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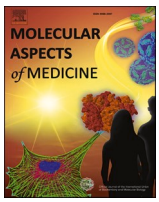

Review

Immunomodulation: A new approach to cancer cachexia, potentially suitable for aging

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ABSTRACT

Cancer cachexia is the prototypical example of comorbidity, occurring in most of cancer patients. It is a direct consequence of tumor growth and of the associated inflammatory/immune response. Cachexia can be exacerbated by anti-cancer therapies, frequently resulting in dose limitation and/or treatment delay or discontinuation. The pathogenesis of cancer cachexia is still unclear and includes nutritional, metabolic, hormonal and immunological components.

Tumor ability to shape the immune response to its own advantage is now well accepted, while the possibility that such an altered immune response could play a role in the onset of cachexia is still an undefined issue. Indeed, most of the immune-related research on cachexia mainly focused on pro-inflammatory mediators, almost totally disregarding the interactions among immune cells and the homeostasis of peripheral tissues. The present review provides an overview of the immune system dysregulations occurring in cancer cachexia, focusing on the possibility that immunomodulating strategies, mainly developed to stimulate the anti-cancer immune response, could be useful to counteract cachexia as well.

Cancer and cachexia are frequent comorbidities of aging. Along this line, cancer- and aging-associated muscle wasting likely coexist in the same patients. Since both conditions share some of the underlying mechanisms, the potential effectiveness of immunomodulation on sarcopenia of aging is discussed.

The management of cancer patients is very frequently complicated by paraneoplastic syndromes, among which cachexia is one of the most relevant. By an international consensus cachexia has been defined as a complex multifactorial syndrome characterized by involuntary body weight loss and skeletal muscle wasting, associated or not with reduced adipose tissue mass, that can be only partially counteracted by nutritional approaches and eventually results in functional impairment (Fearon et al., 2011). According to the currently accepted definition, three phases of cachexia can be identified: pre-cachexia, cachexia, and refractory cachexia. Patient progression through these three levels depends on several extrinsic and intrinsic factors (Fearon et al., 2011).

The prevalence of cachexia among cancer patients is markedly high, although considerable differences can be observed according to tumor type and disease stage (Anker et al., 2019). The management of cancer patients with cachexia is very complicated, due to their poor quality of life associated with reduced tolerance and response to treatments, which eventually result in increased death rates (Roeland et al., 2020). Along this line, about 90% of cancer patients are at risk of developing cachexia, with a mortality rate that can reach 80%/year (von Haehling et al., 2016). Unfortunately, despite its relevance to cancer patient outcome, this syndrome is still largely unrecognized and underdiagnosed. In addition, at present no specific therapies for cachexia are available, mainly due to the lack of data from appropriate pre-clinical and clinical studies supporting new pharmacological and non-pharmacological interventions. The more so, pre-clinical studies frequently overlook the side-effects exerted by anticancer treatments, that further exacerbate whole body wasting (Campelj et al., 2021).

1. Pathogenesis of cachexia

The pathogenetic mechanisms underlying cancer cachexia are only partially elucidated, although the multifactorial nature of this syndrome is now well recognized, including nutritional, metabolic, hormonal and immunological components.

Malnutrition, a frequent occurrence in cancer patients, is predictive of bad outcome. In this regard, patients should be nutritionally assessed as soon as possible during the course of the disease. Indeed, cancer can impinge very early on dietary habits in view of mechanisms directly

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related to tumor localization or resulting from the action of humoral mediators. These latter are of both host and tumor origin and together may affect appetite regulation at the central level but also contribute to anorexia *per se* (Argilés et al., 2017). Differently from simple starvation, reduced food intake in cancer patients does not lead to a convergent metabolic modulation aimed at meeting the lack of nutrients. The result is a persistently negative nitrogen and energy balance that is reflected at the tissue level, affecting skeletal muscle and fat, in particular.

The loss of muscle mass is one of the hallmarks of cancer cachexia and is mainly associated with increased protein breakdown rates. Indeed, several experimental and clinical studies clarified that the main intracellular proteolytic systems, namely proteasome and lysosomes, are activated above the physiological levels in cancer hosts (Penna et al., 2020).

As for the anabolic side of protein turnover, the rates of protein synthesis in the muscle of tumor-bearing animals have been shown to be up-regulated, unchanged or down-regulated, depending on the model system investigated (Argilés et al., 2014). Similar observations have been obtained by studies performed in cancer patients, where the situation is even more confused (Emery et al., 1984; Hanson et al., 2017) (Engelen et al., 2016a) (van Dijk et al., 2015). A number of approaches have been investigated in order to improve muscle anabolism, with very limited success (Costelli et al., 2006) (Penna et al., 2010a) (Engelen et al., 2016b). However, the existence of an exploitable anabolic window in cancer patients has been proposed years ago (Prado et al., 2013).

Several lines of evidence have suggested that altered energy metabolism likely contributes to impair protein turnover, consequently affecting skeletal muscle mass and function. In this regard, hypermetabolism, mainly reflected by increased resting energy expenditure (REE), is long known to occur in cancer patients (Prado and Qian, 2019) (Vazeille et al., 2017). By contrast, only few years ago the impaired energy metabolism featuring cachexia has been associated with mitochondrial dysfunction. This latter is partially accounted for by the reduction of mitochondrial number, due to impaired biogenesis, altered fusion and fission, and/or increased destruction, mainly operated by mitophagy. On the other side, impaired mitochondria oxidative capacity has been reported as well, contributing to the negative energy balance occurring in both tumor-bearing animals and cancer patients. In addition to impinge on energy availability, the altered mitochondrial function also results in increased production of reactive oxygen species and oxidative stress, fueling a vicious cycle that further exacerbates mitochondrial damage. Clearly demonstrated in preclinical models, the occurrence of mitochondrial alterations has also been shown in the muscle of cancer patients with cachexia (Penna et al., 2020).

About one decade ago, impaired muscle regeneration has been proposed to occur in cancer-induced muscle wasting. Indeed, molecular markers of satellite cell activation (Pax7) and of myogenic differentiation (myogenin) are dysregulated in the muscle of cancer hosts (Penna et al., 2010b) (He et al., 2013). Consistently, the physiological regenerative response activated by muscle damage is delayed in tumor-bearing mice in comparison to healthy animals (He et al., 2013) (Costamagna et al., 2020), a phenotype that results from overactivation of both the ERK stress kinase (Penna et al., 2010b) and the transcription factor NF-κB (He et al., 2013). More recently, the signaling pathways regulated by Twist1, ZIP14 or IL-4 have also been involved in altering muscle regeneration in cachexia (Costamagna et al., 2020) (Parajuli et al., 2018) (Wang et al., 2018).

Finally, a new frontier in the pathogenesis of muscle wasting in cachexia is represented by the neuromuscular junction (NMJ). In this regard, myofiber denervation resulting from dismantled NMJ architecture has been reported in both tumor-bearing mice and cancer patients and, at least in the former, precedes muscle wasting (Sartori et al., 2021). Such a pattern can be antagonized by treating tumor hosts with tilorone, a drug able to restore the signaling pathway regulated by bone morphogenetic proteins (BMPs) and the SMAD1/5/8 transcription factor complex (Sartori et al., 2021). Of interest, alterations in the motor unit number as well as in the single motor unit potential have been reported in both tumor-bearing mice and in healthy animals exposed to chemotherapy.

2. Cachexia and inflammation

Systemic inflammation can be considered one of the main drivers of cancer-induced metabolic alterations, including those discussed above. Some cytokines are most frequently upregulated than others in cancer cachexia, including tumor necrosis factor (TNF)α, interleukin (IL)-1β, IL-6 and γ-interferon (γIFN). The origin of systemic inflammation is the tumor itself, which is able to produce pro-inflammatory factors, but also leads, directly and indirectly, to the activation of host inflammatory/immune cells. In addition, cytokines normally entrapped into the extracellular matrix such as transforming growth factor (TGF)β can be released, for example by bone metastasis, and contribute to muscle wasting (Waning et al., 2015). The resulting scenario is that the host organism must face a plethora of mediators that, irrespective of their origin, impinge on tissue trophism and metabolism, triggering and amplifying the multiorgan cross-talk that eventually leads to whole body wasting. Several lines of evidence demonstrate the occurrence of high circulating levels of pro-inflammatory mediators, including acute phase proteins and cytokines, in both tumor-bearing animals and cancer patients (Argilés et al., 2019). By contrast, anti-inflammatory cytokines are frequently down-regulated (Costamagna et al., 2015).

By activating signaling pathways such as those dependent on p38 MAPK, NF-κB, JAK-STAT3 and SMAD1/5/8, pro-inflammatory cytokines up-regulate the expression of molecules pertaining to the protein degradation machinery such as muscle-specific E3s and autophagy-regulating factors (Argilés et al., 2019) (Kumar et al., 2012). Consistently, protective effect against muscle wasting has been reported by pharmacological or genetic inhibition of these signaling pathways (Sartori et al., 2021) (Molinari et al., 2017). In addition to stimulate protein degradation, cytokines can also antagonize anabolism by causing peripheral insulin resistance (Costelli et al., 2003).

Several cytokines induce the production of reactive oxygen/nitrogen species (ROS/RNS). As an example, TNFα acts on mitochondria enhancing ROS production and release. In addition, it causes H_2O_2 overproduction through enzymatic reactions involving NADPH oxidase (Nox) and xantine oxidase (Tzika et al., 2013) (Ábrigo et al., 2018). Conversely, H_2O_2 can impinge on protein breakdown rates by inducing endoplasmic reticulum stress and/or by activating NF-κB and SMAD3, resulting in the induction of muscle-specific E3s and autophagy (Penna et al., 2020). A similar pattern is shared by TGFβ released by osteolytic metastatic lesions, that has been shown to result in increased expression and activation of Nox4 (Wang et al., 2018) (Abrigo et al., 2016). Finally, also cancer-derived pro-inflammatory mediators play a role in causing muscle oxidative stress and protein wasting (Penna et al., 2020).

The interplay between inflammation and oxidative stress is a reciprocal one. Indeed, cytokine-driven transcription factors such as NF-κB, AP-1 and Nrf2 can be also regulated by the redox balance, inducing the production of pro-inflammatory mediators (Penna et al., 2020). Last, but not least, increased ROS/RNS levels in the skeletal muscle of cancer hosts are associated with reduced availability of antioxidants such as superoxide dismutase (SOD)1/2 and glutathione peroxidase (Ábrigo et al., 2018).

While the link between systemic inflammation and cancer cachexia is now well established, it is still unclear how the host response to the tumor is regulated. Indeed, patients bearing the same tumor type and with comparable disease stage may present with markedly different degrees of cachexia, suggesting that individual factors such as sex, age, genotype, environment and lifestyle might play a role. In this regard, years ago the propensity to develop cachexia among a group of gastrointestinal cancer patients has been associated with single nucleotide polymorphisms in the genes coding for IL-1, IL-6 and IL-10 (Deans et al., 2009). More recently, a study performed on cancer patients has reported

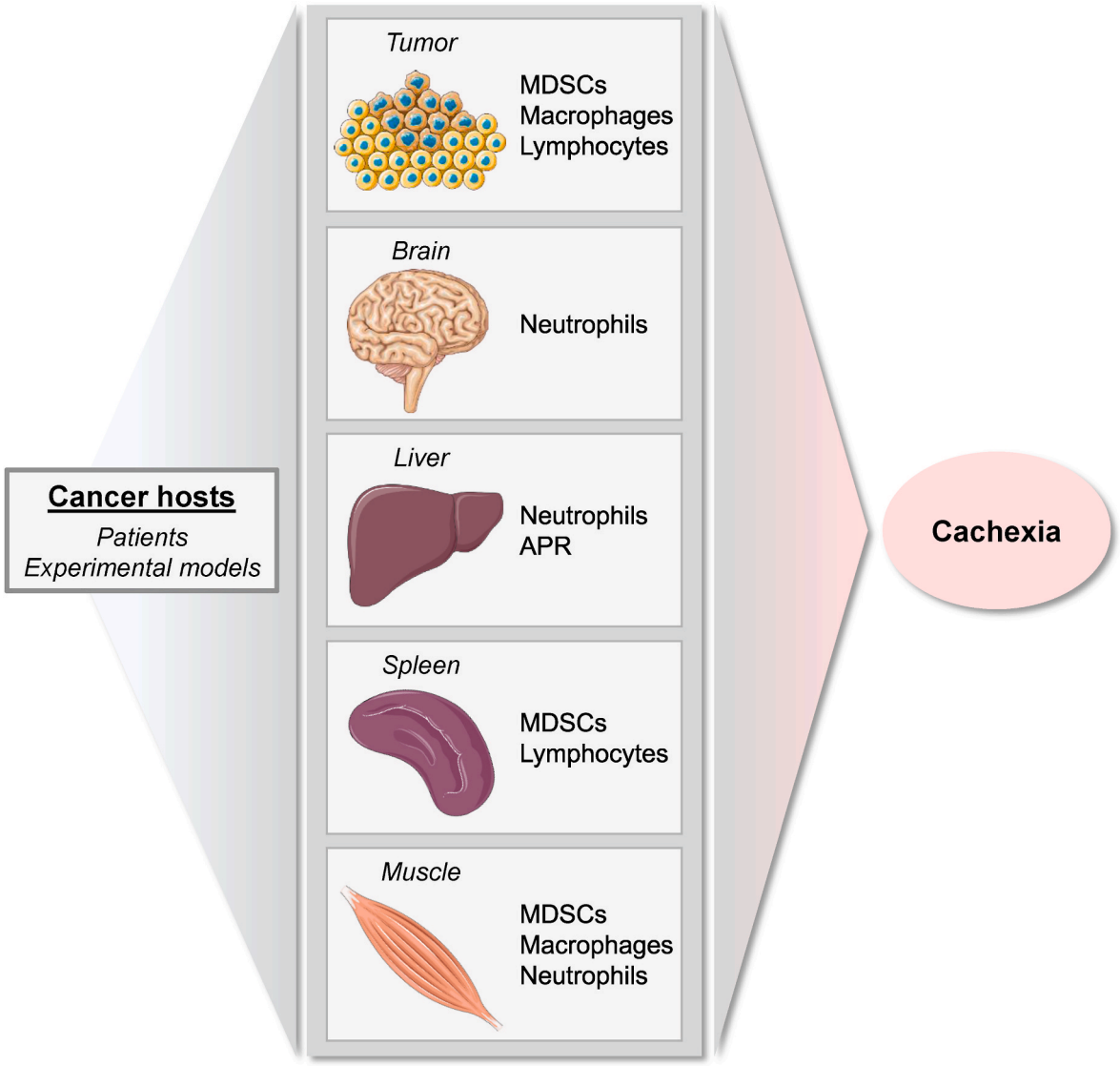

Fig. 1. Immune cells potentially involved in the pathogenesis of cancer cachexia
Cancer growth markedly impinges on both number and function of the immune cells resident in, or recruited to, several body compartments, including the tumor itself. Not all of the immune cell populations are equally represented in the different tissues and are equally affected by the tumor. However, many of them are very likely to eventually converge in contributing to the onset and progression of cachexia. MDSCs: myeloid-derived suppressor cells; APR: acute phase reaction.

the association of a polymorphism in the gene encoding P-selectin with body weight loss and low muscularity (Tan et al., 2012).

Despite the relevance of pro-inflammatory cytokines to the onset and progression of cancer cachexia, specific anti-cytokine treatments revealed unsuccessful in both experimental and clinical studies, likely reflecting the complex pathogenesis of this syndrome. Indeed, more than the action of single cytokines, an interplay among pro-inflammatory mediators, endowed with frequently overlapping biological activities, is likely to take place in cancer patients.

3. Dysregulation of the immune response in cachexia

The ability of cancer to evade both the innate and the adaptive immune response is long known and tumor progression towards malignancy has been shown to require myeloid cells in the tumor microenvironment in order to support angiogenesis and the epithelial-mesenchymal transition. However, the role played by such an altered immune response in the onset of cachexia has long been neglected, in favor of research lines almost totally focused on how circulating pro-inflammatory mediators may impinge on signaling pathways in peripheral tissues, eventually resulting in body wasting. Along this line, little is known about the complex interaction linking immune cells to the regulation of peripheral tissue homeostasis. This is particularly relevant to the cross-talk occurring among the tumor and several distant tissues, which plays a crucial role in the onset and progression of cachexia (Fig. 1).

3.1. Myeloid-derived suppressor cells (MDSCs)

Several years ago, quantitative/qualitative alterations in myeloid cells rather than the production of specific cytokines have been proposed to drive cancer cachexia (Winfield et al., 2008). Specifically, myeloid-derived suppressor cells (MDSCs), characterized by an immunosuppressive phenotype, have been shown to increase in parallel with tumor mass in mice implanted with the 4T1 mammary adenocarcinoma. Starting from this observation, the dimension of MDSC population has been proposed to positively correlate with the occurrence of a cachexia-prone environment, attained by down-regulating the adaptive immune response (thus favoring tumor growth) and by becoming an important source of pro-inflammatory mediators (Winfield et al., 2008).

At present, MDSCs can be classified into two main subgroups: monocyte-like (mMDSCs) and neutrophil (granulocytic)-like (gMDSCs). The latter appear to be more expanded than the former in both experimental and human cancer. MDSCs have been proposed to derive from a sort of 'pathological activation' of myeloid cells, resulting from the prolonged exposure to myeloid-specific growth factors and pro-inflammatory mediators, eventually leading to an enrichment in the peripheral tissues of neutrophils and monocytes endowed with immunosuppressive activity (Veglia et al., 2018). In addition to cells of the innate immune response, MDSCs immunomodulating action also affects T and B lymphocytes and natural killer (NK) cells.

The pathological activation of MDSCs in cancer appears to be linked to metabolic reprogramming, due to either cancer or host-derived mechanisms. In this regard, the energy state can interfere with MDSC ability to adopt a M1 (anti-cancer) or a M2 (tumor promoting) phenotype. Acquisition of the latter is the final step of a chain of events starting in the bone marrow (the so called 'immunometabolic reprogramming') and ending in the tumor microenvironment (Cao et al., 2014). This latter is metabolically shaped by the marked glucose uptake of tumor cells, that mainly rely on this metabolite for energy production, even in normoxic conditions. Consequently, immune cells populating the tumor microenvironment suffer for the lack of glucose and are induced towards an immunosuppressive setting. In addition, other factors could contribute to the switch of MDSCs towards immunosuppression.

i) NAD availability: this cofactor, pivotal to preserve cell energy balance, stimulates sirtuin 1 expression, promoting the shift of MDSCs towards a M2 (immunosuppressive) phenotype (Strauss et al., 2021). NAD levels depend on the activity of NAMPT (nicotinamide phosphoribosyltransferase), an enzyme which is overexpressed in chronic inflammatory illnesses such as autoimmune diseases, metabolic syndrome and cancer. Consistently, NAMPT inhibitors have been developed to reduce tumor growth by impairing the production of ATP and NAD. The same inhibitors also reveal able to restore immunocompetence (Travelli et al., 2019). However, recent observations show that circulating NAD is markedly reduced in both mice bearing cachexia-inducing tumors and cancer patients, suggesting that NAD modulation, possibly also acting on MDSCs, might differentially impinge on cancer and cachexia (Beltrà et al., 2023);
ii) MDSCs overexpress indoleamine 2,3-dioxygenase 1 (IDO1), an enzyme able to produce kynurenins from tryptophan. Kynurenine exerts an immunosuppressive action by depleting T cells of required substrates (L-arginine or cysteine, for example), increasing the number of T regulatory (Treg) cells and impairing dendritic cell activity (Vacchelli et al., 2014);
iii) Signal Transducer and Activator of Transcription protein (STAT) 3 activation: it has been linked to MDSC tumor-promoting effects (M2 phenotype) and has been reported to negatively correlate with tumor infiltration by immune cells. Consistently, its inactivation results in restored anti-tumor immune response (Wu et al., 2011).

While the above reported pathways contribute to the cross-talk in the tumor microenvironment, at least some of them are also relevant to the pathogenesis of cachexia. Indeed, studies performed on experimental tumor models reported that STAT3 activation plays a causative role in muscle wasting, as demonstrated by the observation that its inhibition by both genetic and pharmacological tools is able to preserve the skeletal mass and function without affecting tumor growth (Bonetto et al., 2012) (Huot et al., 2020). Kynurenin administration to mice resulted in reduced myofiber cross sectional area and muscle contractile force, a pattern that is associated with oxidative stress (Kaiser et al., 2019) and that closely resembles cancer cachexia. Consistently, endurance exercise, one of the most promising strategies to counteract muscle wasting in cachexia, reduces circulating kynurenin levels by conversion to kynurenic acid. This is operated by muscle kynurenine-aminotransferases, which expression is under the control of PGC-1α1, a co-transcription factor involved in mitochondrial homeostasis and induced by exercise (Agudelo et al., 2019).

Few studies directly investigated the hypothesis that MDSCs can contribute to cachexia. Some years ago, Cuenca and collaborators (Cuenca et al., 2014) demonstrated in mice bearing the 4T1 mammary tumor that MDSC expansion is associated with both acute phase response and alterations of fat and energy metabolism. By contrast, these features do not occur in animals implanted with a subclone of 4 T tumor whose growth is not associated with MDSC expansion. More recently, partial depletion (>50%) of $Ly6G^+$ cells, which include MDSCs and neutrophils, has been shown to result in protection against cachexia induced by orthotopic pancreatic cancer, in the absence of changes in tumor mass (Deyhle et al., 2022). Finally, polymorphonuclear MDSC expansion has been reported in the skeletal muscle of tumor-bearing mice and to contribute to cachexia by over-producing activin A (Dzierlega et al., 2023).

3.2. Macrophages

As reported above, macrophages play a crucial role in the tumor microenvironment, being able to alternatively assume the M1 or the M2 phenotype, impinging on both tumor growth and local immune response. The same phenotypes can be observed also in peripheral tissues, deriving from both circulating activated monocytes or from resident macrophages (Ji et al., 2024).

In the skeletal muscle, macrophages play a central role in the physiological response to injury, whatever the damaging stimulus is. Indeed, resident macrophages are early activated and rapidly release chemoattractant factors in order to recruit from the circulation other immune cells, mainly neutrophils and monocytes. The latter rapidly differentiate into M1 macrophages producing a pro-inflammatory environment, required to get rid of cell debris but also to allow myogenic cell proliferation and commitment to differentiation. A second recruitment wave will result in M2 macrophages able to release IL-10, TGFβ or IGF-1, required to promote myoblast differentiation and fusion to form new myofibers (Baghdadi and Tajbakhsh, 2017).

At present, the role played by macrophages in the onset and progression of cachexia has been poorly investigated. Inaba and collaborators (Inaba et al., 2018) have shown a reduction of both macrophage and neutrophil number in the skeletal muscle of mice bearing the C26 tumor. By contrast, another study showed that muscle expression of F4/80 and CD206, markers of whole macrophage and M2 populations, respectively, is comparable in control and C26-bearing mice (Costamagna et al., 2020). To better investigate the relationship between cachexia and macrophages, transgenic mice expressing SV40 large T oncogene in the hepatocytes (ASV-B WT), an experimental model of hepatocellular carcinoma, have been cross-bred with mice unable to develop myeloid cell-mediated inflammation. While no differences could be observed between the two strains (ASV-B WT and ASV-B/Hif1A^{MC}) in terms of cancer-induced muscle wasting, the lack of myeloid response is associated with a further reduction of fat mass that does not seem to depend on tumor load, pro-inflammatory cytokine milieu or hypotalamic activation (Erdem et al., 2019). Finally, the protective action exerted by daily administration of IL-4 to mice hosting the C26 colon carcinoma (see above), is associated with increased amount of $CD206^+$ (M2) macrophages in both the skeletal muscle and the tumor, which could partially explain the improvement in terms of animal survival, muscle regeneration and function. The effects of IL-4 appear to be mainly muscle-specific, since the reduction of food intake and the marked depletion of white adipose tissue remain comparable among treated and untreated C26 hosts (Costamagna et al., 2020).

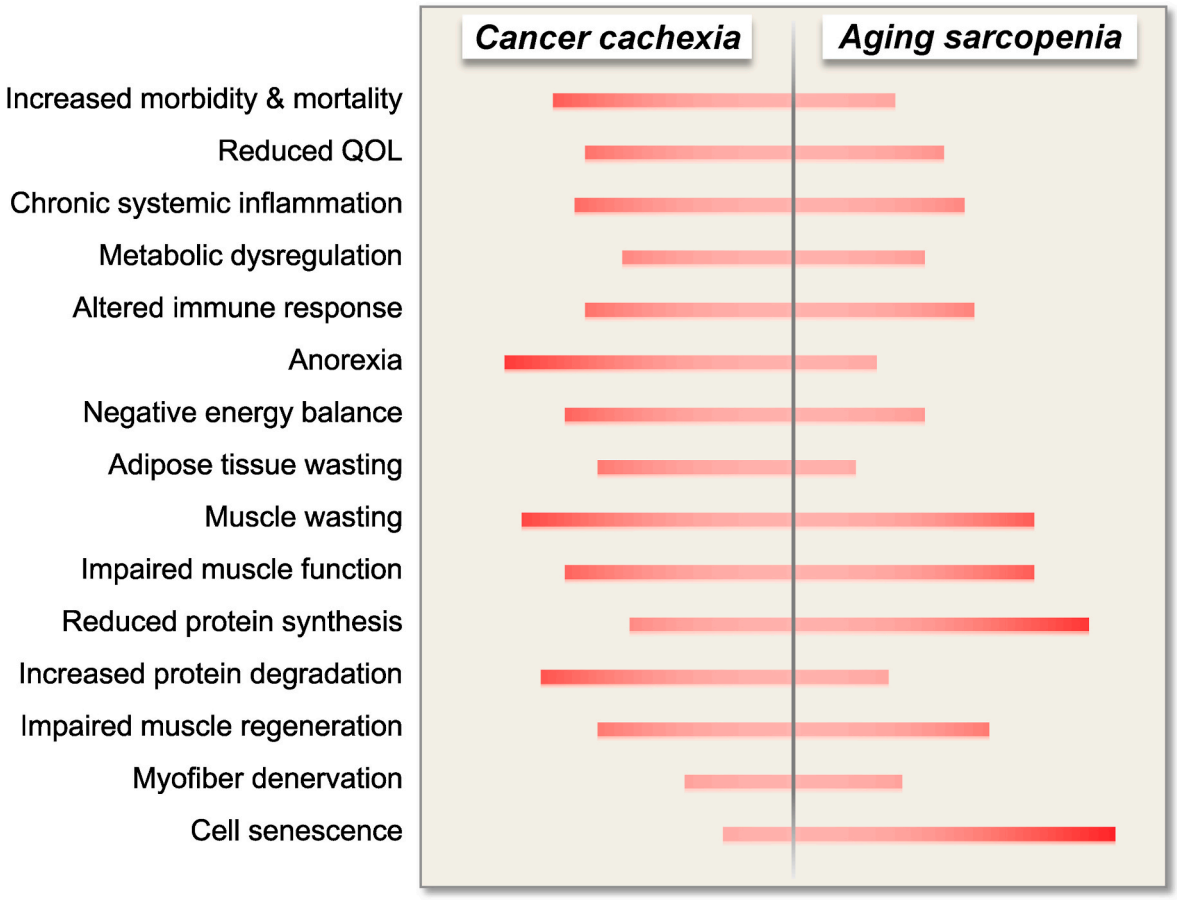

Fig. 2. Shared features between cancer cachexia and sarcopenia of aging
The occurrence of cachexia or sarcopenia results in common significant alterations at both local and systemic level. However, the extent by which such alterations are displayed in cancer patients or in the elderly may be quite different, resulting in similar, though peculiar, phenotypes.

3.3. Neutrophils

Changes in the neutrophil/lymphocyte ratio, likely resulting from the activation of an inflammatory response, have been proposed as early markers of cancer progression (Dusselier et al., 2019) (Barker et al., 2020). However, the relevance of such changes to the pathogenesis of cancer cachexia is still unclear and only in the last few years studies investigating the contribution of neutrophils to cachexia have become available. In animals bearing the KPC pancreatic ductal adenocarcinoma (PDAC), circulating neutrophils have been reported to respond to the tumor-derived chemokine CCL2 by early crossing the blood brain barrier and accumulating in proximity of the brain regions involved in the regulation of appetite and body composition. Consistently, neutrophil accumulation in the brain is markedly reduced and cachexia is improved when the tumor is implanted into mice lacking the CCL2 receptor CCR2 (Burfeind et al., 2020). Brain infiltrating neutrophils are characterized by a peculiar transcriptional profile, which is also reflected by the enhanced CCR2 expression, barely detectable in circulating neutrophils, suggesting that the populations accumulating in the central nervous system displays different functions (Burfeind et al., 2020). The same authors subsequently demonstrated that neutrophils release high amount of lipocalin (LCN)2, which is able to cross the blood brain barrier and is crucially involved in the onset of anorexia in PDAC bearing mice. Similar observations have also been reported in PDAC patients (Olson et al., 2021).

Finally, a recent report shows increased neutrophil number in experimental cancer cachexia, in the tissue compartment before than in the circulation. These neutrophils are endowed with marked glycolytic activity that appears to exert a compensatory action by impinging on cancer-induced lipolysis and altered liver metabolism. Indeed, when such glycolytic activity is inhibited, cachexia worsens (Petruzzelli et al., 2022). The other way around, partial depletion of Ly6G$^+$ cells has been reported to improve cancer-associated muscle wasting in mice orthotopically implanted with the KPC pancreatic cells (Deyhle et al., 2022). The mechanism underlying such an effect still needs to be elucidated, however the lack of tumor mass changes rules out the possibility that the improvement of cachexia can be accounted for by reduced tumor burden.

3.4. Lymphocytes

Cancer patients frequently present with altered number of circulating CD8$^+$ and CD4$^+$ T cells, including Treg and Th17 cells. In particular, high frequency of Treg lymphocytes associated with high levels of CD8$^+$ memory cells (but low number of CD8$^+$ naive cells), have been correlated with poor prognosis. Consistently, elevated levels of pro-inflammatory cytokines coupled with reduced concentrations of anti-inflammatory mediators has been proposed as a marker of good outcome. No specific direct evidence of T lymphocyte alterations in experimental and human cachexia has been reported, yet observations suggesting that this cell compartment could be involved as well are available. In this regard, while T cell activity against cancer might result in improved muscle and adipose tissue wasting in view of a reduced tumor burden, the same response could negatively impinge on those compartments by enhancing the inflammatory environment.

Previous observations have shown that the infusion of naive T helper

cells into tumor-bearing mice results in protection against muscle atrophy (Lu et al., 2021). More recently, a study performed on gastrointestinal cancer patients reported that levels of naive and memory T lymphocytes correlate with muscle function, while changes in body mass index correlate with Treg abundance. Of interest, such correlations are absent in non-cancer patients, despite comparable frequency of immune cells in the two groups of volunteers. Another recent report suggests that the loss of adipose tissue occurring in cancer patients is achieved, partially at least, by macrophages and cytotoxic T cells. Indeed, while the latter contribute to enhance the expression of γ-interferon, depletion of the former has been shown to protect against adipose tissue wasting and cachexia in tumor-bearing animals (Han et al., 2022).

3.5. Complement

The complement system, discovered in the late XIX century, pertains to the innate immunity and is a central player in the interaction with the adaptive response. It includes more than thirty soluble or cell-bound proteins, produced by several cell types including immune cells, hepatocytes, adipocytes, but also tumor and stromal cells (Lu et al., 2021). There are three different ways to activate the complement system, all of which rely on the production of protein fragments through a cascade of enzymatic reactions, ultimately resulting in biological activities ranging from opsonization and chemoattraction to amplification of the inflammatory response and cell death.

The relevance of the complement system to oncology is mainly related to its activity in the tumor microenvironment. Indeed, complement protein fragments have been reported to modulate the T cell response, to directly act on cancer cell proliferation and death, to impinge on cancer-associated processes such as angiogenesis, invasion and metastasis, and to shape the resistance to anti-cancer treatments. The observation that high circulating levels of some complement components has been reported in cancer patients suggested their use as biomarkers useful for both diagnosis and monitoring procedures (Speth et al., 2022).

Data reported in the literature show that complement factors are elevated in cancer patients (Senent et al., 2021) (Felberg et al., 2020) (Lin et al., 2014), however at present very few studies investigated the involvement of this system in the pathogenesis of cachexia. In this regard, a recent report shows that circulating levels of C3a and TCC (Terminal Complement Complex) are significantly higher in cachectic than in non-cachectic cancer patients (Deng et al., 2021). Consistently, mice bearing the C26 tumor show increased C3 gene expression in the skeletal muscle, which is associated with high C3 circulating levels (Massart et al., 2020).

4. Similarities between cancer cachexia and aging-associated sarcopenia

Cancer is one of the most frequent comorbidities of aging; along this line, cachexia and sarcopenia frequently coexist. Both are systemic conditions characterized by multiple organ/tissue/cell interactions, ultimately resulting in chronic inflammation and metabolic dysregulation. As in cancer cachexia, loss of skeletal muscle mass and function is a typical feature of sarcopenia, which prevalence is estimated in about 25% and 50% of individuals aged >70 and > 80, respectively (Yazar and Olgun Yazar, 2019). Reduced muscle mass and function in aging are risk factors for frailty and loss of independence, resulting in poor quality of life and increased health care needs.

Although at a different extent, cancer- and aging-associated muscle wasting share several pathogenetic mechanisms, among which overactivation of protein breakdown, reduced protein synthesis, persistent low-grade inflammation and modulations of the immune response (Fig. 2). In aging, these latter are broadly referred to as immunosenescence, which includes inflammaging, reduced defence against infections or cancer and increased autoimmunity (Goronzy and Weyand, 2013). High number of senescent T-cells, reduced efficiency of natural immune cells and reduced cellularity in the bone marrow are among the main features of immunosenescence. Along this line, a shift from the differentiation in the lymphoid lineage towards the myeloid one has been reported, resulting in increased circulating mature myeloid cells (Dorshkind et al., 2020). Since these latter, macrophages in particular, play a crucial role in the skeletal muscle response to stress conditions, the increase in their number likely contributes to frailty in the elderly (Tidball, 2017). Another relevant issue in aging-associated immune dysregulation is the induction of high circulating levels of pro-inflammatory mediators such as IL-1, IL-6, IL-8, TNFα, TGFβ, C-reactive protein (CRP) and serum amyloid A (Ferrucci and Fabbri, 2018). More recently, factors produced by the muscle, and for this reason defined as myokines, have been proposed to play a role in immunosenescence. At present, more than 300 myokines have been found in the muscle secretome, some of which involved in modulating the immune response such as leukemia inhibitory factor (LIF), IL-6, IL-7 and IL-15. Consistently, IL-7 and IL-15 plasma levels appear to inversely correlate with age. The other way around, IL-15 also plays a crucial role in the immune system, regulating both number and functions of NK cells and B and T lymphocytes, and impinging on the innate immune response, manily favoring neutrophil action (Nelke et al., 2019).

One of the hallmarks of aging is cell senescence, a non-apoptotic response to lethal damage that confers cells unique attributes. These include a generally irreversible cell cycle arrest, the expansion of the lysosomal compartment and a vigorous secretory phenotype (henceforth referred to as senescence associated secretory phenotype: SASP). While senescence crucially contributes to tumor suppression and to other physiological processes, excessive amounts of senescent cells play a causative role in several age-associated chronic diseases (Van Deursen, 2014). The SASP, which encompasses a variety of inflammatory mediators and tissue remodelling factors, enables the spreading of the senescent phenotype to otherwise normal/healthy cells, and accounts for the systemic dysfunctions linked to the elevated burden of senescent cells across the organism (López-Otín et al., 2023). In particular, SASP released by senescent cells in the muscle might account for changes in myofiber morphology and function, likely providing an additional link between immunosenescence and sarcopenia. Senolytic compounds have been developed to face the aberrant accumulation of senescent cells and/or the high levels of SASP mediators (Gasek et al., 2021). Along this line, senescent cell depletion by senolytics in aged mice resulted in improved muscle mass and function (Xu et al., 2018).

The complex interaction between the skeletal muscle and the immune system clearly stands up when considering injury-induced regeneration. Such a physiological process is impaired during aging, also because of immunosenescence (Nelke et al., 2019). In addition to macrophages, also the homeostasis of regulatory T cells (Treg) is altered in aged mice (Kuswanto et al., 2016), likely reflecting reduced expression of IL-33. Consistently, IL-33 replacement in aged mice restores Treg function, rescuing the muscle regenerative potential.

On the whole, aging likely impinges on the muscle-immune system cross-talk generating a reciprocal causative relationship between sarcopenia and immunosenescence. Indeed, some of the hallmarks of aging such as dysmetabolism, inflammaging and reduced physical activity drive the progressive loss of muscle mass and function. On the other side, the presence of sarcopenia leads to alterations of the immune regulatory activity normally exerted by the muscle cell. The overall scenario is an auto-amplifying dysfunction of the muscle-immune system physiology (Nelke et al., 2019).

Finally, another level of complexity at the organismal level is that immunosenescence markedly contributes to one of the most typical features of aging, namely multimorbidity. Indeed, elderly people very frequently present with increased propensity to infections and chronic inflammatory diseases, including autoimmune disorders and cancer. Along this line, not only cachexia and sarcopenia share common

pathogenic mechanisms, they are also frequently occurring in the same individuals. These considerations support the idea that therapeutic strategies aimed at reducing inflammation and improving the immune response could make the difference in terms of elderly people management and quality of life maintenance/improvement.

5. Immunomodulating strategies

Modulations of the immune system might crucially impinge on the crossroad between health and disease. Indeed, both excessive or defective immune response have been reported to contribute to the pathogenesis of several illnesses. Along this line, plenty of studies investigated the mechanisms underlying both the innate and the adaptive immune response, ultimately resulting in the discovery and exploitation of molecules/cells able to act as immunomodulators. Most of the studies in this area have been developed in the oncology field but can be potentially translated to other pathophysiological conditions.

While the idea to defeat cancer by modulating the immune response is not a new one, only in the last decade significant progress was achieved in this field. As an example, in 2010 FDA approved the first dendritic cell-based vaccine (Cheever and Higano, 2011) and the effectiveness of the first immune check-point inhibitor has been reported (Hodi et al., 2010). Chimeric antigen receptor (CAR) T-cell therapy, based on the possibility to genetically engineer the T cell receptor to target a specific tumor-associated antigen, has been approved by FDA in 2017 (Mullard, 2017).

Immune checkpoint inhibitors. Immune checkpoints are regulatory 'turning points' of the specific immune response, since they negatively affect T lymphocyte functions. Such a property is exploited by tumor cells, which reveal able to modulate the expression of immune checkpoint molecules, escaping the immune surveillance. Along this line, strategies inhibiting the immune checkpoints result in restored and enhanced anti-cancer T cell response. At present the FDA approved nine agents directed against four immune checkpoints, namely Programmed cell death-1 (PD-1), Programmed death-ligand 1 (PD-L1), Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and Lymphocyte activation gene 3 (LAG3), for the treatment of different types of cancers such as melanoma, hepatocellular carcinoma, stomach, colorectal and non-small cell lung cancer, among others (Guo et al., 2023). Quite recently, molecules acting as immunometabolites such as spermidine have been proposed to enhance the effectiveness of immune checkpoint inhibitors (Chamoto et al., 2023).

Anti-cancer vaccines. Therapeutic or prophylactic vaccines are available, both able to stimulate the innate and the adaptive immune response against tumor-associated antigens (TAA). The most relevant issue in this regard is that, being autologous antigens, TAAs are characterized by low immunogenicity, which markedly reduces the effectiveness of the vaccine-based approaches. To circumvent this problem, vaccines using tumor or dendritic cells have been developed. Despite the former provide several TAAs at the same time, the induced immune response remains modest, due to the low immunogenicity of tumor cells, which can be improved by using adjuvants (Guo et al., 2023). Dendritic cell vaccines lead to the production of antigen presenting cells activated against TAAs, which could result in the induction of specific T cell response. At present the only FDA-approved dendritic cell vaccine is Sipuleucel-T, designed to stimulate reactions against prostate cancer antigens (Guo et al., 2023). The scenario of cancer vaccines is completed by strategies based on nucleic acids. Indeed, DNA or RNA can be transfected into antigen presenting cells, where specific TAAs are expressed and exposed in association with histocompatibility antigens to be presented to T cells.

Cell-based immunotherapy. The most recent achievement in terms of cancer immunotherapy is represented by chimeric antigen receptor (CAR)-T cells. These are patient derived T lymphocytes wihch are genetically modified to express a TCR endowed with the ability to recognize specific TAAs. After transfection, such cells are expanded in vitro, then reinfused into the patient, where they are able to overcome the escape from immune surveillance. FDA approved by now two anti-CD19 CAR-T cell protocols, for the treatment of two different B cell malignancies. A similar approach is exploiting NK cells rather than T lymphocytes, allowing the use of allogeneic NK cells and markedly limiting the occurrence of cytokine storms (Guo et al., 2023).

Other immunomodulating strategies include small molecules inhibitors targeting immunosuppressive pathways such as that relying on indoleamine-pyrrole 2,3-dioxygenase and oncolytic virotherapy, while the use of nanotechnology has been proposed to improve both delivery and effectiveness of immunomodulating tools (Fan et al., 2021).

Despite the availability of different immunomodulating approaches, at present cancer immunotherapy is beneficial only for selected groups of patients, pointing out several needs such as: i) to find out additional tools; ii) to identify patient subpopulations likely non-responsive to immunotherapy, also taking into account age, the presence of cachexia and the extent of tumor burden; iii) to define personalized treatment approaches. On the other side, similarly to other therapeutic strategies, immunomodulation is not free from side-effects on the host organism, including the induction/exacerbation of cachexia, an issue that must be taken into account. Not only, the occurrence of cachexia has been proposed as a predictive factor for the effectiveness of cancer immunotherapy. Indeed, cancer patients treated with antibodies against PD-1 showed a negative correlation between muscle wasting and progression-free survival, while presenting with high drug toxicity which lead to treatment discontinuation (Roch et al., 2020) (Brocco et al., 2019). Moreover, patients characterized by flawed immune response have been proposed to be identified by assessing skeletal muscle density, which could be exploited as a marker to predict the effect of the PD-1 inhibitor ipilimumab and to calculate drug dosage (Chu et al., 2020).

5.1. Immunotherapy and its relevance to cachexia and sarcopenia

The possibility to use CAR-T cells or immune checkpoint inhibitors, alone or combined with chemotherapy, started a new era in the clinical management of cancer patients, leading to long term remissions or in some cases to tumor eradication. As reported above, however, such beneficial effects could be achieved only in a portion of patients, due to high toxicity, anaphylaxis or resistance (Sharma et al., 2017). In this regard, both patient age and the occurrence of cachexia could be factors impinging on the possibility to take advantage of immunomodulation. Different studies performed on patients with advanced lung cancer have shown that cachexia works as a predictive factor for the clinical response to the treatment with immune checkpoint inhibitors (Madeddu et al., 2023) (Makrakis et al., 2023). As for aging, two randomized clinical trials have reported that older patients respond worse than younger ones to anticancer immunotherapy (Kelly et al., 2021) (André et al., 2020), although opposite observations have been reported as well (Ontiveros et al., 2023). Just as an example, immune checkpoints such as PD-1, PDL1/2, CD80, Tim3 and Lag3 are more expressed in immune cells of aged than young people. The other way around, aging results in reduced CD28 expression on T cells, suggesting a lower propensity to activation in comparison to T lymphocytes in the young (Ontiveros et al., 2023). An important issue is that systemic inflammation and metabolic derangements featuring both aging and cachexia could result not just in reduced treatment tolerance, but also in enhanced immunosuppression and drug resistance (Flint et al., 2017). Along this line, immunomodulating strategies should be designed to achieve the best anticancer activity as possible, also taking into account the age-specific inhibition of the immune response such as immune checkpoint overexpression and T cell exhaustion.

Many humoral factors, including cytokines and chemokines, produced by cancer cells and/or by the host cells in response to the tumor have been shown to contribute to cachexia. Some of these factors, however, also negatively interfere with the immune response against the tumor. As an example, TNFα, well known for its ability to stimulate both

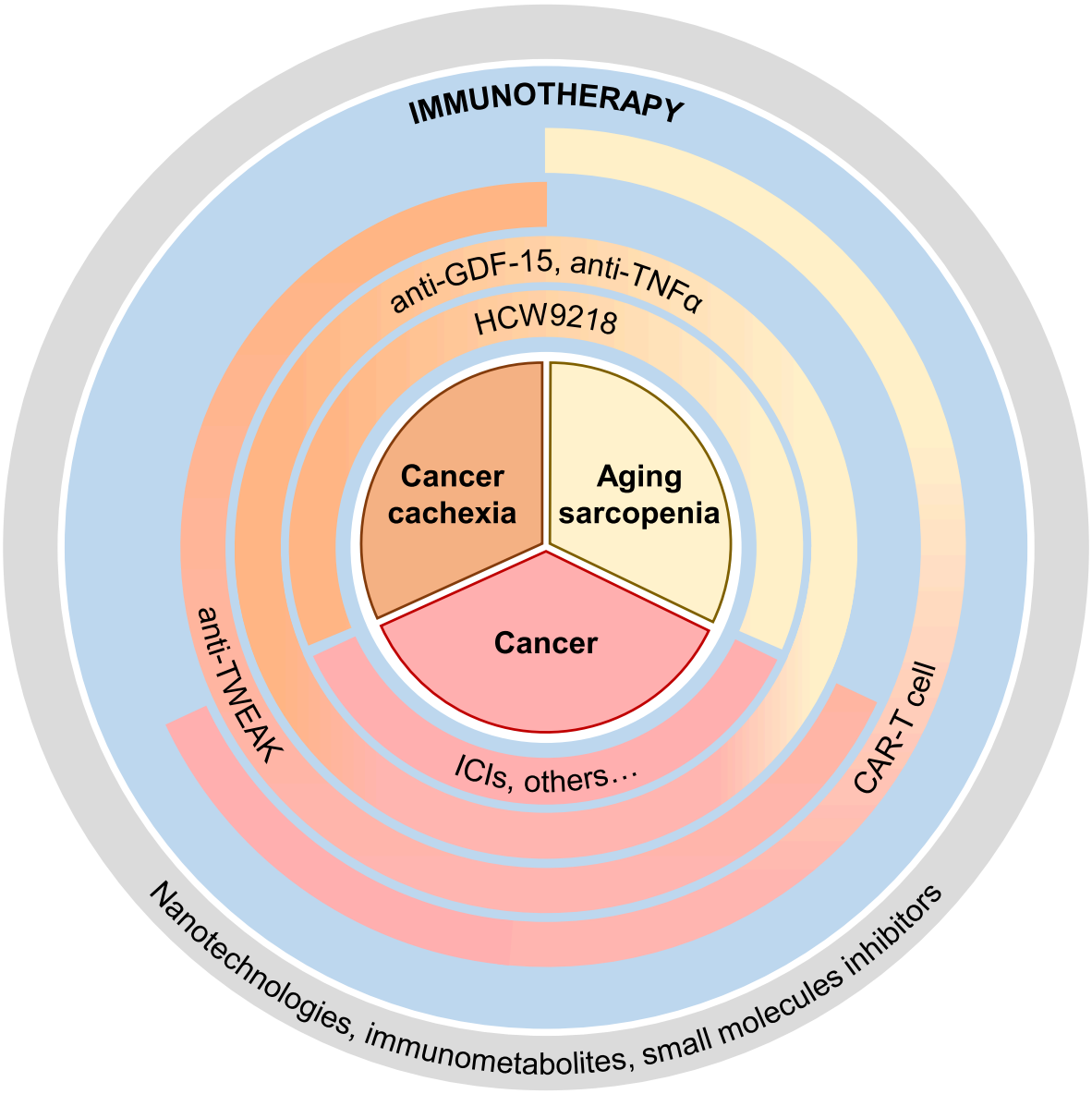

Fig. 3. Immunomodulation in the treatment of cancer, cachexia and sarcopenia
Initially developed to stimulate the immune response against cancer, several lines of investigations support the possibility that at least some of the immunomodulating strategies available could be effective to manage cachexia and/or sarcopenia. The interest in extending the use of immunotherapy to non-conventional targets is further enhanced when taking into account the possibility of a combined action with new tools such as small molecule inhibitors and nanotechnologies. ICIs: immune check-point inhibitors; CAR-T: chimeric antigen T cell receptor; HCW9218: example of immunotherapeutic drug; anti-GDF15, anti-TNFα, anti-TWEAK: antibodies against cytokines.

protein and lipid catabolism in the tissues of cancer hosts, also results in reduced T cell response against the tumor, decreasing both the number and function of infiltrated cytotoxic T lymphocytes (Bertrand et al., 2017). Consistently, administering tumor-bearing animals with anti-TNFα antibodies improves cachexia (Costelli et al., 1993) and restores the sensitivity to immunotherapy directed against PD1 (Bertrand et al., 2017). The combination of immune check-point inhibitors with anti-TNFα antibodies is currently being tested in advanced melanoma patients (NCT03293784). Another mediator endowed with a dual role as inducer of cachexia and inhibitor of the immune response is TWEAK. It is a member of the TNFα superfamily, shown to contribute to skeletal muscle wasting by activating the signaling pathway dependent on the engagement of its receptor Fn14 (Johnston et al., 2015). On the other side, TWEAK inhibits the activation of the transcription factor STAT1, compromizing the release of interferon γ and IL-12, two cytokines involved in the anti-tumor response (Maecker et al., 2005). Inhibition of TWEAK-dependent signaling in cancer hosts results in improved immune response and reduced tumor burden (Ye et al., 2017). Both TNFα and TWEAK have been shown to be associated with sarcopenia of aging as well (Li et al., 2019). Of interest, aged mice exposed to Etanercept, a specific anti-TNFα biological drug, have shown improved muscle mass and function, together with increased lifespan (Sciorati et al., 2020). Along the same line, very recently high circulating levels of GDF-15, a factor known for its ability to induce anorexia and to contribute to cachexia (Siddiqui et al., 2022), have been reported to correlate with reduced effectiveness of PD-1 inhibitors in both experimental and human melanoma (Haake et al., 2023). GDF-15 has been proposed to act itself as an immune checkpoint, suggesting an additional target for immunotherapy (Wischhusen et al., 2020). Interestingly, high GDF-15 plasma levels have been associated with body weight loss and reduced score at the short physical performance battery test in elderly people (Raffin et al., 2023) (Fielding et al., 2023), suggesting that this is an

immunosuppressive mechanism that could be targeted to improve the management of cancer patients and sarcopenia of aging.

Recently, the immunotherapeutic drug HCW9218 has been shown to enhance the NK-dependent clearance of senescent cells induced by chemotherapy administration to tumor-bearing animals (Liu et al., 2021) (Chaturvedi et al., 2022), suggesting that aging-associated senecence could be addressed by approaches aimed at stimulating the immune system. Consistently, the same authors have shown that HCW9218 administered to 76 weeks old mice results in improved proliferation and metabolic functions of NK cells and cytotoxic T lymphocytes isolated from both spleen and liver. Such an effect is associated with reduced expression of senescence-associated genes and SASP in tissues such as liver and kidneys (Shrestha et al., 2023). Along this line, few years ago senescent cell deletion in aged mice has been reported to improve both cognitive impairment and sarcopenia (Kirkland and Tchkonia, 2017). Exposure of aged animals to HCW9218 results in improved physical performance, likely reflecting positive effects at both the neuromuscular and locomotor levels (Shrestha et al., 2023). Of interest, the drug used in these studies exerts its immunomodulatory action impinging on both the TGFβ and the IL15-dependent signaling pathways. In this regard, previous observations have shown that IL15 supplementation to tumor-bearing rats is able to counteract cancer-induced muscle wasting (Carbó et al., 2000), further supporting the idea that impinging on the immune system could be beneficial in both cachexia and aging.

The effectiveness of cell-based immunotherapy as well can be affected by body composition. Indeed, recent observations have shown that in patients affected by relapsed/refractory large B-cell lymphoma treated with CD19 CAR-T, increased survival is negatively associated with muscle wasting (Rejeski et al., 2023). Similarly, cachexia has been reported to negatively impinge on the outcomes of CAR-T cell approach in patients affected by non-Hodgkin B cell lymphoma (Roy et al., 2022).

Another relevant issue to take into consideration is that cell senescence might significantly impinge on CAR-T efficiency from two different points of view: while senescent T cells are mainly isolated from elderly patients, such a feature becomes even worse when engineered CAR-T lymphocytes are reinfused, due to the inflammaging occurring in the host organism. Along this line, several strategies to achieve CAR-T cell rejuvination are currently being investigated (Noll et al., 2023). The other way around, cell-based immunotherapy could reveal useful to get rid of excessive senescent cell accumulation, which contributes to the onset and progression of several chronic diseases. Along this line, CAR-T cells targeting senescence-associated antigens have been shown to exert a senolytic activity. Indeed, senescent cells are characterized by the expression of specific markers (senoantigens) such as the natural killer group 2 member D ligands (NKG2DLs) and the urokinase-type plasminogen activator receptor (uPAR), among many others. Quite recent observations show that CAR-T cells directed against NKG2DLs infused into mice effectively reduce the number of senescent cells, irrespective of the causative stimuli. Such an effect has been associated with improved aging-associated comorbidities and physical performance, likely impinging on both muscle mass and function (Yang et al., 2023). Similarly, CAR-T cells targeting uPAR-positive senescent cells induced in mice by unhealthy diet or by treatment with CCl_4 improve liver fibrosis (Amor et al., 2020). Along this line, since senolytic agents have been reported to positively impinge on mice lifespan as well as on muscle function, the possibility that senoantigen-specific CAR-T cells could share the same properties should not be disregarded (Baker et al., 2023).

6. Conclusions

Cancer- and age-associated loss of muscle mass result in increased risk of hospitalization and nursing home placement, increased home healthcare and health care expenditure. The pathogenesis of cancer cachexia and aging-associated sarcopenia is very complex and partially overlapping. Although several common and specific underlying mechanisms have been partially unraveled, the whole scenario still needs to be elucidated in order to define suitable therapeutic strategies. In the last decade a lot of interest has been paid to the causative role played by alterations of the immune response, frequently coupled to metabolic dysfunctions. The other way around, the altered body composition occurring in cachexia and aging has been reported to impinge on the response to anticancer treatments, including those acting to stimulate the anti-tumor immune response. On the whole, several lines of evidence are now pointing at the possibility to use immunomodulating strategies developed for cancer treatment to manage both cancer- and aging-associated body wasting, trying to impinge on the muscle-immune system including in this axis, when present, also the tumor. Along this line, immunomodulating tools could be included in the multimodal therapeutic approach required for the treatment of both cachexia and sarcopenia, in view of their multifactorial etiopathogenesis. Additional interest to such an approach arises from the possibility to further enhance the effectiveness of immunotherapy by coupling with novel tools such as nanotechnologies and small molecule inhibitors (Fig. 3).

CRediT authorship contribution statement

Fabio Penna: Writing – review & editing. **Giacomo Rubini:** Writing – review & editing. **Paola Costelli:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abrigo, J., Rivera, J.C., Simon, F., Cabrera, D., Cabello-Verrugio, C., 2016. Transforming growth factor type beta (TGF-β) requires reactive oxygen species to induce skeletal muscle atrophy. Cell. Signal. 28 (5), 366–376 [Internet], [cited 2019 Aug 20], Available from: http://www.ncbi.nlm.nih.gov/pubmed/26825874.

Ábrigo, J., Elorza, A.A., Riedel, C.A., Vilos, C., Simon, F., Cabrera, D., et al., 2018. Role of oxidative stress as key regulator of muscle wasting during cachexia. Oxid. Med. Cell. Longev. 2018, 2063179 [Internet], [cited 2018 Oct 24], Available from: https://www.hindawi.com/journals/omcl/2018/2063179/.

Agudelo, L.Z., Ferreira, D.M.S., Dadvar, S., Cervenka, I., Ketscher, L., Izadi, M., et al., 2019. Skeletal muscle PGC-1α1 reroutes kynurenine metabolism to increase energy efficiency and fatigue-resistance. Nat. Commun. 10 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31235694/.

Amor, C., Feucht, J., Leibold, J., Ho, Y.J., Zhu, C., Alonso-Curbelo, D., et al., 2020. Senolytic CAR T cells reverse senescence-associated pathologies. Nature 583 (7814), 127–132 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/32555459/.

André, T., Shiu, K.K., Kim, T.W., Jensen, B.V., Jensen, L.H., Punt, C., et al., 2020. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N. Engl. J. Med. 383 (23), 2207, 18. [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33264544/.

Anker, M.S., Holcomb, R., Muscaritoli, M., von Haehling, S., Haverkamp, W., Jatoi, A., et al., 2019. Orphan disease status of cancer cachexia in the USA and in the European Union: a systematic review. J Cachexia Sarcopenia Muscle 10 (1), 22–34 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/30920776/.

Argilés, J.M., Busquets, S., Stemmler, B., López-Soriano, F.J., 2014. Cancer cachexia: understanding the molecular basis. Nat. Rev. Cancer 14 (11), 754–762.

Argilés, J.M., López-Soriano, F.J., Stemmler, B., Busquets, S., 2017. Novel targeted therapies for cancer cachexia. Biochem. J. 474 (16), 2663–2678.

Argilés, J.M., López-Soriano, F.J., Busquets, S., 2019. Mediators of cachexia in cancer patients. Nutrition 66, 11–15 [Internet], [cited 2019 Aug 21], Available from: http://www.ncbi.nlm.nih.gov/pubmed/31177056.

Baker, D.J., Arany, Z., Baur, J.A., Epstein, J.A., June, C.H., 2023. CAR T therapy beyond cancer: the evolution of a living drug. Nature 619 (7971), 707–715 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37495877/.

Barker, T., Fulde, G., Moulton, B., Nadauld, L.D., Rhodes, T., 2020. An elevated neutrophil-to-lymphocyte ratio associates with weight loss and cachexia in cancer. Sci. Rep. 10 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/32371869/.

Beltrà, M., Pöllänen, N., Fornelli, C., Tonttila, K., Hsu, M.Y., Zampieri, S., et al., 2023. NAD+ repletion with niacin counteracts cancer cachexia. Nat. Commun. 14 (1), 1849 [Internet], [cited 2023 Apr 8], Available from: https://pubmed.ncbi.nlm.nih.gov/37012289/.

Bertrand, F., Montfort, A., Marcheteau, E., Imbert, C., Gilhodes, J., Filleron, T., et al., 2017. TNFα blockade overcomes resistance to anti-PD-1 in experimental melanoma. Nat. Commun. 8 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/29273790/.

Bonetto, A., Aydogdu, T., Jin, X., Zhang, Z., Zhan, R., Puzis, L., et al., 2012. JAK/STAT3 pathway inhibition blocks skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia. Am. J. Physiol. Endocrinol. Metab. 303 (3) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/22669242/.

Brocco, D., Di Marino, P., Grassandonia, A., 2019. From cachexia to obesity: the role of host metabolism in cancer immunotherapy. Curr. Opin. Support. Palliat. Care 13 (4), 305–310 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31389842/.

Burfeind, K.G., Zhu, X., Norgard, M.A., Levasseur, P.R., Huisman, C., Buenafe, A.C., et al., 2020. Circulating myeloid cells invade the central nervous system to mediate cachexia during pancreatic cancer. Elife 9, 1–27 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/32391790/.

Campelj, D.G., Goodman, C.A., Rybalka, E., 2021. Chemotherapy-induced myopathy: the dark side of the cachexia sphere. Cancers 13 (14) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/34298829/.

Cao, W., Ramakrishnan, R., Tuyrin, V.A., Veglia, F., Condamine, T., Amoscato, A., et al., 2014. Oxidized lipids block antigen cross-presentation by dendritic cells in cancer. J. Immunol. 192 (6), 2920–2931 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/24554775/.

Carbó, N., López-Soriano, J., Costelli, P., Busquets, S., Alvarez, B., Baccino, F.M., et al., 2000. Interleukin-15 antagonizes muscle protein waste in tumour-bearing rats. Br. J. Cancer 83 (4), 526–531 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/10945502/.

Chamoto, K., Zhang, B., Tajima, M., Honjo, T., Fagarasan, S., 2023. Spermidine - an old molecule with a new age-defying immune function. Trends Cell Biol. [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37723019/.

Chaturvedi, P., George, V., Shrestha, N., Wang, M., Dee, M.J., Zhu, X., et al., 2022. Immunotherapeutic HCW9218 augments anti-tumor activity of chemotherapy via NK cell-mediated reduction of therapy-induced senescent cells. Mol. Ther. 30 (3), 1171, 87. [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/35051615/.

Cheever, M.A., Higano, C.S., 2011. PROVENGE (Sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. Clin. Cancer Res. 17 (11), 3520–3526 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/21471425/.

Chu, M.P., Li, Y., Ghosh, S., Sass, S., Smylie, M., Walker, J., et al., 2020. Body composition is prognostic and predictive of ipilimumab activity in metastatic melanoma. J Cachexia Sarcopenia Muscle 11 (3), 748–755 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/32053287/.

Costamagna, D., Costelli, P., Sampaolesi, M., Penna, F., 2015. Role of inflammation in muscle homeostasis and myogenesis. Mediat. Inflamm. 2015.

Costamagna, D., Duelen, R., Penna, F., Neumann, D., Costelli, P., Sampaolesi, M., 2020. Interleukin-4 administration improves muscle function, adult myogenesis, and lifespan of colon carcinoma-bearing mice. J Cachexia Sarcopenia Muscle 11 (3), 783–801.

Costelli, P., Carbó, N., Tessitore, L., Bagby, G.J., Lopez-Soriano, F.J., Argilés, J.M., et al., 1993. Tumor necrosis factor-alpha mediates changes in tissue protein turnover in a rat cancer cachexia model. J. Clin. Invest. 92 (6), 2783–2789 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/8254032/.

Costelli, P., Carbó, N., Busquets, S., López-Soriano, F.J., Baccino, F.M., Argilés, J.M., 2003. Reduced protein degradation rates and low expression of proteolytic systems support skeletal muscle hypertrophy in transgenic mice overexpressing the c-ski oncogene. Cancer Lett. 200 (2).

Costelli, P., Muscaritoli, M., Bossola, M., Penna, F., Reffo, P., Bonetto, A., et al., 2006. IGF-1 is downregulated in experimental cancer cachexia. Am. J. Physiol. Regul. Integr. Comp. Physiol. 291 (3).

Cuenca, A.G., Cuenca, A.L., Winfield, R.D., Joiner, D.N., Gentile, L., Delano, M.J., et al., 2014. Novel role for tumor-induced expansion of myeloid-derived cells in cancer cachexia. J. Immunol. 192 (12), 6111, 9, [Internet], [cited 2024 Feb 1],. Available from: https://pubmed.ncbi.nlm.nih.gov/24829407/.

Deans, D.C., Tan, B.H., Ross, J.A., Rose-Zerilli, M., Wigmore, S.J., Howell, W.M., et al., 2009. Cancer cachexia is associated with the IL10 −1082 gene promoter polymorphism in patients with gastroesophageal malignancy. Am. J. Clin. Nutr. 89 (4), 1164–1172 [Internet], [cited 2019 Aug 20], Available from: http://www.ncbi.nlm.nih.gov/pubmed/19244371.

Deng, M., Vaes, R.D.W., van Bijnen, A.A.J.H.M., Olde Damink, S.W.M., Rensen, S.S., 2021. Activation of the complement system in patients with cancer cachexia. Cancers 13 (22) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/34830921/.

Van Deursen, J.M., 2014. The role of senescent cells in ageing. Nature 509 (7501), 439–446 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/24848057/.

Deyhle, M.R., Callaway, C.S., Neyroud, D., D'lugos, A.C., Judge, S.M., Judge, A.R., 2022. Depleting Ly6G positive myeloid cells reduces pancreatic cancer-induced skeletal muscle atrophy. Cells 11 (12) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/35741022/.

van Dijk, D.P., van de Poll, M.C., Moses, A.G., Preston, T., Olde Damink, S.W., Rensen, S. S., et al., 2015. Effects of oral meal feeding on whole body protein breakdown and protein synthesis in cachectic pancreatic cancer patients. J Cachexia Sarcopenia Muscle 6 (3), 212–221.

Dorshkind, K., Höfer, T., Montecino-Rodriguez, E., Pioli, P.D., Rodewald, H.R., 2020. Do haematopoietic stem cells age? Nat. Rev. Immunol. 20 (3), 196–202 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31740804/.

Dusselier, M., Deluche, E., Delacourt, N., Ballouhey, J., Egenod, T., Melloni, B., et al., 2019. Neutrophil-to-lymphocyte ratio evolution is an independent predictor of early progression of second-line nivolumab-treated patients with advanced non-small-cell lung cancers. PLoS One 14 (7) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31314761/.

Dzierlega, K., Chakraborty, M., Lee, M., Soliman, A.M., Parker, D., Khan, S., et al., 2023. Activin A-expressing polymorphonuclear myeloid-derived suppressor cells infiltrate skeletal and cardiac muscle and promote cancer cachexia. J. Immunol. 211 (3), 497–507 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37294291/.

Emery, P.W., Edwards, R.H., Rennie, M.J., Souhami, R.L., Halliday, D., 1984. Protein synthesis in muscle measured in vivo in cachectic patients with cancer. Br. Med. J. 289 (6445), 584–586.

Engelen, M.P.K.J., van der Meij, B.S., Deutz, N.E.P., 2016a. Protein anabolic resistance in cancer. Curr. Opin. Clin. Nutr. Metab. Care 19 (1), 39–47.

Engelen, M.P.K.J., van der Meij, B.S., Deutz, N.E.P., 2016b. Protein anabolic resistance in cancer. Curr. Opin. Clin. Nutr. Metab. Care 19 (1), 39–47 [Internet], [cited 2017 Nov 3], Available from: http://www.ncbi.nlm.nih.gov/pubmed/26560520.

Erdem, M., Möckel, D., Jumpertz, S., John, C., Fragoulis, A., Rudolph, I., et al., 2019. Macrophages protect against loss of adipose tissue during cancer cachexia. J Cachexia Sarcopenia Muscle 10 (5), 1128, 42, [Internet], [cited 2024 Feb 1],. Available from: https://pubmed.ncbi.nlm.nih.gov/31318182/.

Fan, Y.N., Zhao, G., Zhang, Y., Ye, Q.N., Sun, Y.Q., Shen, S., et al., 2021. Progress in nanoparticle-based regulation of immune cells. Medical review 3 (2), 152–179, 2023 Apr 1, [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37724086/.

Fearon, K., Strasser, F., Anker, S.D., Bosaeus, I., Bruera, E., Fainsinger, R.L., et al., 2011. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol [Internet] 12 (5), 489–495 [cited 2014 Jul 15], Available from: http://www.ncbi.nlm.nih.gov/pubmed/21296615.

Felberg, A., Taszner, M., Urban, A., Majeranowski, A., Jaskuła, K., Jurkiewicz, A., et al., 2020. Monitoring of the complement system status in patients with B-cell malignancies treated with rituximab. Front. Immunol. 11 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33329558/.

Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15 (9), 505–522 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/30065258/.

Fielding, R.A., Atkinson, E.J., Aversa, Z., White, T.A., Heeren, A.A., Mielke, M.M., et al., 2023. Biomarkers of cellular senescence predict the onset of mobility disability and are reduced by physical activity in older adults. J Gerontol A Biol Sci Med Sci [Internet], [cited 2024 Feb 1]; Available from: https://pubmed.ncbi.nlm.nih.gov/37948612/.

Flint, T.R., Fearon, D.T., Janowitz, T., 2017. Connecting the metabolic and immune responses to cancer. Trends Mol. Med. 23 (5), 451–464 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/28396056/.

Gasek, N.S., Kuchel, G.A., Kirkland, J.L., Xu, M., 2021. Strategies for targeting senescent cells in human disease. Nat Aging 1 (10), 870–879 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/34841261/.

Goronzy, J.J., Weyand, C.M., 2013. Understanding immunosenescence to improve responses to vaccines. Nat. Immunol. 14 (5), 428–436 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/23598398/.

Guo, Y., Gao, F., Ahmed, A., Rafiq, M., Yu, B., Cong, H., et al., 2023. Immunotherapy: cancer immunotherapy and its combination with nanomaterials and other therapies. J. Mater. Chem. B 11 (36), 8586–8604 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37614168/.

Haake, M., Haack, B., Schäfer, T., Harter, P.N., Mattavelli, G., Eiring, P., et al., 2023. Tumor-derived GDF-15 blocks LFA-1 dependent T cell recruitment and suppresses responses to anti-PD-1 treatment. Nat. Commun. 14 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37474523/.

von Haehling, S., Anker, M.S., Anker, S.D., 2016. Prevalence and clinical impact of cachexia in chronic illness in Europe, USA, and Japan: facts and numbers update 2016. J Cachexia Sarcopenia Muscle 7 (5), 507–509 [Internet], [cited 2018 Sep 22], Available from: http://www.ncbi.nlm.nih.gov/pubmed/27891294.

Han, J., Wang, Y., Qiu, Y., Sun, D., Liu, Y., Li, Z., et al., 2022. Single-cell sequencing unveils key contributions of immune cell populations in cancer-associated adipose wasting. Cell Discov 8 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/36376273/.

Hanson, E.D., Nelson, A.R., West, D.W.D., Violet, J.A., O'Keefe, L., Phillips, S.M., et al., 2017. Attenuation of resting but not load-mediated protein synthesis in prostate cancer patients on androgen deprivation. J. Clin. Endocrinol. Metab. 102 (3), 1076–1083.

He, W.A., Berardi, E., Cardillo, V.M., Acharyya, S., Aulino, P., Thomas-Ahner, J., et al., 2013. NF-κB-mediated Pax7 dysregulation in the muscle microenvironment promotes cancer cachexia. J. Clin. Invest. 123 (11), 4821–4835 [Internet], [cited 2015 Sep 25], Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3809785&tool=pmcentrez&rendertype=abstract.

Hodi, F.S., O'Day, S.J., McDermott, D.F., Weber, R.W., Sosman, J.A., Haanen, J.B., et al., 2010. Improved survival with ipilimumab in patients with metastatic melanoma. N. Engl. J. Med. 363 (8), 711–723 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/20525992/.

Huot, J.R., Novinger, L.J., Pin, F., Bonetto, A., 2020. HCT116 colorectal liver metastases exacerbate muscle wasting in a mouse model for the study of colorectal cancer cachexia. Dis Model Mech 13 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31915140/.

Inaba, S., Hinohara, A., Tachibana, M., Tsujikawa, K., Fukada, S ichiro, 2018. In: Asakura, A. (Ed.), Muscle Regeneration Is Disrupted by Cancer Cachexia without Loss of Muscle Stem Cell Potential, vol. 13. PLoS One, e0205467 (10) [Internet], [cited 2018 Nov 30]Available from: http://www.ncbi.nlm.nih.gov/pubmed/30300394.

Ji, S., Shi, Y., Yin, B., 2024. Macrophage barrier in the tumor microenvironment and potential clinical applications. Cell Commun. Signal. 22 (1), 74 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/38279145/.

Johnston, A.J., Murphy, K.T., Jenkinson, L., Laine, D., Emmrich, K., Faou, P., et al., 2015. Targeting of Fn14 prevents cancer-induced cachexia and prolongs survival. Cell 162 (6), 1365–1378 [Internet], [cited 2017 Dec 22], Available from: http://www.ncbi.nlm.nih.gov/pubmed/26359988.

Kaiser, H., Yu, K., Pandya, C., Mendhe, B., Isales, C.M., McGee-Lawrence, M.E., et al., 2019. Kynurenine, a tryptophan metabolite that increases with age, induces muscle atrophy and lipid peroxidation. Oxid. Med. Cell. Longev. 2019. [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31737181/.

Kelly, R.J., Ajani, J.A., Kuzdzal, J., Zander, T., Van Cutsem, E., Piessen, G., et al., 2021. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N. Engl. J. Med. 384 (13), 1191–1203 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33789008/.

Kirkland, J.L., Tchkonia, T., 2017. Cellular senescence: a translational perspective. EBioMedicine 21, 21–28 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/28416161/.

Kumar, A., Bhatnagar, S., Paul, P.K., 2012. TWEAK and TRAF6 regulate skeletal muscle atrophy. Curr. Opin. Clin. Nutr. Metab. Care 15 (3), 233–239 [Internet], [cited 2015 Jul 6], Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3397822&tool=pmcentrez&rendertype=abstract.

Kuswanto, W., Burzyn, D., Panduro, M., Wang, K.K., Jang, Y.C., Wagers, A.J., et al., 2016. Poor repair of skeletal muscle in aging mice reflects a defect in local, interleukin-33-dependent accumulation of regulatory T cells. Immunity 44 (2), 355–367 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/26872699/.

Li, C wei, Yu, K., Shyh-Chang, N., xun, Li G., Jiang, L juan, lin, Yu S., et al., 2019. Circulating factors associated with sarcopenia during ageing and after intensive lifestyle intervention. J Cachexia Sarcopenia Muscle 10 (3), 586–600 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/30969486/.

Lin, K., He, S., He, L., Chen, J., Cheng, X., Zhang, G., et al., 2014. Complement component 3 is a prognostic factor of non-small cell lung cancer. Mol. Med. Rep. 10 (2), 811–817 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/24819254/.

Liu, B., Zhu, X., Kong, L., Wang, M., Spanoudis, C., Chaturvedi, P., et al., 2021. Bifunctional TGF-β trap/IL-15 protein complex elicits potent NK cell and CD8+ T cell immunity against solid tumors. Mol. Ther. 29 (10), 2949–2962 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/34091051/.

López-Otín, C., Pietrocola, F., Roiz-Valle, D., Galluzzi, L., Kroemer, G., 2023. Meta-hallmarks of aging and cancer. Cell Metabol. 35 (1), 12–35 [Internet], [cited 2023 Apr 8], Available from: https://pubmed.ncbi.nlm.nih.gov/36599298/.

Lu, P., Ma, Y., Wei, S., Liang, X., 2021. The dual role of complement in cancers, from destroying tumors to promoting tumor development. Cytokine 143 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33849765/.

Madeddu, C., Busquets, S., Donisi, C., Lai, E., Pretta, A., López-Soriano, F.J., et al., 2023. Effect of cancer-related cachexia and associated changes in nutritional status, inflammatory status, and muscle mass on immunotherapy efficacy and survival in patients with advanced non-small cell lung cancer. Cancers 15 (4) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/36831431/.

Maecker, H., Varfolomeev, E., Kischkel, F., Lawrence, D., LeBlanc, H., Lee, W., et al., 2005. TWEAK attenuates the transition from innate to adaptive immunity. Cell 123 (5), 931–944 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/16325585/.

Makrakis, D., Rounis, K., Tsigkas, A.P., Georgiou, A., Galanakis, N., Tsakonas, G., et al., 2023. Effect of body tissue composition on the outcome of patients with metastatic non-small cell lung cancer treated with PD-1/PD-L1 inhibitors. PLoS One 18 (2) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/36763597/.

Massart, I.S., Paulissen, G., Loumaye, A., Lause, P., Pötgens, S.A., Thibaut, M.M., et al., 2020. Marked increased production of acute phase reactants by skeletal muscle during cancer cachexia. Cancers 12 (11), 1–24 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33142864/.

Molinari, F., Pin, F., Gorini, S., Chiandotto, S., Pontecorvo, L., Penna, F., et al., 2017. The mitochondrial metabolic reprogramming agent trimetazidine as an 'exercise mimetic' in cachectic C26-bearing mice. J Cachexia Sarcopenia Muscle 8 (6).

Mullard, A., 2017. FDA approves first CAR T therapy. Nat. Rev. Drug Discov. 16 (10), 669 [Internet], [cited 2024 Feb 1]Available from: https://pubmed.ncbi.nlm.nih.gov/28959944/.

Nelke, C., Dziewas, R., Minnerup, J., Meuth, S.G., Ruck, T., 2019. Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine 49, 381–388 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/31662290/.

Noll, J.H., Levine, B.L., June, C.H., Fraietta, J.A., 2023. Beyond youth: understanding CAR T cell fitness in the context of immunological aging. Semin. Immunol. 70 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37729825/.

Olson, B., Zhu, X., Norgard, M.A., Levasseur, P.R., Butler, J.T., Buenafe, A., et al., 2021. Lipocalin 2 mediates appetite suppression during pancreatic cancer cachexia. Nat. Commun. 12 (1) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33824339/.

Ontiveros, C.O., Murray, C.E., Crossland, G., Curiel, T.J., 2023. Considerations and approaches for cancer immunotherapy in the aging host. Cancer Immunol. Res. 11 (11), 1449–1461 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37769157/.

Parajuli, P., Kumar, S., Loumaye, A., Singh, P., Eragamreddy, S., Nguyen, T.L., et al., 2018. Twist1 activation in muscle progenitor cells causes muscle loss akin to cancer cachexia. Dev. Cell 45 (6), 712–725.e6 [Internet], [cited 2018 Oct 24], Available from: https://linkinghub.elsevier.com/retrieve/pii/S1534580718304192.

Penna, F., Bonetto, A., Muscaritoli, M., Costamagna, D., Minero, V.G., Bonelli, G., et al., 2010a. Muscle atrophy in experimental cancer cachexia: is the IGF-1 signaling pathway involved? Int. J. Cancer 127 (7), 1706–1717.

Penna, F., Costamagna, D., Fanzani, A., Bonelli, G., Baccino, F.M., Costelli, P., 2010b. Muscle wasting and impaired Myogenesis in tumor bearing mice are prevented by ERK inhibition. PLoS One 5 (10).

Penna, F., Ballarò, R., Costelli, P., 2020. The redox balance: a target for interventions against muscle wasting in cancer cachexia? Antioxidants Redox Signal. 33 (8), 542–558 [Internet], [cited 2022 Mar 25], Available from: https://pubmed.ncbi.nlm.nih.gov/32037856/.

Petruzzelli, M., Ferrer, M., Schuijs, M.J., Kleeman, S.O., Mourikis, N., Hall, Z., et al., 2022. Early neutrophilia marked by aerobic glycolysis sustains host metabolism and delays cancer cachexia. Cancers 14 (4) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/35205709/.

Prado, B.L., Qian, Y., 2019. Anti-cytokines in the treatment of cancer cachexia. In: Annals of Palliative Medicine, vol. 8. AME Publishing Company, pp. 67–79.

Prado, C.M., Sawyer, M.B., Ghosh, S., Lieffers, J.R., Esfandiari, N., Antoun, S., et al., 2013. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Am. J. Clin. Nutr. 98 (4), 1012–1019 [Internet], [cited 2017 Nov 3], Available from: http://www.ncbi.nlm.nih.gov/pubmed/23966429.

Raffin, J., Rolland, Y., Parini, A., Lucas, A., Guyonnet, S., Vellas, B., et al., 2023. Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: a longitudinal mediation analysis. J Cachexia Sarcopenia Muscle 14 (2), 771–780 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/36999490/.

Rejeski, K., Cordas dos Santos, D.M., Parker, N.H., Bücklein, V.L., Winkelmann, M., Jhaveri, K.S., et al., 2023. Influence of adipose tissue distribution, sarcopenia, and nutritional status on clinical outcomes after CD19 CAR T-cell therapy. Cancer Immunol. Res. 11 (6), 707–719 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37040425/.

Roch, B., Coffy, A., Jean-Baptiste, S., Palaysi, E., Daures, J.P., Pujol, J.L., et al., 2020. Cachexia - sarcopenia as a determinant of disease control rate and survival in non-small lung cancer patients receiving immune-checkpoint inhibitors. Lung Cancer 143, 19–26 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/32200137/.

Roeland, E.J., Bohlke, K., Baracos, V.E., Bruera, E., Fabbro, E Del, Dixon, S., et al., 2020. Management of cancer cachexia: ASCO guideline. J. Clin. Oncol. 38 (21) [Internet], [cited 2023 Apr 8], 2438–53. Available from: https://pubmed.ncbi.nlm.nih.gov/32432946/.

Roy, I., Smilnak, G., Burkart, M., Hamilton, E., Thorp, K., Miyata, S., et al., 2022. Cachexia is a risk factor for negative clinical and functional outcomes in patients receiving chimeric antigen receptor T-cell therapy for B-cell non-Hodgkin lymphoma. Br. J. Haematol. 197 (1), 71–75 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/35141891/.

Sartori, R., Hagg, A., Zampieri, S., Armani, A., Winbanks, C.E., Viana, L.R., et al., 2021. Perturbed BMP signaling and denervation promote muscle wasting in cancer cachexia. Sci. Transl. Med. 13 (605) [Internet], [cited 2022 Mar 25], Available from: https://pubmed.ncbi.nlm.nih.gov/34349036/.

Sciorati, C., Gamberale, R., Monno, A., Citterio, L., Lanzani, C., De Lorenzo, R., et al., 2020. Pharmacological blockade of TNFα prevents sarcopenia and prolongs survival in aging mice. Aging 12 (23), 23497–23508 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33260150/.

Senent, Y., Ajona, D., González-Martín, A., Pio, R., Tavira, B., 2021. The complement system in ovarian cancer: an underexplored old path. Cancers 13 (15) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/34359708/.

Sharma, P., Hu-Lieskovan, S., Wargo, J.A., Ribas, A., 2017. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 168 (4), 707–723 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/28187290/.

Shrestha, N., Chaturvedi, P., Zhu, X., Dee, M.J., George, V., Janney, C., et al., 2023. Immunotherapeutic approach to reduce senescent cells and alleviate senescence-associated secretory phenotype in mice. Aging Cell 22 (5) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/36967480/.

Siddiqui, J.A., Pothuraju, R., Khan, P., Sharma, G., Muniyan, S., Seshacharyulu, P., et al., 2022. Pathophysiological role of growth differentiation factor 15 (GDF15) in obesity, cancer, and cachexia. Cytokine Growth Factor Rev. 64, 71–83 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/34836750/.

Speth, C., Bellotti, R., Schäfer, G., Rambach, G., Texler, B., Thurner, G.C., et al., 2022. Complement and fungal dysbiosis as prognostic markers and potential targets in PDAC treatment. Curr. Oncol. 29 (12), 9833, 54. [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/36547187/.

Strauss, L., Guarneri, V., Gennari, A., Sica, A., 2021. Implications of metabolism-driven myeloid dysfunctions in cancer therapy. Cell. Mol. Immunol. 18 (4), 829–841 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/33077904/.

Tan, B.H.L., Fladvad, T., Braun, T.P., Vigano, A., Strasser, F., Deans, D.A.C., et al., 2012. P-selectin genotype is associated with the development of cancer cachexia. EMBO Mol. Med. 4 (6), 462–471 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/22473907/.

Tidball, J.G., 2017. Regulation of muscle growth and regeneration by the immune system. Nat. Rev. Immunol. 17 (3), 165–178 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/28163303/.

Travelli, C., Consonni, F.M., Sangaletti, S., Storto, M., Morlacchi, S., Grolla, A.A., et al., 2019. Nicotinamide phosphoribosyltransferase acts as a metabolic gate for mobilization of myeloid-derived suppressor cells. Cancer Res. 79 (8), 1938–1951 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/30777853/.

Tzika, A.A., Fontes-Oliveira, C.C., Shestov, A.A., Constantinou, C., Psychogios, N., Righi, V., et al., 2013. Skeletal muscle mitochondrial uncoupling in a murine cancer cachexia model. Int. J. Oncol. 43 (3), 886–894 [Internet], [cited 2015 Sep 25], Available from: http://www.ncbi.nlm.nih.gov/pubmed/23817738.

Vacchelli, E., Aranda, F., Eggermont, A., Sautès-Fridman, C., Tartour, E., Kennedy, E.P., et al., 2014. Trial watch: Ido inhibitors in cancer therapy. OncoImmunology 3 (10), e957994, 1-e957994-10. [Internet], [cited 2024 Feb 1], Available from:/pmc/articles/PMC4292223/.

Vazeille, C., Jouinot, A., Durand, J.P., Neveux, N., Boudou-Rouquette, P., Huillard, O., et al., 2017. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am. J. Clin. Nutr. 105 (5), 1139–1147.

Veglia, F., Perego, M., Gabrilovich, D., 2018. Myeloid-derived suppressor cells coming of age. Nat. Immunol. 19 (2), 108–119 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/29348500/.

Wang, G., Biswas, A.K., Ma, W., Kandpal, M., Coker, C., Grandgenett, P.M., et al., 2018. Metastatic cancers promote cachexia through ZIP14 upregulation in skeletal muscle. Nat. Med. 24 (6), 770–781 [Internet], [cited 2018 Oct 24], Available from: http://www.ncbi.nlm.nih.gov/pubmed/29875463.

Waning, D.L., Mohammad, K.S., Reiken, S., Xie, W., Andersson, D.C., John, S., et al., 2015. Excess TGF-β mediates muscle weakness associated with bone metastases in mice. Nat. Med. 21 (11), 1262–1271 [Internet], [cited 2018 Sep 25], Available from: http://www.ncbi.nlm.nih.gov/pubmed/26457758.

Winfield, R.D., Delano, M.J., Pande, K., Scumpia, P.O., LaFace, D., Moldawer, L.L., 2008. Myeloid-derived suppressor cells in cancer cachexia syndrome: a new explanation for an old problem. JPEN - J. Parenter. Enter. Nutr. 32 (6), 651–655 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/18974247/.

Wischhusen, J., Melero, I., Fridman, W.H., 2020. Growth/differentiation factor-15 (GDF-15): from biomarker to novel targetable immune checkpoint. Front. Immunol. 11 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/32508832/.

Wu, L., Du, H., Li, Y., Qu, P., Yan, C., 2011. Signal transducer and activator of transcription 3 (Stat3C) promotes myeloid-derived suppressor cell expansion and immune suppression during lung tumorigenesis. Am. J. Pathol. 179 (4), 2131–2141 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/21864492/.

Xu, M., Pirtskhalava, T., Farr, J.N., Weigand, B.M., Palmer, A.K., Weivoda, M.M., et al., 2018. Senolytics improve physical function and increase lifespan in old age. Nat. Med. 24 (8), 1246–1256 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/29988130/.

Yang, D., Sun, B., Li, S., Wei, W., Liu, X., Cui, X., et al., 2023. NKG2D-CAR T cells eliminate senescent cells in aged mice and nonhuman primates. Sci. Transl. Med. 15 (709) [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/37585504/.

Yazar, T., Olgun Yazar, H., 2019. Prevalance of sarcopenia according to decade. Clin Nutr ESPEN 29, 137–141 [Internet], [cited 2024 Feb 1], Available from: https://pubmed.ncbi.nlm.nih.gov/30661677/.

Ye, S., Fox, M.I., Belmar, N.A., Sho, M., Chao, D.T., Choi, D., et al., 2017. Enavatuzumab, a humanized anti-TWEAK receptor monoclonal antibody, exerts antitumor activity through attracting and activating innate immune effector cells. J Immunol Res [Internet], [cited 2024 Feb 1];2017. Available from: https://pubmed.ncbi.nlm.nih.gov/29075649/.

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