Immunity & Ageing

REVIEW

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Harnessing immunomodulation to combat sarcopenia: current insights and possible approaches

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Abstract

Sarcopenia is a complex age-associated syndrome of progressive loss of muscle mass and strength. Although this condition is influenced by many factors, age-related changes in immune function including immune cell dynamics, and chronic inflammation contribute to its progression. The complex interplay between the immune system, gut-muscle axis, and autophagy further underscores their important roles in sarcopenia pathogenesis. Immunomodulation has emerged as a promising strategy to counteract sarcopenia. Traditional management approaches to treat sarcopenia including physical exercise and nutritional supplementation, and the emerging technologies of biophysical stimulation demonstrated the importance of immunomodulation and regulation of macrophages and T cells and reduction of chronic inflammation. Treatments to alleviate low-grade inflammation in older adults by modulating gut microbial composition and diversity further combat sarcopenia. Furthermore, some pharmacological interventions, nano-medicine, and cell therapies targeting muscle, gut microbiota, or autophagy present additional avenues for immunomodulation in sarcopenia. This narrative review explores the immunological underpinnings of sarcopenia, elucidating the relationship between the immune system and muscle during ageing. Additionally, the review discusses new areas such as the gut-muscle axis and autophagy, which bridge immune system function and muscle health. Insights into current and potential approaches for sarcopenia management through modulation of the immune system are provided, along with suggestions for future research directions and therapeutic strategies. We aim to guide further investigation into clinical immunological biomarkers and identify indicators for sarcopenia diagnosis and potential treatment targets to combat this condition. We also aim to draw attention to the importance of considering immunomodulation in the clinical management of sarcopenia.

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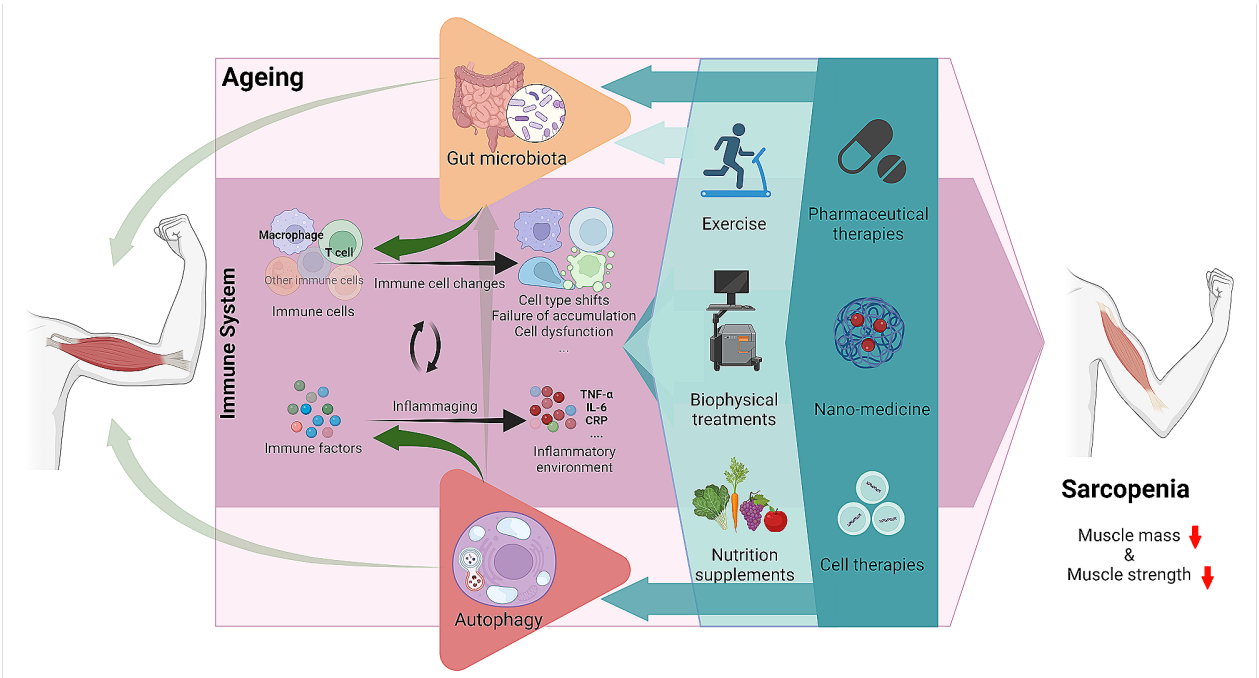
Graphical Abstract



Keywords Sarcopenia, Immune system, Gut microbiota, Autophagy, Immunomodulatory approaches

Introduction

Sarcopenia is an age-associated syndrome characterized by progressive loss in muscle mass and strength. This condition puts the patients at a higher risk of falls and subsequent fractures, leading to increased functional disabilities, dependency, morbidity, and even mortality. Sarcopenia is prevalent among older individuals, with rates ranging from 5 to 13% in those aged 60–70 years and up to 50% in those over 80 years old [1, 2]; thus, sarcopenia represents a growing concern on a global scale and brings a heavy burden to the financial and societal cost of public health.

The definition of sarcopenia has evolved over time and now includes both muscle mass and function, with a particular emphasis on muscle strength [3]. Several working groups such as the Asian Working Group for Sarcopenia (AWGS) [2], the European Working Group on Sarcopenia in Older People (EWGSOP) [4], and the International Working Group on Sarcopenia (IWGS) [5] have published and revised their consensus on the definition and diagnosis of sarcopenia based on the measurements of muscle mass in addition to muscle strength and/or physical performance. However, the current consensus of sarcopenia remains challenging in clinical practice due to the cumbersome diagnostic process and the possibility of overdiagnosis; these concepts are continuously being updated, leading to variability in the diagnostic criteria and guidelines. A study comparing sarcopenia diagnoses based on IWGS and EWGSOP criteria among 408 older participants revealed significant variations in prevalence based on muscle mass indices [6]. Future research efforts should focus on elucidating the underlying mechanisms of the development of sarcopenia to identify precise diagnostic biomarkers and therapeutic targets. Recently, the Global Leadership Initiative in Sarcopenia (GLIS) has created the first global conceptual definition of sarcopenia, which includes muscle mass, muscle strength, and muscle-specific strength as components of sarcopenia [7]. More importantly, the current diagnosis has not been conclusively linked to improved prognosis [8]. Investigating the underlying mechanisms is essential to address the challenges of the current diagnosis.

Sarcopenia is a multifactorial syndrome and ageing is categorized as the primary factor that causes and worsens muscle quantity and quality, the secondary factors include disease, inactivity, and malnutrition [4]. However, the underlying mechanisms have not been fully uncovered. Increasing evidence indicates that age-associated changes in the immune system play critical roles in the progression of sarcopenia [9]. Changes in immune cells in the older person, including T cells [10] and macrophages [11] could impair the function of muscle precursor cells

or satellite cells, which are essential for muscle maintenance and regeneration. In addition to the immune cells, the inflammatory catabolic processes with ageing could enhance the decline of muscle mass and strength, which are highly associated with sarcopenia based on clinical observational, interventional studies and randomized controlled trials [12]. Ageing results in a baseline level of low-grade, chronic and systemic inflammation ("inflammaging") [13, 14] and it has been reported that individuals with pronounced low-grade inflammation showed lower muscle mass and strength [15]. Inflammatory indicators and cytokines, in particular of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α) levels in serum, are mostly reported in clinical investigations regarding sarcopenia [12]. Despite these findings, the systemic and specific immune alterations in sarcopenia remain poorly understood. Future research should elucidate the immune mechanisms of sarcopenia, identify accurate diagnostic biomarkers, and explore therapeutic strategies.

This is a narrative review. In the designated sections, we conducted a literature search on the PubMed and Web of Science databases by employing a combination of immune-related keywords, including specific immune cells such as macrophages and T cells, specific cytokines such as IL-6, inflammation, gut microbiota, autophagy, and immunomodulation, in conjunction with sarcopenia or muscle. Most of the included papers were published from 2010 to 2024 (131 out of 146), several papers (15 out of 146) before 2010 were also included in this narrative review. This review delves into the immunological basis of sarcopenia, examining the interplay between the immune system and muscle during ageing. Emerging areas like the gut-muscle axis and autophagy, which link immune system function and muscle health, are also explored. We discuss the current and potential approaches to combat sarcopenia through immune system modulation and offer insights into future research directions and therapeutic avenues.

Immunological basis of sarcopenia

The immune system plays a crucial role in maintaining muscle homeostasis and can determine the success or failure of tissue regeneration after muscle injuries or chronic muscle disorders [16]. While the immune system participates in both of these scenarios, the nature of its involvement differs. In sarcopenia, the chronic, age-related changes in immune function, contribute significantly to the development and progression of this muscle wasting [14]. Age-related immune dysfunction is marked by alterations in multiple facets of immune components including changes in the structure and function of immune cells, and chronic inflammation (inflammaging). It leads to a diminished capacity to effectively respond to pathogens and maintain tissue homeostasis, and an elevated risk of developing age-related diseases, particularly in the context of sarcopenia [17].

Immune cells and sarcopenia

The immune cells that infiltrate the muscle post-injury play a crucial role in clearing damaged myofibers and initiating a cascade that regulates the behavior of muscle stem cells [18]. Regarding chronic muscular disorders, a notable feature of inflammatory immune cell infiltration is also observed [16, 19]. Macrophages are complex populations involved in muscle disorders. The balance and polarization of the M1 pro-inflammatory phenotype and the M2 anti-inflammatory phenotype has been identified as a transient factor that can impact the inflammatory phase and muscle regeneration [20, 21]. Age-related differences and altered responses following muscle damage in macrophage phenotype in human skeletal muscle have been revealed by clinical studies. Muscle biopsy from older adults (aged 60–75 years) showed significantly higher $CD68^+$ $CD11b^-$ macrophage and significantly lower $CD68^+$ $CD11b^+$ M1 macrophage number compared to younger adults (aged 18–35 years). Additionally, an 8-week program of lower limb eccentric exercise rehabilitation led to a greater increase of $CD206^+$ M2 macrophages among older adults than in young adults [22]. Another study observed a greater proportion of $CD206^+$ macrophages and a markedly lower proportion of $CD11b^+$ macrophages in muscle biopsies from older subjects (71±7 years) compared to young subjects (aged 22±2 years) after a muscle-damaging exercise [23]. Macrophage dysfunction could further contribute to the change in muscle along with ageing. Recently, single-cell RNA sequencing revealed that some pro-inflammatory and senescence-related markers were found to increase within macrophage clusters derived from the muscles of older mice [24]. A decline in IFN-γ response in macrophage was also found to contribute to the satellite cell dysfunctions in aged skeletal muscles revealed by an in vivo study using a mouse model [11]. Age-related decreases in macrophage expression of growth differentiation factor-3 (GDF3) will lead to a decline in the numbers and myogenic potential of satellite cells in the muscles of aged mice by disturbing the regulatory interactions between macrophages and satellite cells [25]. These findings suggest that older macrophages exhibit reduced capacity to adapt to a sustained inflammatory insult, possibly contributing to impaired muscle stem cell activation and the progression of sarcopenia.

T cells, which have been recognized as important participants in tissue regeneration, can be divided into several subsets, such as $CD4^+$ helper T cells, $CD8^+$ cytotoxic T cells, and regulatory T cells (Tregs). T cells emerge as important contributors to the modulation of muscle

during damage or injury based on clinical and pre-clinical studies [26–28]. A five-year interval of 433 older individuals aged 61–85 showed a decrease of $CD3^+$, $CD4^+$, and $CD8^+$ T cells in the blood that might be associated with the progress of sarcopenia [29]. A cross-sectional study of 60 sarcopenic patients found skeletal muscle mass index was negatively correlated with circulating $CD4^+CD28^{null}$ T cells in peripheral blood [30]. Furthermore, the failure of T cell accumulation in skeletal muscle emerges as a critical factor contributing to the impaired regenerative capacity of aged muscles and the progression of sarcopenia based on pre-clinical evidence. Kuswanto et al. found that compromised muscle regeneration in aged mice is linked to a defect in local accumulation of Tregs in skeletal muscle [31]. This is possibly due to the deficiency of IL-33 in the muscle and reduced expression of chemokine receptors in T cells, which regulate their accumulation or migration. Schaap et al. found that deficiency in IL6Rα on T cells exhibits deficiencies in muscle Tregs during exercise resulting in a more pronounced decline in muscle mass in sarcopenia in a clinical study involving 986 participants [32]. Furthermore, the heightened effect observed in muscle progenitor cell proliferation, induced by splenic T cells, was conspicuously absent when applied to aged muscle progenitor cells in an in vitro study using rat cells [10], suggesting a critical role of T cells in mediating the function of muscle progenitor cells.

The immune system is a complex network involving numerous immune cells in addition to macrophages and T cells. While the direct roles of other specific immune cell types have not been delineated, evidence suggests the importance of other immune cell lineages in sarcopenia. Gradual decrease in Natural killer (NK) cells was found along with ageing and associated with the reduction in lean mass observed in clinical characteristics in older adults [29]. NK cell immune senescence and sarcopenia might share a common mechanism by reviewing the effect of myokines, especially interleukin (IL)-15 changes during ageing [33]. $CD19^+$ B cells also showed a consistent decline with age and the progress of sarcopenia in older adults [29]. By investigating 343 hospitalized renal cell carcinoma patients, the high neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were found to be associated with sarcopenia risk [34]. Analysis of gene expression by RNA-sequencing in human muscle biopsies has been conducted to profile immune cell changes during the onset and progression of sarcopenia, highlighting a lower enrichment score in B-cell receptor signaling, apoptosis, and the adaptive immune response pathways in low muscle mass and physical performance of patients [35].

Age-related changes include shifts in macrophage phenotypes, age-related macrophage dysfunction, reductions in certain T cell populations, and their accumulation in muscle are associated with sarcopenia. Additionally, although not directly involved, other immune cells such as NK cells and B cells may also contribute to the progression of sarcopenia.

Inflammatory immune cell infiltration and changes especially macrophages and T cells have been identified as critical factors in age-related muscle changes in clinical and pre-clinical studies, which could play a significant role in the progress of sarcopenia. However, the existing evidence regarding alterations in immune cells throughout the progression of sarcopenia remains ambiguous and sometimes even contentious. With the help of comprehensive analytical techniques, encompassing transcriptomics, spatial transcriptomics, and high-dimensional mass cytometry, future research endeavors should elucidate the overarching and detailed modifications in immune cells, including the emergence of novel immune cell populations associated with sarcopenia. Such insights will be critical in the identification of precise diagnostic biomarkers and the development of effective therapeutic strategies.

Inflammaging and sarcopenia

The actions of immune cells are linked to the initiation and perpetuation of inflammation within the skeletal muscle microenvironment via the secretion of growth factors, cytokines, chemokines, and other factors. These molecules serve as a regulatory mechanism influencing the activation of muscle stem cells and myofibroblasts. Recent evidence underscores age-related low-grade chronic inflammation ("inflammaging") [13, 14], which is often characterized by a subtle increase in pro-inflammatory markers, as a significant causative factor for sarcopenia [36, 37]. Older individuals exhibiting pronounced chronic low-grade inflammation often manifest sarcopenic characteristics, including lower muscle mass and reduced muscle strength [15]. The association between higher systemic inflammatory levels and lower muscle strength and mass has been observed in clinical studies [32, 38]. Elevated levels of pro-inflammatory cytokines during inflammaging contribute to an inflammatory environment that exacerbates muscle wasting. Pro-inflammatory markers of chronic low-grade inflammation including IL-6 and TNF-α, have been extensively studied in relation to sarcopenia based on clinical studies including observational, interventiaonal studies and randomized controlled trails [12]. Elevated IL-6 is linked with sarcopenia in older patients with end-stage renal disease [36], sarcopenic obesity in postmenopausal women [39], and increased risk of reduction of muscle mass and strength [32] in the older person. A meta-analysis of 33,160 participants aged 60–88 showed IL-6 was associated with sarcopenia in people aged less than 75, and community-dwelling older adults with sarcopenia

exhibited higher levels of TNF-α compared to their robust and non-sarcopenic counterparts [40]. Independent of sarcopenia state, a clear link between higher levels of IL-6 and TNF-α with lower handgrip and muscle mass in older people has been shown by a meta-analysis of 149 cross-sectional and 19 longitudinal studies [41]. Increased ubiquitin [42] and E3 ligase [43] protein and mRNA as well as proteasome activity [44] were linked to the elevated IL-6 expression. Clinical studies has been shown that a ubiquitin ligase which leads to increased ubiquitination of muscle proteins could be upregulated by TNF-α [12]. The evidence suggests that IL-6 and TNF-α may contribute to muscle degradation through the ubiquitin-proteasome pathway. IL-6 and TNF-α can induce the age-related upregulation of 11βHSD1 based on in vitro investigations involving humans and rodents [45], thereby amplifying the synthesis of cortisol and contributing to muscle catabolism in sarcopenia [46]. The pro-inflammatory cytokines like IL-6 and TNF-α also activate the NF-κB pathway, contributing to progressive muscle loss and function with ageing [47]. Furthermore, inflammaging is associated with the accumulation of reactive oxygen species (ROS) leading to oxidation and subsequent damage of cellular components, and increased inflammation [48]. Elevated ROS levels play a critical role in sarcopenia and it can also enhance the expression of the inflammatory factor IL-6 and the transcription factor NF-κB during periods of oxidative stress [49]. Oxidative stress and activation of the NF-κB pathway are key links between chronic low-grade inflammation and sarcopenia [12]. However, the use of serum levels of IL-6 and TNF-α as the diagnostic markers of sarcopenia is still controversial. A meta-analysis of 11,249 participants from 17 studies revealed no significant difference in serum IL-6 and TNF-α levels between sarcopenic and non-sarcopenic subjects [50]. C-reactive protein (CRP), a well-established biomarker of acute and chronic inflammation [51] is consistently elevated in individuals with sarcopenia compared to those without [40, 50, 52] and associated with lower muscle strength and muscle mass [32, 41] in the older population. Furthermore, chronic inflammation could further suppress the growth hormone-insulin-like growth factor-1 axis which is important for regulating the growth and differentiation of skeletal muscle [53]. In addition to pro-inflammatory cytokines, the anti-inflammatory cytokine IL-10 is involved in sarcopenia. Studies using IL-10 knockout mice as a model of sarcopenia have shown decreased muscle strength with age with a significantly increased IL-6 level [54]. However, associations between IL-10 and sarcopenia are still unclear in humans. A clinical study on 73 older patients (≥60 years old with a diagnosis of chronic obstructive pulmonary disease) found a significant correlation between systemic IL-6 and sarcopenia, but IL-10 was not statistically significant [55]. Skeletal muscle is now recognized as a paracrine and endocrine organ [56] with immune regulatory properties and the central link between sarcopenia and age-related changes in the immune system [57]. Myokines, cytokines released by ageing muscle, such as IL-6, could also participate in the inflammaging [57]. The onset and progression of sarcopenia involves bidirectional inflammatory interactions between the muscle and immune system.

Clinical studies reveal that higher inflammaging levels including pro-inflammatory cytokines like IL-6, TNF-α are associated with reduced muscle strength and mass in older people. These cytokines contribute to muscle degradation through the ubiquitin-proteasome pathway activation of NF-κB pathway and oxidative stress. Additionally, anti-inflammatory cytokines such as IL-10, and the suppression of hormone-insulin-like growth factor-1 axis by inflammaging with ageing contribute to the progression of sarcopenia. While inflammation has been definitively linked to the progression of sarcopenia and CRP consistently correlates with sarcopenia, the concentrations of inflammatory cytokines and other indicators associated with sarcopenia remain a subject of debate. Notably, the levels of these factors in muscle tissue and circulating levels in the bloodstream sometimes exhibit divergent patterns. The application of high-dimensional detection techniques to the subjects under investigation and benchmarking the changes in these levels in muscle and bloodstream are essential for the development of new diagnostic biomarkers and the identification of regulatory targets to combat sarcopenia.

Gut-muscle axis, the link between the immune system and sarcopenia

The gut-muscle axis has recently gained significant attention in sarcopenia research, highlighting the complex interplay between the gut microbiota and muscle health [58–60]. In older individuals, the gut-muscle axis is implicated in the development of muscle wasting through various mechanisms, including the transmission of pro-anabolic signals from dietary nutrients, modulation of insulin sensitivity, and regulation of inflammation [61]. The immune system is involved in these processes, as it is both influenced by the composition of the microbiome and contributes to shaping microbial communities. Alterations in the composition and function of the gut microbiota during aging, resulting in dysbiosis, can impact inflammaging through continuous stimulation of the immune system [14]. Age-associated changes in gut microbiota are caused by immunosenescence and inflammaging, which accompany many age-associated diseases [62]. Recent studies have highlighted the potential role of gut microbiota in influencing muscle mass and function. Experimental studies, primarily conducted in

animal models, suggest a mechanistic link between the gut microbiota and muscle, mediated via the modulation of systemic amino acid availability and low-grade inflammation. A study in which fecal samples from two groups of high-functioning and low-functioning older adults based on the percentage of whole body lean mass (67.3±6.39, 62.2±6.43, respectively, $p=0.02$) and measures of physical function (short physical performance battery score was ≥11 or ≤8, respectively), were transferred into germ-free mice; the mice receiving fecal samples from the high-functioning group exhibited significantly increased grip strength compared to those receiving samples from the low-functioning group [63]. The age-related muscle mass loss is shown to be correlated with a specific composition of fecal microbiota related to inflammatory and immune status using senile Wistar rats of adult (8 months of age), early-sarcopenic (18 months of age), and sarcopenic (24 months of age) models [64]. This composition includes a reduction in several taxa known for their purported anti-inflammatory and pro-anabolic effects on host tissues, such as *Clostridium* XIVa cluster and *Sutterella*. The impact of altered gut microbiota on the immune system is underscored by the increased susceptibility of patients with inflammatory bowel disease (IBD) to sarcopenia. It has been noted that more than one-third of IBD patients suffer from sarcopenia [65]. IBD is a recurrent chronic gut inflammatory condition affecting the intestinal tract and leads to significant alterations in the gut microbiota. The mechanisms underlying sarcopenia in IBD primarily involve chronic intestinal inflammation and dysbiosis of the gut microbiota [66, 67]. The inflammatory state observed in the intestines of IBD patients may activate pathways shared with sarcopenia, including the excessive production of pro-inflammatory cytokines such as TNF-α and IL-6 [65, 68]. Gut microbiota dysbiosis and sarcopenia commonly occur in older population.

The concept of the gut-muscle axis has been proposed, with the gut microbiota serving as a bridge between the immune system and muscle. Age-associated gut microbiome dysbiosis is suggested to be caused by immunosenescence and inflammaging, and in turn, to impact inflammaging. These changes in the composition, diversity, and functional features of gut microbiota further affect muscle phenotypes, potentially by influencing inflammation levels and hindering muscle metabolism [69]. The gut-muscle axis has gained attention in sarcopenia research, emphasizing the connection between gut microbiota and muscle health. In older individuals, this axis contributes to muscle wasting through mechanisms including inflammation regulation. The immune system is involved, influenced by gut microbiome composition. Experimental studies suggest a link between gut microbiota and muscle function. Patients with inflammatory bowel disease (IBD) are more susceptible to sarcopenia due to gut dysbiosis. However, the causal relationship between gut microbiota and sarcopenia remains to be elucidated. Further comprehensive studies in humans to establish a clear correlation between them are warranted [59, 70]. Understanding this axis is crucial for addressing sarcopenia and promoting healthy aging. Future research should focus on interventions targeting the gut microbiota, including probiotics, prebiotics, short-chain fatty acids (SCFAs), and bacterial products. These interventions warrant further investigation for their potential role in modulating immune responses during sarcopenia and enhancing muscle mass and performance. Such strategies could offer a promising avenue for immunomodulatory therapy in sarcopenia.

Autophagy - the immune microenvironment regulator for Sarcopenia

Autophagy is a physiological mechanism that degrades cytoplasmic components, protein aggregates, and organelles, and could regulate the cellular structure biologically via encompassing adaptation to metabolic stress, differentiation of stem cells, and immunomodulation. Evidence has shown that autophagy plays an essential role in the development of sarcopenia. It provides a protective shield against sarcopenia by enhancing the regenerative potential of muscle stem cells and myoblasts, mitigating oxidative stress, regulating immune cells, and curbing the inflammatory response [71, 72]. In vitro and in vivo studies using cell lines and mice has demonstrated that impaired autophagy impairs myoblast proliferation, and differentiation and contributes to the mechanisms involved in sarcopenia [73]. Deficiency of autophagy in rat and mouse models showed declined muscle mass and function which are significant characteristics of sarcopenia [74, 75]. The relationship between autophagy and immunity is complex. Autophagy prevents monocytes from apoptosis and induces macrophage differentiation from monocytes [76]. In addition, autophagy enforces the functional integrity of Tregs [77], which is another important participant immune cell in sarcopenia previously discussed. Additionally, autophagy modulates the functions of immune cells and the production of cytokines including IL-1, IL-18, TNF-α, and Type I IFN. In turn, certain cytokines including TNF-α, IL-1, and IL-6, and immune cells can induce autophagy, while others like IL-10 and IL-13 have inhibitory effects [78]. Furthermore, disruption of autophagy could alter gut microbiota and further trigger inflammation in IBD. In murine models, elevated gut serotonin (5-HT) levels suppressed autophagy, rendering the mice more susceptible to colitis. Conversely, mice with reduced 5-HT exhibited upregulated autophagy through the mammalian target of the rapamycin (mTOR) pathway, resulting in a significant

reduction in the severity of colitis [79]. Emerging evidence that linked autophagy with the gut-muscle axis provides us with a new insight into the role of autophagy in immunomodulation on sarcopenia [80].

Autophagy, a cellular self-protection mechanism, has demonstrated its protective effect on sarcopenia by modulating muscle stem cells and suppressing inflammatory responses. Despite some promising discoveries in targeting autophagy to modulate inflammation and the gut-muscle axis to combat sarcopenia, identifying novel therapies specifically targeting autophagy remains challenging. Future studies elucidating the direct relationship between autophagy, inflammation, and sarcopenia and tests of autophagy regulators on sarcopenia are warranted.

Current and potential immunomodulatory approaches

Given the close association between immune response and sarcopenia, immunomodulatory approaches have emerged as promising strategies to combat this condition. Some interventions alter immune profiles that regulate the gut-muscle axis or autophagy, further targeting muscle restoration in sarcopenia. In this review, we discussed both current interventions and potential approaches, highlighting their immunomodulatory effects aimed at addressing sarcopenia.

Physical exercise

Among the interventions aimed at preventing or mitigating the progression of sarcopenia, physical exercise is the most recommended approach for older adults [81]. Notably, although further research is warranted to investigate the impact of various forms of physical exercise and different intervention times on immune cell function and phenotype, some forms of exercise (such as aerobic exercise) with appropriate "dose" exhibit an anti-inflammatory effect and exert an anti-immunosenescence effect, potentially delaying the onset of immunological ageing or even rejuvenating aged immune profiles [82]. Cross-sectional studies have demonstrated that individuals who maintain an active lifestyle with regular exercise training exhibit superior immune functions compared to their inactive counterparts, including the older population [83, 84]. Exercise affects the immune cells in muscle. A period of 14 weeks of progressive heavy resistance training stimulated an increase in the count of anti-inflammatory M2 macrophages ($CD11b^+/CD206^+$), as well as the total number of macrophages ($CD11^+$), in the skeletal muscle of older individuals [85]. Furthermore, a 12-week period of resistance exercise [86], or endurance exercise training [87] can prompt a shift in macrophages towards an M2 phenotype in human muscle, and 48 h after downhill exercise using 2-month-old rats showed a similar trend of gene expressions of macrophage polarization [88]. But this shift is particularly noticeable in young, healthy muscles; whether exercise could shift the macrophage phenotype in aged muscle is still largely unknown. Evidence was also indicated that exercise could potentially regulate the T cells in aged individuals. A randomized controlled trial (RCT) of 46 participants aged over 65 with sarcopenia found significant changes in peripheral blood T cell gene expression after a 12-week-treatment of combined (20–30 min resistance exercise and 20 min aerobic exercise on a weekly basis) and nutrition supplementation (two sachets daily with each sachet contained 231 calories, 8.61 g protein, 1.21 g β-hydroxy β-methylbutyrate, 130 IU vitamin D, and 0.29 g omega-3 fatty acid) [38]. The research group further demonstrated that this treatment improved lower limb muscle mass (0.23 kg increase. 95% CI at 0.01–0.44, $p=0.015$) and performance (leg extension, 3.73 kg increase. 95% CI at 2.28–5.18, $p<0.0001$) of the sarcopenic patients aged over 65 in another RCT of 113 subjects [89].

Exercise has been found to reduce basal inflammatory status and age-related chronic inflammation [12, 90]. Exercise significantly impacted the expression levels of certain cytokines in ageing muscle including IL-6 and TNF-α [91], which are important participants in inflammaging and sarcopenia [12]. A 3-month resistance exercise in frail older people decreased the age-related elevated TNF-α mRNA and protein levels [92]. IL-6 and TNF-α are cytokines as well as myokines sourced from immune cells and muscle cells; 3-months of resistance exercise regulated these factors by affecting both muscle and immune cells such as macrophages [25]. The effects of exercise on immune cells were demonstrated by the effects on leukocyte-derived cytokines such as IL-10. Although the associations between IL-10 and sarcopenia are still unclear in humans, as an anti-inflammatory leukocyte-derived cytokine, IL-10 plays a crucial role in modulating immune responses, macrophage polarization, and chronic inflammation. The expression of IL-10 mRNA was upregulated in the muscles of lifelong exercisers (50+years) with aerobic exercise compared with the age-matched non-exercisers [91].

Furthermore, exercise can potentially influence the composition of the intestinal microbiome and is considered a positive modulator of gut microbiota biodiversity [61]. In a case-control study, the α diversity of the microbiota was significantly higher in a group of professional rugby players compared to age-, sex-, and body size-matched controls who did not engage in sports [93]. As shown previously, the gut-muscle axis is the link between immune system and sarcopenia, in this context, exercise is potentially an immunomodulator that links gut microbiota and muscle health.

Exercise plays a pivotal role in preventing or mitigating sarcopenia. Some exercises exhibit anti-inflammatory effects and may even rejuvenate aged immune profiles. Active individuals demonstrate superior immune functions, and resistance and endurance exercises can shift macrophages toward an anti-inflammatory phenotype. Additionally, exercise modulates cytokines like IL-6 and TNF-α, which are crucial in inflammaging and sarcopenia. Furthermore, exercise positively influences gut microbiota biodiversity, linking the gut-muscle axis and overall muscle health. Nevertheless, the specific immunomodulatory effects of exercise on sarcopenia are complex and can be influenced by various factors, including the type, intensity, frequency, and duration of the exercise, as well as individual characteristics. Further research is needed to explore the impact of different exercise forms and intervention times on immune cell function. Appropriate exercise, especially those that have immunomodulatory effects, remains the promising approach to combat sarcopenia in clinical practice.

Biophysical interventions

While exercise remains a cornerstone in managing sarcopenia, non-invasive biophysical stimulations may provide an attractive alternative, especially for older individuals who face challenges or are physically unfit for performing complex exercises or resistance training. Biophysical stimulations can precisely target specific muscle groups without requiring physical effort, thereby minimizing physical strain and fatigue. Whole-body electrical myostimulation (85 Hz, 350 μsec impulse breadth, 6 s of electromyostimulation and 4 s of rest intermittently treatment) has emerged as a promising biophysical stimulation method, demonstrating positive effects on parameters of sarcopenia in clinical trials [94, 95]. Another well-studied biophysical stimulation, low-intensity pulsed ultrasound (LIPUS) is the current standard of care for muscle injury. Its preventative effects of muscle wasting were also shown by animal studies. LIPUS (100mW/cm^2 spatial-peak temporal-average intensity, 20 min/day) effectively prevented symptoms of sarcopenia associated with chronic kidney disease, including reduced grip strength, muscle mass, and cross-sectional areas of muscle fibers [96]. LIPUS has shown the potential to modulate immune responses, which could further impact sarcopenia. The cytokine and immune cell response induced by LIPUS has been studied in both young and older mice. LIPUS at 2 W/cm^2 low-intensity pulsed ultrasound increased levels of IL-15 and promoted the presence of more M2 macrophages compared to M1 macrophages 1-hour post-treatment in young muscle. Furthermore, in muscles of aged mice, the LIPUS led to decreased levels of IL-1, IL-6, and macrophage colony-stimulating factor [97].

Whole-body vibration has also garnered increasing attention as a potential treatment for sarcopenia. In a large-scale RCT with 710 older participants over 60 years old, subjects in the biophysical treated group who received 20 min of 35 Hz, 0.3 g low-magnitude whole-body vibration per day for 18 months showed enhanced muscle strength (2.46 kg increase in quadriceps strength. 95% CI at 1.70–3.22, $p<0.001$), balancing ability and reduced the risk of fall or fractures (HR=0.56, 95% CI at 0.40–0.78, $p=0.001$ [98]. Pre-clinical studies using rodent models have demonstrated that whole-body vibration of 35 Hz, 0.3 g [99, 100] and 30 Hz, 0.5–1.5 g [101] has an immunomodulatory effect by shifting macrophage polarization from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. Additionally, whole-body vibration (21 Hz, intensity 40 by the vertical vibration instrument from Weibutexun, Jinan, China) significantly increased the population of $CD4^+CD25^+FOXP3^+$ Tregs in the mouse spleen [102]. Tregs, important immune regulators, play a crucial role in sarcopenia. In human subjects, evidence of immune responses induced by biophysical vibration stimulation can be found in a clinical trial involving elite enduro mountain bike athletes [103]. This trial revealed a significant relationship between whole body vibration exposure and the redistribution of several $CD4^+$ T cell subtypes and NK cells in the blood samples. As an easy-access physical intervention, vibration has the potential to regulate the immune response in older patients with sarcopenia, which might further improve muscle performance.

The regulatory effect of biophysical stimulation, specifically vibration, on the microbiota has been further investigated. Whole-body vibration significantly reduced the α-diversity of mouse intestinal microbiota and increased the β-diversities of both mice and human fecal microbiota [102]. Additionally, Yu et al. have shown that whole-body vibration triggers changes in the microbial composition and diversity of mouse models [101]. These findings suggest that whole-body vibration has the capacity to modulate the gut microbiota and associated immunity, leading to anti-inflammatory responses that downregulate the inflammatory state and mitigate adverse consequences, including sarcopenia.

These discoveries underscore the potential of biophysical interventions to modulate immune responses. They offer an alternative for managing sarcopenia, especially for older individuals who may struggle with complex exercises. Notable approaches such as whole-body vibration enhance muscle strength, balance, and fall prevention, while also modulating immune responses. Additionally, whole-body vibration has the potential to regulate gut microbiota and associated immunity, downregulating inflammation and mitigating sarcopenia. Coupled with more comprehensive insights into the

effects of biophysical stimulation on immune modulation and muscle regeneration, these findings present a newly developed immunomodulatory approach to combat sarcopenia in clinical practice.

Nutritional supplements

Nutritional supplements play a pivotal role in the current management of sarcopenia [104]. The leucine metabolite β-hydroxy-β-methylbutyric acid (HMB) supplement is one of the most extensively studied interventions for attenuating the progression of sarcopenia [105, 106]. Notably, HMB has demonstrated positive immunomodulatory effects alongside its efficacy in sarcopenia management [107]. The immunomodulatory effects of HMB have been demonstrated by in vitro and pre-clinical studies. The proliferation and the effector functions of chicken macrophages could be induced by HMB exposure [108]. Additionally, supplementation with HMB during pregnancy in sows has led to significant increases in colostrum and serum IgG levels [109]. Furthermore, piglets born from HMB-supplemented sows exhibited heavier spleens [110], indicating potential improvements in immune function as a result of HMB supplementation. An RCT involving 40 male participants (22.3±2.4 years old) demonstrated that HMB-free acid decreased TNF-α and TNFR1 expression after intense exercise, indicating its capacity to regulate the initial immune response [111]. Although further evidence is needed to fully understand the immunomodulatory effects of HMB in humans, a clinical trial demonstrated the potential of combining HMB with exercise to modulate immune responses in sarcopenic individuals. In this trial, a 12-week treatment regimen of HMB combined with resistance exercise and aerobic exercise in sarcopenic patients aged over 65 led to significant changes in T lymphocyte gene expression in peripheral blood [38].

Low serum 25(OH)D levels have been associated with sarcopenia in older individuals [112], highlighting the essential role of vitamin D in this condition. Vitamin D acts as an immunomodulator, regulating immune cells such as macrophages and T cells, and reducing inflammatory responses involving IL-6, TNF-α, and IL-10 [113]. Given these dual roles, vitamin D should be considered as an important component of immunomodulatory supplements for sarcopenia. In clinical practice, compound nutritional supplements are also utilized in sarcopenia treatment. A study employing computational systems biology analysis revealed that phytonutrients (Fruit/Berry/Vegetable juice powder) containing bioactive compounds including luteolin, epicatechin, epigallocatechin gallate, lycopene, quercetin, vitamin A, vitamin C, and vitamin E could significantly attenuate the low-grade chronic inflammation [114]. This finding presents a novel option for nutritional supplements capable of modulating immune responses in sarcopenic patients.

We have explored the significance of the gut-muscle axis in connecting the immune system with sarcopenia. Probiotic and prebiotic supplementation has emerged as a potential strategy to foster a healthy gut microbiota. Probiotics are live microorganisms that are intended to have health benefits when consumed or applied to the body. Prebiotics are selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health [115] Supplementation with prebiotics, probiotics, or symbiotics (mixtures of probiotics and prebiotics) not only fosters the production of SCFAs but also has the potential to alleviate low-grade inflammation in older adults by modulating the gut microbiota [116]. These supplements, aimed at influencing the gut-muscle axis, hold promise as strategies to mitigate the risk of sarcopenia.

Nutritional supplements play a crucial role in managing sarcopenia. HMB has demonstrated positive immunomodulatory effects alongside its efficacy in sarcopenia management. HMB influences immune responses and T lymphocyte gene expression. Additionally, vitamin D, acting as an immunomodulator, plays an essential role in sarcopenia. Phytonutrients containing bioactive compounds can attenuate chronic inflammation. Probiotic and prebiotic supplementation, fostering a healthy gut microbiota, holds promise for mitigating sarcopenia risk. Understanding the interplay between nutritional supplements and immune responses in sarcopenia is crucial for devising effective strategies to address this age-related condition. In ongoing therapeutic intervention trials, nutritional supplements are often combined with other treatments like exercise and biophysical interventions for managing sarcopenia [117]. Future research endeavors should prioritize well-designed trials that consider the type, components, timing, and dosages of nutritional supplements that exhibit positive immunomodulatory effects in sarcopenia.

Pharmaceutical therapeutic approaches

Currently, there are no approved pharmaceutical drugs specifically for treating sarcopenia. Treatments targeting muscle dystrophies, often involving immunomodulation such as corticosteroids, can have adverse effects when applied to sarcopenia. For example, in Duchenne muscular dystrophy (DMD) patients, prednisone has been shown to shift macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype and reduce autoreactive T lymphocytes. Additionally, neutralizing antibodies against pro-inflammatory cytokine receptors, like the TNF-α receptor, have demonstrated promise in DMD mice [118]. The administration

of anti-inflammatory cytokines, such as IL-4 and IL-10, has shown immunoregulatory effects in muscle disorders. However, the chronic nature of sarcopenia poses challenges for the use of cytokines, including dosage regimen, pharmacokinetics, and controlling their pleiotropic effects, particularly when these molecules may affect various tissues [119]. Despite these challenges, with appropriate delivery and control, these immunomodulatory approaches hold promise as strategies for treating sarcopenia.

Efforts have been dedicated to exploring potential pharmaceutical immunomodulatory approaches for sarcopenia. Some Non-steroidal anti-inflammatory drugs (NSAIDs), showed their potential to ameliorate sarcopenia by inhibiting or reducing the choronic inflammation. In a prospective cohort study involving 354 older individuals (mean age 85.8±4.9 years), NSAID users (NSAIDs category in this study includes nimesulide, celecoxib, diclofenac, piroxicam, ketoprofen, indometacin, rofecoxib, and ketorolac) exhibited a nearly 80% lower risk of sarcopenia (OR 0.21, 95% CI 0.07–0.61) compared to non-users. After adjusting for potential confounders, NSAID users still had a lower risk of sarcopenia compared to non-users (OR 0.26, 95% CI: 0.08–0.81), suggesting that long-term NSAID use may confer a protective effect against the loss of muscle mass and function [120]. Celecoxib demonstrated significant efficacy in ameliorating skeletal muscle atrophy and improving skeletal muscle function in a murine model of diabetic sarcopenia induced by streptozotocin. It also reduced infiltration of inflammatory cells, along with lowering levels of IL-6 and TNF-α, and suppressed the activation of NF-κB, Stat3, and NLRP3 inflammasome pathways in the diabetic sarcopenia muscles in an in vivo study using mouse model [121]. Another study demonstrated that 5 months of treatment with ibuprofen reduced low-grade inflammation and restored muscle protein anabolism in aged rats (20 months old). This treatment further decreased the loss of muscle mass during the period from 20 to 25 months of age [122]. The evidence suggests that targeting low-grade inflammation using NSAIDs could be a promising approach to combat sarcopenia.

Myostatin inhibitors, which counteract the negative effects of myostatin, a regulator of muscle growth, are being investigated in relation to sarcopenia [123]. Preclinical studies have demonstrated that subcutaneous injections of myostatin inhibitors can reverse the loss of muscle mass and reduce circulating inflammatory cytokines such as TNF-α and IL-6 in mouse models of chronic kidney disease [124]. Apart from their anti-inflammatory properties, myostatin inhibitors offer other benefits to muscles, including enhanced activation and differentiation of satellite cells, as well as improved mitochondrial function [125]. Several myostatin inhibitors, including Trevogrumab (REGN1033) and Bimagrumab (BYM338), have been subjected to clinical trials for sarcopenia. However, further studies are needed to investigate their impact on the immune system and elucidate their potential anti-inflammatory properties. Before these inhibitors can be approved for clinical use, further research is necessary to establish their long-term safety and effectiveness. Additionally, determining the optimal dosage and treatment duration for sarcopenia is crucial.

Melatonin, renowned for its role in regulating circadian rhythms, also serves as a scavenger of free radicals and a modulator of the immune system [126]. In its capacity as an immunomodulator, melatonin regulates age-associated diseases specifically inflammaging, by suppressing pro-inflammatory cytokines and activating anti-inflammatory networks [127]. Supplementation with melatonin has been shown to reverse sarcopenic alterations in aged animals, which is significantly enhanced by the lack of NLRP3 inflammasome activation [128]. Melatonin increased autophagic flux, mitigating oxidative stress and inflammatory responses via the FOXO3a pathway [129]. In situations of disrupted homeostasis and elevated oxidative stress levels which are also characteristics of sarcopenia, melatonin activation of autophagy may confer protective effects [130]. This positive impact may be further corroborated by melatonin's influence on gut microbiota, acting as a probiotic agent to counteract high-fat diet-induced gut microbiota dysbiosis [131]. Although our understanding of melatonin's clinical efficacy in treating sarcopenia is still evolving, it offers a promising pharmaceutical approach that intersects immunomodulation, autophagy, and probiotic effects.

Autophagic inducers hold promising potential in alleviating sarcopenia. Rapamycin, known as an immunomodulatory molecule, not only reduces the T cell inflammatory infiltrate and increases the amount of Tregs [132] but also acts as an mTOR inhibitor, thereby inducing autophagy. Studies have demonstrated its efficacy in combating mTORC1-induced deterioration of the neuromuscular junction (NMJ) and the development of sarcopenia in ageing skeletal muscle [133]. Additionally, rapamycin improves gut microbial homeostasis, thereby slowing muscle ageing and preventing further inflammatory damage [71, 134]. However, long-term rapamycin treatment has been associated with severe side effects of testicular degeneration in mice [133]. Safer mTORC1 inhibitors are needed for new therapies. Ezetimibe, which activates autophagy in human hepatocytes by suppressing mTORC1 [135], has shown promise in preventing fibrofatty infiltration in skeletal muscle and muscle wasting in DMD mice [136]. It has been found to block the activation of the NLRP3 inflammasome, a process dependent on the activation of autophagy induced by AMPK activation based on in vitro study using human liver

samples and cells [137]. Another autophagic inducer, spermidine, has demonstrated effectiveness in restoring mitochondrial function, enhancing the elasticity of cardiomyocytes, and suppressing inflammatory responses [138]. With more studies investigating the effects of spermidine on sarcopenia, it emerges as a potential pharmaceutical approach for addressing this condition.

We have explored phytonutrients as potential agents to attenuate low-grade chronic inflammation, offering a novel avenue for nutritional supplements to modulate immune responses in sarcopenic patients. Researchers have also turned their attention to pharmaceutical ingredients derived from herbs, with studies indicating promising benefits. For instance, animal studies have shown that *Schisandra chinensis* extract possesses various advantages, including reducing protein degradation, increasing protein synthesis, and exhibiting antioxidant and anti-inflammatory effects on skeletal muscle fibers [139, 140]. Additionally, a recent RCT demonstrated that *Schisandra chinensis* extract enhanced thigh muscle strength in older women [141]. Bagherniya et al. have discussed the therapeutic benefits of several plant-derived natural products for sarcopenia treatment, highlighting the anti-inflammatory properties of substances such as curcumin, resveratrol, green tea, isoflavones, flavonoids, and quercetin [142]. These plant-based products offer potential immunomodulatory pharmaceutical approaches to combat sarcopenia.

Sarcopenia lacks approved pharmaceutical drugs, but pharmaceutical approaches that could modulate the immune responses are being explored. NSAIDs show promise by inhibiting chronic inflammation. Celecoxib and ibuprofen improve muscle function and reduce inflammation. Myostatin inhibitors counteract muscle growth regulation and reverse muscle mass loss and could reduce circulating inflammatory cytokines such as TNF-α and IL-6. Clinical trials for inhibitors like Trevogrumab and Bimagrumab to treat sarcopenia are ongoing. Melatonin, an immune modulator, reverses sarcopenic changes and influences gut microbiota. Autophagic inducers, including rapamycin and spermidine, combat muscle aging and inflammation. Herbal ingredients like *Schisandra chinensis* offer anti-inflammatory benefits for sarcopenia. Pharmaceutical treatments are critical parts of clinical practice for sarcopenia. Understanding immunomodulation management is crucial for developing effective sarcopenia drugs.

Other potential future immunomodulatory approaches

While these immunomodulatory agents show significant potential in treating sarcopenia, they often come with considerable off-target effects and adverse reactions at therapeutic doses. Nanoparticles offer a promising avenue for nano-immunomodulation in sarcopenia treatment, potentially reducing the required effective dose or enhancing target selectivity [143]. These nanoscale carriers can deliver therapeutic bioactive compounds to modulate the immune response in ageing muscles. Raimondo et al. created a chronic muscle injury murine model by daily microdamage and a toxin injury murine model by intramuscular injection of Notexin Np. They discovered that their gold nanoparticles conjugated with IL-4 and IL-10 reduced inflammation by decreasing cytotoxic T cells and increasing Treg cells, leading to improved muscle strength in a murine model of advanced muscular dystrophy [144]. Certain nanomaterials possess intrinsic immunomodulatory properties [145]. In a study investigating the inflammatory responses of mouse macrophages RAW 264.7 exposed to nanoparticles, the cells exposed to silver nanoparticles showed a greater increase in IL-6 production and NF-κB activation compared with aluminum, carbon black, carbon-coated silver, and gold nanoparticles [146], further highlighting their potential as pharmaceutical immunomodulators for sarcopenia. By harnessing these nanomaterials, carefully designed and controlled pharmaceutical interventions hold great promise for the future management of sarcopenia.

Several novel immunomodulatory methods have not yet been widely utilized in the management of sarcopenia but hold potential for future applications. One such approach involves modifying immune cells or stem cells to enhance their immunomodulatory functions [147, 148], thereby benefiting the mitigation of sarcopenia. By leveraging advancements in cell engineering and immunotherapy, researchers may unlock new avenues for targeted intervention and treatment of sarcopenia. Further exploration of these novel strategies is warranted to assess their efficacy and safety in combating sarcopenia.

Other potential immunomodulatory approaches such as nanoparticles offer a promising avenue for nano-immunomodulation in sarcopenia treatment, potentially reducing effective doses or enhancing target selectivity. These nano-scale carriers can deliver bioactive compounds to modulate immune responses in aging muscles. For instance, gold nanoparticles conjugated with IL-4 and IL-10 reduced inflammation and improved muscle strength in a murine model of advanced muscular dystrophy. Certain nanomaterials possess intrinsic immunomodulatory properties. Additionally, novel methods involving immune cell or stem cell modification show promise. By leveraging advancements in cell engineering and immunotherapy, researchers may unlock new avenues for targeted sarcopenia intervention. Further exploration of these strategies is needed to assess their efficacy and safety.

Conclusions

Sarcopenia represents a growing concern on a global scale, with prevalence rates ranging from 5 to 13% among individuals aged 60–70 years and soaring to as high as 50% among those over 80 years old [1, 2]. The population is ageing much faster than in the past. According to the Ageing and Health Report from the World Health Organization, by 2030, the share of the population aged 60 years and over will increase from 1 billion in 2020 to 1.4 billion. By 2050, the world's population of people aged 60 years and older will double (2.1 billion). The number of persons aged 80 years or older is expected to triple between 2020 and 2050 to reach 426 million. Given these projections, the impact of sarcopenia, currently afflicting over 80 million individuals, is forecasted to escalate dramatically, affecting more than 320 million people over the next three decades [125]. Accurate diagnosis or biomarkers as well as therapeutic approaches for sarcopenia are essential for the ageing population.

The complex interplay between the immune system and muscle highlights the potential of immunomodulation as a therapeutic strategy for combating this condition. However, there are no viable immunomodulatory or anti-inflammatory therapies to mitigate sarcopenia at present. Various approaches targeting immune cells and inflammatory responses have demonstrated promise in both preclinical and clinical studies. Traditional methods to improve muscle strength and mass, such as physical exercise, biophysical stimulations, and nutritional supplements, have demonstrated important immunomodulatory effects. Additionally, pharmaceutical therapeutic approaches targeting myokines, autophagy, and gut microbiota have shown their immunomodulatory potential which could further contribute to treating sarcopenia.

As advancements continue in immunomodulatory tools and techniques, including nano-scale materials and genetic modification, we anticipate the emergence of safer and more efficient approaches for targeting immunomodulation in sarcopenia. Given that sarcopenia is a multifactorial age-associated syndrome, immunomodulatory therapies should be approached as prolonged and nuanced processes, considering the complex interactions involved. Sole treatment may not suffice, and efforts to combine nutritional supplements with exercises and/or biophysical interventions, or multiple pharmaceutical agents, have been explored in both preclinical studies and clinical trials [38, 106, 149, 150]. This review outlines current and potential options for combined treatments aimed at immunomodulation to combat sarcopenia. Integrated approaches, such as delivering pharmaceutical immunomodulators via nanoparticles to the muscle or supplementing SCFAs to modulate gut microbiota alongside whole-body vibration, hold promise for effectively addressing the complex pathophysiology of sarcopenia and improving outcomes for affected older individuals.

While more studies on immunomodulatory approaches to combat sarcopenia are still urgently needed, these novel methods hold the potential to enhance safety and efficacy while minimizing the adverse effects of current and potential treatments, paving the way for more personalized and effective therapeutic interventions.

Abbreviations

AWGS	Asian Working Group for Sarcopenia
EWGSOP	European Working Group on Sarcopenia in Older People
IWGS	International Working Group on Sarcopenia
CRP	C-reactive protein
IL	Interleukin
TNF-α	Tumor necrosis factor-alpha
GDF3	Growth differentiation factor 3
Tregs	Regulatory T cells
NK cells	Natural killer cells
ROS	Reactive oxygen species
IBD	Inflammatory bowel disease
SCFAs	Short-chain fatty acids
RCT	Randomized controlled trial
LIPUS	Low-intensity pulsed ultrasound
HMB	β-hydroxy-β-methylbutyric acid
DMD	Duchenne muscular dystrophy
NSAIDs	Non-steroidal anti-inflammatory drugs
NMJ	Neuromuscular junction

Acknowledgements

Not applicable.

Author contributions

N Zhang and WH Cheung conceived the manuscript. N Zhang, L Zhai, RMY Wong, C Cui, and SW Law collected the related references and wrote the manuscript. SKH Chow, SB Goodman, and WH Cheung gave constructive guidance and made critical revisions. All authors approved the final manuscript.

Funding

This work was supported by Collaborative Research Grant (Ref: C4032-21GF), General Research Fund (Ref: 14114822), and CUHK Direct Grant for Research (Ref: 4054760).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 21 May 2024 / Accepted: 24 July 2024
Published online: 05 August 2024

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