Interleukin-6: Unravelling its role in sarcopenia pathogenesis and exploring therapeutic avenues

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Received 14 November 2023 ♦ Accepted 14 November 2023 ♦ Published 8 December 2023


Abstract

This review explores the intricate relationship between interleukin-6 (IL-6) and sarcopenia, a prevalent condition characterized by progressive skeletal muscle loss, particularly in aging populations. Emphasizing the rising prevalence and health challenges posed by sarcopenia, the paper delves into the multifunctional roles of IL-6 in immune response, inflammation and inflammaging associated with sarcopenia. Significantly elevated in sarcopenic individuals, IL-6 prompts an exploration of its molecular impact on muscle wasting. The review critically assesses IL-6 as a potential biomarker for sarcopenia diagnosis and prognosis while also examining therapeutic interventions targeting IL-6 signaling pathways, offering a foundation for future research and the development of targeted therapeutic strategies to alleviate the impact of this debilitating condition.

Keywords

Interleukin-6, Sarcopenia, Muscle wasting, Inflammation, inflammaging, Cytokines, Muscle atrophy, anti-IL-6 drugs, JAK inhibitors

Introduction

Sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, poses a significant health challenge, particularly in aging populations (Landi et al. 2018). A growing body of research underscores the need for a deeper understanding of the molecular mechanisms driving sarcopenia to develop targeted interventions (Rong et al. 2018). However, the pathophysiological mechanisms of sarcopenia are still elusive. Recent understanding of the problem hypothesizes the role of low-grade systemic inflammation associated with age (Franceschi et al. 2000), the so-called “inflamming” (Antuna et al. 2022; Liang et al. 2022; Miteva and Velikova 2023). Moreover, it is thought that proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNFa), play a pivotal role in sarcopenia. In contrast, anti-inflammatory cytokines (i.e., IL-10) decrease in this condition (Baylis et al. 2023).

Within this context, IL-6, a multifunctional and primarily regulatory cytokine with dual roles in immune response and inflammation, has emerged as a potential key player in the pathogenesis of sarcopenia. At the molecular level, IL-6 is intricately linked to the pathogenesis of sarcopenia (Xie et al. 2023). Since elevated IL-6 levels have been consistently observed in sarcopenic individuals, this
prompts a deeper investigation into its role in mediating muscle wasting. Understanding the molecular underpinnings of IL-6 in sarcopenia is critical for developing targeted interventions for preserving muscle health and functionality. This paper explores the intricate relationship between IL-6 and sarcopenia, delving into existing literature to provide a comprehensive overview. By examining IL-6 as a potential biomarker, elucidating its impact on muscle physiology, and assessing therapeutic options, this paper seeks to contribute valuable insights into developing more effective interventions for sarcopenia.

**Search strategy**

For our narrative review, we searched the following databases: PubMed, MEDLINE, and Scopus, using both Mesh Terms (“Interleukin-6”, “Sarcopenia”, “Muscle Atrophy”, “Aging”, “Cytokines”, “Muscle Proteins”) and free text terms (“IL-6 and Sarcopenia”, “Interleukin-6 in Muscle Wasting”, “Skeletal Muscle Loss and Aging”, “IL-6 Signaling Pathways”, “Therapeutic Strategies for Sarcopenia”) and a combination of terms (“Interleukin-6” OR “IL-6”) AND (“Sarcopenia” OR “Muscle Atrophy”) AND (“Aging” OR “Cytokines”); (“IL-6 in Muscle Wasting” AND “Skeletal Muscle Loss”); (“IL-6 Signaling” OR “Cytokine Regulation”) AND “Therapeutic Approaches for Sarcopenia”), with date range up to 2023, written in English, publication types: reviews, original articles, communications, limited to human and animal studies and clinical trials. We retrieved approximately 150 relevant papers based on the specified search strategy. The selection process involved screening titles, abstracts, and full texts to ensure the inclusion of the most pertinent and recent literature on the role of IL-6 in sarcopenia pathogenesis and therapeutic options.

**An overview of biological functions of IL-6**

IL-6, recognized not only for its association with sarcopenia but also as a critical immune regulatory cytokine, exerts a dual influence in physiological and pathological contexts. As an immune modulator, IL-6 is crucial in orchestrating the body’s response to infections and tissue damage. However, dysregulation of IL-6 signaling has been implicated in chronic inflammatory conditions, including inflammation, cancer and sarcopenia. The pleiotropic function of IL-6 is linked to the induction of a variety of other cytokines and protein production (i.e., fibrinogen, hepcidin, C-reactive protein (CRP) and serum amyloid A), responsible for various immune mechanisms and pathways – acute and chronic inflammation, proliferation and differentiation of immune cells, etc. (Uciechowski et al. 2020).

Given its connection with inflammation and T-helper cells, it was recently confirmed that IL6 is essential for both inflammation and carcinogenesis (acting as an autocrine tumor growth factor, facilitating escaping the immune surveillance, suppressing p53 activity, inhibiting apoptosis, etc.) (Dalbeni et al. 2023), significantly contributing to Th17 cells development (Velikova et al. 2020).

**IL-6 and sarcopenia pathophysiology**

Although increased levels of proinflammatory cytokines, including IL-6, were demonstrated in subjects with reduced muscle mass and strength, along with functional decline of muscles in elderly individuals, the delicate mechanisms are not known. A possible proposed mechanism is the increased catabolism due to inflammation (Ferrucci et al. 2002) observed in rheumatoid arthritis patients (Torri et al. 2023). Animal models showed proteolysis and muscle atrophy in rats infused with IL-6 and TNFα (Haddad et al. 1985; Goodman 1991). Protein synthesis in muscles was also declined when CRP, IL-6 and TNF receptor-2 were elevated (Toth et al. 2005).

Rong et al. (2018) found increased IL-6, IL-10 and IL-6/IL-10 ratio levels in 118 elderly subjects with sarcopenia. Similarly, Schaap et al. (2006) demonstrated higher levels of IL-6 and CRP in a prospective, population-based study including 986 men, associated with increased risk of muscle loss and strength. Pedersen et al. (2003) investigated plasma levels of IL-6 and TNFα in elderly diabetic patients and found an association between their increased levels and sarcopenia. Similar results were obtained by Viser et al. (2002) in healthy older persons, by Taafee et al. (2000) in 880 high-functioning men and women (aging and elderly), and by Legrand et al. (2014) in people aged 80 and older, where physical performance and reduced muscle strength were associated with increased mortality, hospitalization and disability.

Furthermore, Pedersen et al. (2003) showed the potential of exercise as an immunomodulatory intervention in sarcopenia cannot be overlooked. Via exploring the dynamic relationship between exercise, IL-6, and muscle health, contrary to the traditional view of IL-6 as solely proinflammatory, the study highlighted its anti-inflammatory effects during exercise, showcasing the complexity of IL-6’s role in muscle physiology. Tailoring exercise interventions to harness the immunomodulatory effects of IL-6 presents a novel approach to the holistic management of sarcopenia. It is also plausible that the cytokines secreted from skeletal muscles in response to physical activity, called myokines, could play a key immunomodulatory role and reduce IL-6 levels and thus the low-grade inflammation (Buford et al. 2010; Thalacker-Mercer et al. 2010).

It is unclear whether IL-6 could be used as a biomarker for sarcopenia. Dalbeni et al. (2023) demonstrated that IL-6 is a marker for advanced sarcopenic hepatocellular carcinoma (HCC). As 48.1% of patients with HCC suffered from sarcopenia, the investigators were interested in evaluating IL-6 as a proinflammatory biomarker associated with sarcopenia.
No studies are assessing the potential predictive value of IL-6 in identifying sarcopenic individuals for various pathologic conditions. However, Bermejo-Bescos et al. (2020) demonstrated that IL-6, but not sarcopenia, predicts one year’s mortality after hip fracture in elderly individuals.

In summary, it would appear that IL-6 is a key player in the complex pathophysiology of sarcopenia in the context of low-grade inflammation. A proposed mechanism for this interrelation is presented on Fig. 1.

**IL-6 as a potential target for immunomodulatory therapy in sarcopenia**

As stated above, sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, is a multifaceted condition predominantly associated with aging. The intricate interplay between inflammatory mediators and muscle homeostasis is increasingly recognized, positioning cytokines like IL-6 at the forefront of research into potential therapeutic interventions.

Several therapeutic agents have undergone assessment for inhibiting IL-6, its receptor signaling, or target kinases (e.g., JAK/STAT) linked to these pathways (Doles and Olwin 2014; Uciechowski et al. 2023). Tocilizumab, an anti-IL-6R humanized antibody, has gained approval for treating conditions like rheumatoid arthritis, cytokine release syndrome, and idiopathic multicentric Castleman’s disease. Siltuximab, an IL-6 antagonist, has been approved for Castleman’s disease exclusively. Although not all IL-6-related diseases exhibit a positive response to IL-6 blockade, a deeper understanding of IL-6 pathway mechanisms may shortly guide the development of optimal treatments for IL-6-associated diseases.

One avenue of exploration involves inhibiting IL-6 signaling pathways to curtail its detrimental effects on muscle tissue. Small molecules and antibodies targeting IL-6 receptors or downstream signaling molecules are under investigation. Tocilizumab, an anti-IL-6 receptor antibody, has shown promise in mitigating muscle loss in experimental models. By blocking IL-6 receptor activation, these therapeutic agents aim to disrupt the cascade of events that lead to muscle wasting, offering a potential avenue for preventing or treating sarcopenia. Doles and Olwin (2014) speculate that JAK/STAT pathway targeting could be employed to avoid debilitating muscle waste in mice based on the crucial involvement of this inflammatory signaling pathway in muscle metabolism and regeneration.

In line with this, Bermejo et al. (2023) showed that pharmacological inhibition of the IL6/JAK/STAT pathway enhanced muscle mass restoration in an experimental model of sarcopenia associated with rheumatoid arthritis (i.e., rheumatoid cachexia). Furthermore, the authors observed decreased atrogen expression and restored baseline of muscle cell differentiation markers in muscle tissue while gaining muscle mass (assessed by increased creatine kinase levels).

Another study by Bermejo-Alvarez (2023) demonstrated the effects of tofacitinib on muscle remodeling in an experimental animal model of rheumatoid sarcopenia. Similarly, tofacitinib increased the muscle mass by attenuating the IL-6/JAK/STAT axis, although it did not alter CRP levels.

Zhaowej et al. (2021) further demonstrated the effects of JAK inhibitors combined with exercise mimetics to alleviate IFN-g-induced wasting in an experimental engineered skeletal muscle, revealing the critical roles of STAT1 activation in proinflammatory cytokines action. Addinsall et al. (2021) also established the critical role of JAK/STAT inhibition in altering the complement cascade and muscle monocyte infiltration, improving muscle outcomes in a rat model of critical illness myopathy.

Another mechanism of IL-6/JAK/STAT3 inhibition to rescue denervation in induced skeletal muscle atrophy was proposed by Huang et al. (2020). In their study, pharmacological blocking of IL-6 by tocilizumab along with pharmacological/genetic suppression of JAK/STAT3 pathway by ruxolitinib/C188-9 and STAT3 short hairpin RNA lentivirus lead to reduced muscle atrophy and

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*Figure 1. IL-6 role in sarcopenia: IL-6 is part of the inflammatory secretome during Inflammaing, resulting in sarcopenia, along with immune, inflammatory and other factors.*
mitophagy, decreased expression of atrophic (MuRF1 and MAFbx) and autophagy-related genes (PINK1, BNIP3, Beclin 1, ATG7, and LC3B).

In line with these results is the previous review of Bonetto et al. (2012) suggesting JAK/STAT3 pathway inhibition 2 for ceasing skeletal muscle wasting downstream of IL-6 and in experimental cancer cachexia.

Regarding IL-6 blockers, there is not much data on their use in patients with sarcopenia. Nevertheless, Lambert (2021) pointed out that anti-cachexia therapy should be multiplex, considering metabolism, inflammatory cytokines and hormones (i.e., androgens in hormone-independent cancers).

However, Hein et al. (2022) in their systematic review of nine studies and meta-analysis on the effect of disease-modifying anti-rheumatic drugs (DMARD) on skeletal muscle mass in rheumatoid arthritis patients, did not find evidence of a significant effect of DMARD therapy on muscle mass (including conventional synthetic DMARDs, such as methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine; and biological and targeted synthetic DMARDs, such as monoclonal antibodies against TNF (infliximab, adalimumab, certolizumab, and golimumab), IL-6 (tocilizumab and sarilumab), soluble receptor for TNF (etanercept), an inhibitor of T-cell co-stimulation (abatacept), and anti-CD20 B-cell depleting monoclonal antibody (rituximab), and JAKinhbitors. The authors concluded that these outcomes should be verified in more studies.

On the contrary, the outcomes from a systematic review and meta-analysis of Patsalos et al. (2020) on inhibiting the IL-6 signaling pathway on weight and body mass index differed. They included 10 studies and 1,531 patients, confirming the role of IL-6 in weight regulation and implying that targeting IL-6 could be employed in treating cachexia.

However, immunomodulatory interventions addressing IL-6-mediated sarcopenic changes need a proper balance between the immune response and inflammation to prevent excessive muscle breakdown. Torri et al. (2023) demonstrated that sarcopenia in rheumatoid arthritis patients should be managed complexity – via exercise therapy, nutritional adjustments, and supplementation (i.e., vit. D, carotenoids, etc.). In line with this, dietary supplements, exercise regimens, and pharmacological agents targeting IL-6 expression are being explored for their potential to attenuate the impact of elevated IL-6 in sarcopenia. Exercise, in particular, has been shown to have both direct and indirect effects on IL-6 levels, promoting an anti-inflammatory environment and potentially mitigating the progression of muscle wasting.

Moreover, the therapeutic landscape is not without challenges. The heterogeneity of sarcopenia and the multifaceted role of IL-6 in various physiological processes necessitates carefully considering potential side effects and limitations associated with IL-6-targeted therapies. Striking a balance between modulating IL-6 for therapeutic benefit and avoiding adverse effects remains a critical challenge in developing effective interventions.

Taken together, the existing data so far showed that IL-6 stands as a promising target for immunomodulatory therapy in sarcopenia. The evidence from studies exploring IL-6 modulation, whether through receptor blockade or exercise interventions, suggests a potential avenue for mitigating muscle wasting in aging individuals. However, a cautious approach is warranted to navigate the complexities of IL-6 dual nature and its systemic effects. As research in this field advances, a deeper understanding of IL-6 role in sarcopenia and the development of targeted immunomodulatory strategies hold the key to effective therapeutic interventions for this prevalent and debilitating condition.

Some challenges and considerations about anti-IL-6 for immunotherapy for sarcopenia are related to the heterogeneity of Sarcopenia, pleiotropic IL-6 responses, difficulties in balancing IL-6 Modulation for therapeutic benefits and the potential side effects and limitations of IL-6 targeted therapies. Therefore, therapeutic approaches targeting IL-6 in sarcopenia hold promise for addressing the complex mechanisms underlying muscle wasting. However, the field is still in its infancy, requiring further research to optimize these approaches. As our understanding of IL-6 in sarcopenia deepens, developing targeted therapies may offer new hope for preserving muscle mass and function in aging populations, ultimately improving the quality of life for individuals affected by this prevalent and debilitating condition.

A summary of IL-6 modulation strategies for sarcopenia is enlisted in Table 1.

**Table 1. IL-6 Modulation Strategies in Sarcopenia.**

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Mechanism of Action</th>
<th>Findings/Results</th>
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<tbody>
<tr>
<td>IL-6 Receptor Blockade</td>
<td>Inhibition of IL-6 signaling pathways</td>
<td>Significant preservation of muscle mass and function</td>
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<tr>
<td>ExerciseModulation</td>
<td>Modulation of IL-6 expression during exercise</td>
<td>Highlighted anti-inflammatory effects of IL-6</td>
</tr>
<tr>
<td>Combined Approaches</td>
<td>Integration of IL-6 modulation with other interventions</td>
<td>Addressing potential systemic effects and challenges</td>
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**Future perspectives of anti-IL-6 therapy for sarcopenia**

Unraveling the specific pathways through which IL-6 influences muscle metabolism, regeneration, and systemic inflammation will provide a more precise understanding of its role in sarcopenia pathogenesis. This knowledge is essential for developing targeted interventions that selectively modulate IL-6 effects on muscle tissue without compromising its vital functions in immune regulation. Moreover, exploring the potential for personalized therapeutic approaches represents a promising avenue. Given the heterogeneity of sarcopenia and variations in individual responses to IL-6 modulation, tailoring interventions based on patientspecific characteristics may enhance treatment efficacy. Identifying biomarkers that predict an individu-
a’s susceptibility to IL-6-mediated muscle wasting could guide the development of personalized strategies for early intervention and preventive measures.

The integration of novel technologies, such as advanced imaging techniques and omics approaches, holds significant promise in enhancing our understanding of sarcopenia at the molecular level. These tools can provide comprehensive insights into the dynamic changes in muscle tissue in response to IL-6 and aid in identifying specific targets for therapeutic intervention.

Furthermore, the potential synergies between IL-6-targeted therapies and existing interventions, such as exercise regimens and nutritional strategies, warrant exploration. Combining modalities that directly target IL-6 with those that promote overall muscle health may offer a more comprehensive and synergistic approach to managing sarcopenia.

In conclusion, future research in IL-6 and sarcopenia should strive to uncover the intricate details of IL-6’s role, embrace personalized medicine approaches, leverage advanced technologies, and explore synergies with existing interventions. By addressing these aspects, the scientific community can pave the way for more effective, targeted, and personalized therapeutic strategies to mitigate the impact of sarcopenia, ultimately enhancing the quality of life for aging populations.

Conclusion

The significance of unraveling the role of IL-6 in sarcopenia lies in its intricate involvement in modulating muscle metabolism, regeneration, and systemic inflammation. While elevated IL6 levels have been observed in sarcopenic individuals, the precise mechanisms through which IL-6 influences muscle wasting remain complex and multifaceted. Recognizing the interplay between IL-6 and sarcopenia enhances our comprehension of the disease’s underlying processes and opens avenues for targeted therapeutic strategies. Moreover, the critical evaluation of therapeutic interventions targeting IL-6 signaling pathways offers insights into potential avenues for mitigating the debilitating effects of sarcopenia. As we navigate this complex interplay, understanding IL-6 emerges as a crucial element, paving the way for future research and developing targeted strategies to address this challenging health concern.

Aknowledgement

The authors acknowledge financial support from Bulgarian National Science Fund, Research Grant N KPI-06-M43/3/2020.

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