrophy and fibrosis, induced by a high-fat diet; this protective effect has been partially attributed to the regulation of the PGC-1α/FoxO3 signaling pathway [134].

Senolytic therapeutic strategy has demonstrated beneficial effects also in the context of muscular dystrophy-related immunosenescence. Indeed, in knock-out mice for both dystrophin and utrophin (a murine model for DMD) the treatment with the senolytic drug fisetin reduces the number of senescent infiltrated macrophages, leading to the increase of muscle stem cells number and the improvement of dystrophic muscle phenotype [118].

5.2. Cytokine modulation and anti-inflammatory approaches

A variety of inflammatory cytokines, such as IL-1, IL-6, IFN-γ and TNFα have been associated with anorexia and hypermetabolism and have been implicated in skeletal muscle atrophy and cancer cachexia induction, mediated via the ubiquitin proteosome pathway [135]. Therapies that target specific inflammatory cytokines could thus help managing chronic inflammation in elderly individuals, benefiting both muscle preservation and cancer treatment. In this context, TNF inhibitors and IL-6 blockers, have been tested or are currently in clinical trials as treatment candidates for cancer cachexia as well as many anti-inflammatory drugs, commonly used in the clinical practice. For example, the role of non-steroidal anti-inflammatory drugs (NSAIDs) has been systematically investigated [136] because of their good analgesic and anti-inflammatory activity and overall safety profile in the general population. However, the currently available data from randomized controlled trials do not provide robust evidence to determine whether some of them, such as indomethacin or ibuprofen, are effective or safe for use in patients with cancer cachexia. The last systematic review on this topic have reported that Celecoxib is safe at the tested doses (200–400 mg/day), but due to the high heterogeneity among the studies included, the results regarding efficacy are contrasting [137].

5.3. Immunotherapies

The significance of tumor immunotherapy for elderly population with cancer is still a subject of debate in terms of effectiveness and immune-related side effects. Although rejuvenating or boosting immune responses through immunotherapies (either alone or combined with chemotherapy) has shown promise in the treatment of younger cachectic individuals, the limited clinical data involving elderly patients suggest a negative impact of immunosenescence on immunotherapy effectiveness [138].

Preclinical observations yet highlight the potential of immunotherapy in treating cancer cachexia. A recent study using C26 tumor-bearing mice have found that treatment with R-ketorolac, an immunomodulator, mitigates the symptoms and the cachectic weight loss independent of nutrition intake and tumor growth, globally increasing murine survival rate. In addition, R-ketorolac increases lymphocyte count and reduces IL-6 blood levels, providing evidence of its marked immunomodulatory effect. Of note, in the same C26 mice, combined R-ketorolac and chemotherapy resulted in a 100 % survival rate [139]. In addition, the recent proof of concept trial KetoROCX (NCT05336266), involving patients with pancreatic ductal adenocarcinoma, is aimed at gathering preliminary evidence demonstrating the clinical feasibility and efficacy of ketorolac treatment in reducing cancer cachexia symptoms [140].

Several clinical studies involving patients with advanced cancer have shown that cachexia is a predictive factor for the clinical response to the treatment with immune checkpoint inhibitors [141,142]. Moreover, immune checkpoints such as PD-1, PDL1/2, CD80, Tim3 and Lag3 are more expressed in immune cells of aged than young people. In this regard, three FDA-approved immune checkpoint blocking antibodies (against CTLA-4, PD-1 and PD-L1) were preclinically tested using a mouse model of transplantable, orthotopic B16 melanoma to test age effects. All three agents were highly effective in treating young tumor-bearing hosts, while aged mice displayed different responsiveness, with anti-PD-1 showing the most promising effects [143]. It is worth mentioning that to maximize the therapeutic potential of these new-generation drug treatments, important issues including treatment tolerance, and drug resistance must be considered along with the age-specific inhibition of the immune response such as immune checkpoint overexpression and T-cell exhaustion as well [144]. Further studies are needed to improve the efficacy of immunotherapy in novel combinatorial strategies to overcome the reduced treatment tolerance, immunosuppression and drug resistance in patients with cachexia.

5.4. Healthy lifestyle and nutritional approaches

Maintaining a healthy lifestyle through regular physical activity, a balanced diet that limits caloric intake, and sufficient sleep can reduce the impact of immunosenescence. Despite physical activity being not the first employed therapeutic intervention, it is still one of the most safe and manageable approach, with positive effects mostly in terms of body weight, BMI, lean mass, muscle strength and functional performance, leading an increased quality of life [145]. Physical activity has been shown to enhance muscle regeneration by reducing chronic inflammation and improving immune cell function in elderly [146]. Specifically, resistance training programs stimulate muscle repair and can shift the immune response towards the one promoting regeneration[147]. Although preclinical studies have shown that increased physical activity attenuates the progression of cancer cachexia [148], there is no clear consensus about the threshold/amount of exercise required to counteract muscle wasting in patients [145]. In general, a regular physical activity has significant beneficial effects for patients by increasing protein synthesis and oxidative metabolism in the muscles, and by reducing inflammation and proteolytic factors. Unfortunately, physical exercise alone is not able to contrast cachectic progression remaining a tool to prevent upstream muscle wasting rather than a treatment. To enhance

the beneficial effects of physical exercise, a combined therapy with anti-inflammatory or anabolic drugs assisted by a nutritional intervention ought to be added [149–151].

Dietary supplements based on immunonutrients, such as omega-3 fatty acids and antioxidants, may reduce inflammation and improve immune function in aging populations, thus positively impacting on muscle mass and function loss as well [152]. Furthermore, given the complex interplay between cellular senescence and alterations in the gut microbiome, the emerging, but not yet sufficiently explored, gut-muscle axis theory has recently underscored the importance of maintaining gut microbiome homeostasis in skeletal muscle metabolism and function [153], especially in elderly people [154]. Accumulating evidence suggests that dysbiosis of gut microbiome in the elderly is associated with an impairment of the mucosal barrier, resulting in systemic chronic inflammation, that in turn affects skeletal muscle composition and function [155]. Time-restricted feeding, diets rich in fibers, restricted in carbohydrates diet and exercise can modify the composition and diversity of gut microbiota [156] enhancing gut and systemic immune functioning. Along with promising preclinical studies showing that reintroducing gut microbiota from conventionally raised mice to germ-free mice increased skeletal muscle mass and reduced muscle atrophy markers, specific microbial genera have been associated with higher lean mass and better physical performance also in older adults [157,158]. In view of this evidence, probiotics represent a strategic intervention for countering alterations in the gut microbiome, and improving systemic immunity in humans, by influencing cytokine production, natural killer cell cytotoxic activity, and secretory immunoglobulin A (IgA) levels [159] that can either prevent or overcome the immunosenescence process.

Table 1
Recently completed and ongoing clinical trials on interventions/treatments for counteracting immunosenescence.

ClinicalTrials.gov ID	*STATUS*	*Study design*	*Intervention/Treatment*	*Objectives of the study*	*Study population*	*Primary outcome measures*
NCT01303484	Completed (2014)	Randomised, Double-blind, Placebo Controlled Cross- Over Study	Dietary Supplement: Bi2muno® GOS Dietary Supplement: Maltodextrin	to determine the effects of prebiotic B-GOS on the immune function, metabolism and gut microbiota of elderly people	Men and women, aged 65–80years, in good general health.	inflammatory/immune biomarkers, faecal microbiota composition, body metabolites
NCT03557463	Completed (2017)	controlled, randomized, double blind pilot stud	Nutritional supplementation using two different protein sources	to enhance vaccine response	Healthy individuals over 60 years of age	Difference in DTaP vaccine antibodies at before and after vaccine
NCT05807243	Completed (2022)	Descriptive comparative study	Nutritional intervention (hypocaloric diet)	to evaluate the differential pattern of molecular markers of immunosenescence in different population groups	18 Years and older with chronic diseases (obesity, cancer and patients who developed severe persistent forms of COVID19)	Molecular Markers of Immunosenescence
NCT04534049	Recruiting	Randomized controlled trial	Different Types of Physical Exercise (Intensive Strength Training; Strength Endurance Training; Flexibility Training)	to identify the mechanisms by which physical exercise can counter inflammation and improve immune function in older persons	65 Years and older suffering from immunosenescence and/or immune suppression	Inflammation and immunosenescence-related genes in peripheral blood mononuclear cells
NCT05857241	Not yet Recruiting	Open-label trial	Dietary Supplement: Fasting mimicking diet (FMD)	to investigate the tolerance of FMD	65 Years and older Institutionalized in Long Term Care Units	Measurement of the rate of occurrence of a clinical event considered to require discontinuation the FMD*
NCT05234203	Completed (2022)	Interventional, single-arm, open-label pilot study	Dietary Supplement: HTB Rejuvenate	to evaluate the effect of a polyphenol-rich nutritional supplement on epigenetic and cellular markers of immune age.	18 Years to 85 Years	Measurement of changes in methylation patterns on DNA related to immune age, leukocyte immune profiles
NCT01066377	Unknown (study start date: 2010)	Randomised, Controlled, Parallel Study	Dietary Supplement: Prebiotic and probiotic mix	to examine the effect of a prebiotic and probiotic mix on the immune response to influenza vaccination	Healthy patients aged 18–35 (young cohort) or 65–85 (older cohort)	Serum vaccine-specific antibodies to the 2010–2011 influenza vaccine
NCT03168503	Completed (2015)	Randomised, Double-blind, Placebo Controlled Cross-over Study	Dietary Supplement: Prebiotic and probiotic mix	to investigate the effect of probiotic-prebiotic mix on the faecal microbiota composition, metabolism and immunity	Healthy individuals aged 60–80 years.	Changes in fecal bacterial abundance and species diversity
NCT04435899	Completed (2018)	Cross- sectional and experimental study (randomised, parallel trial)	Physical exercise (Multi-modal exercise protocol)	to characterize hormonal, immune and psychological well-being	65 Years and older women	Weight and height will be combined to report BMI in kg/m2

*defined as the presence between D14 and D21 of at least one of the following conditions:
Weight loss > 5 %,
Hypoglycemia < 0.5 g/l (< 2.8 mmol/l),
Hypothermia < 35°C,
Heart rate < 50 beats per minute, checked twice at 15-minute intervals,
Low systolic blood pressure < 90 mmHg or > 200 mmHg; or diastolic blood pressure < 60 mmHg or > 110 mmHg; or mean blood pressure < 70 mmHg, checked twice at 15-minute intervals,
Increase of 5 points on the visual analog pain scale between D14 and D21,
A score of 1 on the EVIBE visual analog scale (instantaneous assessment of well-being) between D14 and D21,
Any serious acute clinical event (fall with serious traumatic consequence, acute medical or surgical condition).

5.5. State-of-the-art of clinical trials focused on immunosenescence and cancer cachexia

To identify studies investigating interventions for countering the progressive remodeling of immune functioning during aging and improving the muscle mass, we searched ClinicalTrials.gov, using the term "immunosenescence" and "Cancer Cachexia" in the Condition/Disease section. No studies focused on strategies for cancer cachexia due to immunosenescence have been found. However, the interventions/treatments under investigation (separately) for both immunosenescence and cachexia are similar, suggesting a likely interplay between fields. In the case of immunosenescence, we found 9 studies of interest of which 6 completed within the last ten years and 2 still ongoing. Most of these trials investigated dietary/nutritional supplements such as probiotics, prebiotics, and hypocaloric diet; two studies aimed at identifying the mechanisms by which physical exercise can counter inflammation and the extent to which it improves immune function in older people (Table 1). The studies specifically focused on intervention for cancer cachexia registered within the last ten years are 7; of these, 4 were completed (3 in 2023 and 1 in 2014). For two studies the status is unknown and 1 study is still on-going (recruiting) (Table 2). Most trials explored interventions such as nutritional supplements/education and physical exercise on several outcomes including change in body weight, muscle mass, physical activity, and Quality-of-Life, in cachectic cancer patients. Only 2 studies included anti-inflammatory drug therapy (ibuprofen and celecoxib) in the experimental group as part of a multimodal intervention (along with nutrition and exercise). The first one, completed in 2023 and termed the MENAC trial (Multimodal—Exercise, Nutrition and anti-inflammatory medication for Cachexia- NCT02330926) consisted of ibuprofen to reduce inflammation, a physical exercise program using resistance and aerobic training to increase anabolism, as well as dietary counselling and oral nutritional supplements to promote energy and protein balance. Results from a similar study completed in 2014 are also currently available in literature. In this case, the multimodal approach included Celecoxib as drug therapy associated with oral nutrition and physical activity; the efficacy

Table 2
Recently completed and ongoing clinical trials on interventions/treatments for cancer cachexia.

ClinicalTrials.gov ID	*STATUS*	*Study design*	*Intervention/Treatment*	*Objectives of the study*	*Study population*	*Primary outcome measures*
NCT02330926	Completed (2023)	Randomised, Open-label Trial	Multimodal intervention: Exercise, Nutrition and ibuprofen Plus Standard Care	to early prevent the development of cachexia rather than treatment late in the disease trajectory	18 Years and older diagnosed with cancer	change in body weight, muscle mass, physical activity
NCT05262192	Unknown (study start date estimated: 2023)	Randomised, Controlled, Parallel Study	Nutrition education	to investigate the role of nutritional education for slow cachexia	50 Years to 80 Years cachectic cancer patients	Quality of Life Scale, Body Mass Index Measurement and several biochemical parameters
NCT06651125	Completed (2023)	Open label trial	Adapted Physical Activity	to explore the impact of supervised physical activity intervention	Over 18 cachectic cancer patients	Attrition and compliance rates, serious adverse events
NCT00467844	Completed (2008)	Double-Blind, Placebo-Controlled, Dose-Finding Study	GTx−024	to assess if Gtx−024 is effective in increasing lean body mass.	Child, adult, older adult with cancer cachexia	Change in total body lean mass as measured by dual energy x-ray absorptiometry (DEXA) from baseline to 4 months
NCT01419145	Completed (2014)	A multicenter, open, randomized phase II study	Multimodal intervention (oral nutritional supplements, celecoxib and physical exercise)	To compare a multimodal intervention for cachexia versus standard cancer care	18 Years to 80 Years with cancer cachexia	Enrolment rate, compliance with study intervention, contamination-rate
NCT04136249	Unknown (study start date: 2019)	Randomised, Controlled Study	Dietary Supplement: Over physical activity 105/5000 resistance training combined with nutritional monitoring on maximum strength of knee extensors	To explore if muscle building and nutrition improve neuromuscular function, fatigue and quality of life	18 Years and older with colon cancer requiring chemotherapy	Isometric force
NCT01127386	Completed (2012)	Double-Blind, Placebo-Controlled, Study	lenalidomide (either fixed dose or CRP-guided dose)	to assess the efficacy of lenalidomide on lean body mass and handgrip strength in advanced solid tumour patients with inflammatory cancer cachexia	18 Years and older with cancer cachexia	Lean Body Mass and Handgrip Strength
NCT03144128	Completed (2018)	Prospective, double-blinded randomized controlled clinical trial	5,000IU vitamin D given daily for 12 weeks	To explore the contribution of Vitamin D to muscle metabolic function in cancer cachexia	45 Years to 75 Years with mild cancer cachexia	Non-invasive quantification of muscle lipid distribution; Local muscle oxygen consumption; Muscle Mass; Muscle Strength
NCT05307367	Recruiting	Longitudinal research + interventional controlled study	Behavioral: Exercise training (1 h, or as long as possible, 60–70 % peak workload (PWL), 2–5 days a week)	To identify molecular factors contributing to cancer-associated muscle mass loss and provide clinical evidence for exercise mechanisms to functionally restore muscle in cancer	18 Years to 100 Years with non-small cell lung cancer	Disease outcome Muscle mass

*Attrition rate was the number of patients who completed the baseline and follow-up assessments versus the number of patients who completed initial assessments and started the program. Compliance rate was the number of sessions completed out of the number of sessions prescribed.

of the intervention has not been published yet [160].

The (relatively recent) completed studies and ongoing clinical trials related to the use of a variety of interventions for several conditions associated to immunosenescense and cancer cachexia do not explore new relevant treatments; basically, they were (and are) aimed at confirming the already published data. From a clinical point of view, more efforts are needed to further explore to which extent and in which specific areas promising therapeutic interventions are really effective to treat immunosenescense and/or cancer-associated cachexia, also highlighting a putative etiopathological interconnection between these two conditions that may drive the investigation/use of a unique therapeutic intervention.

6. Conclusion and future directions

Cancer cachexia is a weakening condition associated with muscle and fat loss, unresponsive to nutritional support, and that contributes significantly to morbidity and mortality in cancer patients. Immune dysfunction, associated with immunosenescence and fueled by cytokine imbalance along with inflammation, contributes to cancer cachexia progression. Currently, clinical research on cancer cachexia faces several challenges that hinder the development of effective treatment strategies, including: i) the impact of immune cells senescence within muscle (but also fat tissue); ii) muscle/fat response to inflammation; iii) the lack of accurate mouse models mimicking cancer cachexia that can provide solid preclinical data; iv) the absence of standard diagnostic methods and markers. Many potential therapeutic approaches have been proposed such as exercise, immunonutrients in diet, and pharmacological treatments. Despite both endurance and resistance exercise are promising therapies, as they broadly impact muscle protein turnover, inflammation, and metabolism, however, their implementation is challenging because of the cancer cachexia patients' debilitated conditions [161]. Senolytics, anti-inflammatory and cytokines-based modulating agents, alone or in combination with nutritional intervention, are amongst the most encouraging pharmacological therapies aimed at counteracting or delaying cancer cachexia degeneration. Further mechanistic insights are needed to fully elucidate the whole scenario and to understand how immune cells contribute to cancer- and chemotherapy-associated muscle mass loss and function impairment in cachexia, with the aim of defining suitable therapeutic strategies.

Author's contribution

All authors wrote, revised, and approved the final manuscript.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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