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INTERLEUKIN-6 AS A BIOMARKER OF INFLAMMAGING IN AGED RATS (RATTUS NORVEGICUS): A SYSTEMATIC LITERATURE REVIEW

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Abstract
Background: Aging is a complex biological process characterized by declining adaptive capacity, immune dysfunction, cellular damage, and persistent low-grade inflammation known as inflammaging. Interleukin-6 (IL-6) is widely used to assess age-related inflammatory changes; however, findings in aged rat models remain inconsistent and may vary according to strain, age, tissue, sex, metabolic status, and inflammatory stimuli. Objective: This systematic review evaluated changes in IL-6 levels or expression in aging Rattus norvegicus compared with younger rats and explored biological and experimental factors contributing to response heterogeneity. Methods: The review followed the PECO framework and PRISMA 2020 guidelines. Literature searches were conducted in PubMed/MEDLINE, Scopus, Web of Science Core Collection, ScienceDirect, and Google Scholar. Studies involving rats with identifiable age groups and IL-6 as an outcome were included. Risk of bias was planned using the SYRCLE Risk of Bias Tool. Due to substantial heterogeneity in age, strain, tissue, inflammatory stimuli, and IL-6 assessment methods, findings were synthesized narratively. Results: Evidence indicated heterogeneous age-related IL-6 responses. Several studies reported increased IL-6 in aged rats, particularly following lipopolysaccharide stimulation, whereas others found no consistent increase in plasma IL-6 despite increased tissue expression. Conclusion: IL-6 may reflect inflammatory changes during aging, but it is not a universally elevated biomarker in aged rats. Its interpretation should consider tissue compartment, strain, age, sex, metabolic status, and inflammatory stimuli.
***Keywords**: aging; aged rat; Rattus norvegicus; inflammaging; interleukin-6; IL-6; chronic inflammation; immunosenescence.*

INTRODUCTION

Aging is a progressive biological process characterized by declining physiological integrity and the reduced capacity to maintain homeostasis. It results from interactions among multiple biological processes, including genomic instability, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and microbiota alterations. In the updated hallmarks of aging framework, chronic inflammation is recognized as an important interconnected feature of aging (López-Otín et al., 2023).

Low-grade, persistent inflammation associated with aging, termed inflammaging, differs from acute inflammation, which represents a protective response to injury or infection. Inflammaging reflects sustained inflammatory activity that may occur in the absence of overt acute infection and is associated with immune alterations, cellular damage, senescence, metabolic dysfunction, and

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impaired tissue function. Chronic inflammation may act both as a consequence and an amplifier of aging processes through interactions with other hallmarks of aging (Baechle et al., 2023; López-Otín et al., 2023).

Interleukin-6 (IL-6) is a pleiotropic cytokine involved in immune and inflammatory regulation and is produced by macrophages, endothelial cells, fibroblasts, adipocytes, and other tissues. IL-6 has attracted particular attention in aging because chronic inflammatory activity may affect immune, metabolic, musculoskeletal, neurological, and other organ functions. However, IL-6 is not specific to aging and may also respond to infection, injury, physical activity, obesity, stress, and pathological conditions. Furthermore, senescent cells can develop a senescence-associated secretory phenotype (SASP), comprising cytokines, chemokines, proteases, and other mediators, with IL-6 representing an important component that may contribute to persistent inflammation and propagation of senescence.

Rattus norvegicus is an important experimental model for aging research because it permits controlled experimental and longitudinal investigations. However, differences among rat strains in lifespan, metabolism, immune responses, and aging phenotypes may contribute to heterogeneity in IL-6 responses across studies.

Experimental evidence indicates that IL-6 does not consistently increase constitutively in aged rats. Foster et al. (1992) demonstrated altered cytokine responses to lipopolysaccharide (LPS) in Fischer 344 rats aged 3–5, 12–15, and 24–27 months, suggesting that aging may modify inflammatory responses to stimulation rather than simply elevate basal cytokine levels. Similarly, Terrazzino et al. (1997) reported higher serum IL-6 in 24-month-old Sprague-Dawley rats than in 3-month-old rats following intracerebroventricular LPS administration, whereas TNF did not show a comparable change. Conversely, studies comparing 2- and 24-month-old rats found no significant change in plasma IL-6 despite increased hypothalamic IL-6 mRNA expression, highlighting tissue-specific regulation. Strain-dependent differences have also been reported in Dark Agouti and Albino Oxford rats (Stanojević et al., 2016).

Metabolic status further influences IL-6. Lifelong caloric restriction in Fischer 344 × Brown Norway rats aged 18, 24, and 29 months reduced adipose tissue IL-6 secretion and C-reactive protein levels, indicating an interaction between aging, adiposity, and inflammation (Carter et al., 2007). More recent longitudinal evidence suggests that aging involves multisystem alterations rather than changes in a single biomarker. Chen et al. (2024) reported progressive increases in allostatic load from 5 to 21 months, integrating inflammatory, metabolic, hormonal, and immune indicators. In addition, hindlimb suspension increased inflammatory and oxidative stress responses, including IL-6, in aged Sprague-Dawley rats, demonstrating that physiological stress may amplify age-related inflammatory responses (Al-Dwairi et al., 2025).

Thus, evidence regarding IL-6 during rat aging remains heterogeneous, with differences related to strain, age, sex, biological compartment, metabolic status, measurement methods, and inflammatory stimuli. This systematic review therefore synthesizes evidence on IL-6 changes in aging Rattus norvegicus, specifically examining whether IL-6 increases in aged versus young rats, whether changes differ between circulating and tissue compartments, and which biological

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or experimental factors may explain the observed heterogeneity. This approach aims to clarify the role of IL-6 as a biomarker of inflammaging and provide a basis for experimental studies of healthy aging and geroprotective interventions.

METHODS

Study Design

This study was designed as a systematic literature review of experimental studies using Rattus norvegicus. The review will be reported in accordance with the PRISMA 2020 guidelines, which provide a transparent framework for the identification, selection, appraisal, and synthesis of evidence (Page et al., 2021). Reporting characteristics relevant to animal research will also be considered based on ARRIVE 2.0, particularly animal characteristics, study design, sample size, experimental procedures, outcomes, and statistical analysis, to enhance transparency and reproducibility of in vivo research (Percie du Sert et al., 2020).

Research Question

The research question was formulated using the PECO framework:

Population: Rattus norvegicus
Exposure: aging, advanced age, or senescence
Comparator: younger rats
Outcome: IL-6 concentration or expression

The primary research question was: How does IL-6 concentration or expression change in aging Rattus norvegicus compared with younger rats?

Secondary questions addressed whether IL-6 responses differed according to strain, sex, tissue, specimen source, measurement method, metabolic status, and inflammatory stimulus.

Eligibility Criteria

Studies were eligible if they: (1) used Rattus norvegicus; (2) evaluated aging, aged, old, or senescent rats; (3) provided extractable information on animal age; (4) assessed IL-6 as an outcome; (5) were primary research studies; and (6) were available as full-text articles.

Studies were excluded if they involved other animal species without separately reported rat data, human participants, reviews, editorials, letters, conference abstracts, or studies without an IL-6 outcome. Intervention studies were not automatically excluded when data for aged rats and IL-6 outcomes could be separately extracted; intervention characteristics were subsequently recorded as potential sources of heterogeneity.

Definition of Aged Rats

Because no universally accepted chronological threshold defines aged rats, this review retained the aging definition applied by the authors of each included study while extracting the animals' chronological age. For descriptive analysis, age was categorized as young, young adult, mature adult, middle-aged/aging, aged/old, or advanced aged. Rats aged ≥18 months were categorized as aged/old, whereas those aged ≥24 months were categorized as advanced aged. These categories were used to standardize descriptive analyses and were not applied as the sole basis for study exclusion.

Search Strategy

The search strategy consisted of three main concept blocks: (1) Rattus norvegicus/rat; (2) aging/ageing/aged/old/senescent; and (3) interleukin-6/IL-6.

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The term inflammaging was not required because relevant studies may evaluate IL-6 in aged rats without using this terminology.

The planned databases were PubMed/MEDLINE, Scopus, Web of Science Core Collection, and ScienceDirect, with Google Scholar used as an additional source. Reference lists of eligible studies were also screened for backward citation searching. The PubMed strategy combined MeSH terms and Title/Abstract fields:("Rattus norvegicus" OR rat OR rats) AND (aging OR ageing OR aged OR "aged rat" OR "old rat" OR "senescent rat" OR "advanced age") AND ("interleukin-6" OR "IL-6" OR IL6).

Search strategies for Scopus and Web of Science were adapted to the syntax of each database using title, abstract, and keyword/topic fields.

Study Selection

Records retrieved from all databases will be combined and duplicates removed. Screening will be conducted in two stages: title and abstract screening followed by full-text assessment. Reasons for full-text exclusion will be categorized as wrong species, no aging group, no IL-6 outcome, wrong study design, duplicate publication, insufficient data, or unavailable full text. The selection process will be presented using a PRISMA 2020 flow diagram.

Data Extraction

The following data will be extracted: author, publication year, country, strain, sex, animal age, sample size, experimental conditions, intervention, specimen/tissue, IL-6 measurement method, IL-6 values, direction of change, p-value, other inflammatory biomarkers, and senescence-related parameters.

IL-6 outcomes will be classified into three categories: (1) circulating IL-6; (2) tissue IL-6 protein; and (3) IL-6 mRNA/gene expression. These categories will not be considered biologically equivalent because they represent different levels of IL-6 regulation and localization.

Risk of Bias Assessment

Risk of bias will be assessed using the SYRCLE Risk of Bias Tool, which was specifically developed for animal studies and adapted from the Cochrane risk-of-bias framework to account for characteristics of experimental animal research (Hooijmans et al., 2014). The assessment will cover selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias.

Data Synthesis

Because substantial heterogeneity among studies is anticipated, the primary synthesis will be narrative. Studies will be grouped according to age, strain, sex, tissue or specimen source, IL-6 measurement method, and experimental condition. Changes in IL-6 will be categorized as increased, unchanged, or decreased.

A meta-analysis will only be considered when a sufficient number of studies provide quantitative data with sufficiently comparable biological characteristics, experimental conditions, and IL-6 measurement methods.

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RESULTS AND DISCUSSIONS

Characteristics of the Identified Evidence

The initial literature search identified several experimental studies that directly evaluated IL-6 in rats of different ages. The available evidence included several strains, namely Fischer 344, Sprague-Dawley, Dark Agouti, Albino Oxford, and Fischer 344 × Brown Norway.

IL-6 was assessed across multiple biological compartments, including plasma, serum, adipose tissue, hypothalamus, peritoneal macrophages, gastrointestinal tissue, and vascular tissue. Differences in biological compartments represented a major source of heterogeneity in the interpretation of IL-6 responses during aging. The key characteristics of the verified studies are presented in Table 1.

Table 1. Characteristics of studies investigating the association between aging and IL-6 in Rattus norvegicus

Study	Strain	Age Groups (months)	Specimen/Tissue	Outcome	Main Findings
Foster et al., 1992	Fischer 344	3–5; 12–15; 24–27	Plasma	IL-6 after LPS stimulation	IL-6 responses were altered in aged rats
Belmin et al., 1995	Rat	10 vs. 30	Aortic wall	IL-6	IL-6 production was higher in aged rats
Terrazzino et al., 1997	Sprague-Dawley	3 vs. 24	Serum	IL-6 after LPS stimulation	IL-6 levels were higher in aged rats
Carter et al., 2007	Fischer 344 × Brown Norway	18–29	Adipose tissue	IL-6 secretion	Caloric restriction reduced IL-6 secretion
Stanojević et al., 2016	Dark Agouti/AO	Young vs. middle-aged	Peritoneal macrophages	IL-6	IL-6 responses were strain-dependent
Katharesan et al., 2016	Sprague-Dawley	3; 12–18; 24	Plasma/brainstem	Cytokines	Inflammatory responses differed between biological compartments

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2018 age-dependent study	Rat	2 vs. 24	Plasma/hypothalamus	IL-6	Plasma IL-6 was unchanged, whereas hypothalamic IL-6 mRNA expression increased
Chen et al., 2024	Naturally aging rats	5–21	Serum	IL-6 and allostatic load	IL-6 contributed to a panel of systemic age-related changes
Al-Dwairi et al., 2025	Sprague-Dawley	24	Ileum/colon	IL-6	IL-6 responses increased following hindlimb suspension

Changes in Systemic IL-6 in Aged Rats

The available evidence suggests that aging may increase systemic IL-6 responses, particularly when the immune system is exposed to an inflammatory stimulus. Foster et al. (1992) evaluated Fischer 344 rats aged 3–5, 12–15, and 24–27 months following lipopolysaccharide (LPS) stimulation and demonstrated altered cytokine responses in the aged group.

These findings are consistent with those of Terrazzino et al. (1997), who reported higher serum IL-6 levels in 24-month-old Sprague-Dawley rats than in 3-month-old rats following intracerebroventricular LPS stimulation. Interestingly, TNF did not show a similar pattern of increase, suggesting that aging may result in selective remodeling of cytokine responses.

However, increased systemic IL-6 is not consistently observed. In an age-dependent study of 2- and 24-month-old rats, plasma IL-6 levels remained relatively unchanged, whereas hypothalamic IL-6 mRNA expression increased in aged rats (2018). These findings indicate that circulating IL-6 measurements may not always serve as a surrogate marker of tissue-specific inflammation.

Influence of Tissue Compartment

Differences between circulating and tissue compartments represent one of the major findings of the available evidence. The 2018 study demonstrated that age-related changes in IL-6 were more evident in the hypothalamus than in plasma. Thus, inflammaging may occur locally without producing a corresponding change in circulating inflammatory biomarkers.

Katharesan et al. (2016) similarly demonstrated that age-related cytokine changes differed between plasma and brainstem. These findings support the

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concept that aging may produce a compartmentalized inflammatory response rather than a uniform increase in inflammation throughout the body.

In adipose tissue, Carter et al. (2007) showed that caloric restriction in aged rats reduced IL-6 secretion. This finding indicates that adipose tissue may serve as a source of inflammatory mediators contributing to inflammaging, particularly in the context of changes in body composition.

Influence of Strain

Stanojević et al. (2016) demonstrated differences in macrophage IL-6 responses between Dark Agouti and Albino Oxford rat strains. In middle-aged Dark Agouti rats, basal IL-6 production was increased, whereas the response to LPS was altered. In contrast, the response pattern in Albino Oxford rats was not identical.

These findings indicate that strain is an important factor to consider in systematic reviews examining aging and IL-6. Findings obtained from Sprague-Dawley rats cannot necessarily be generalized to Fischer 344 or other rat strains.

Influence of Inflammatory Stimuli

One of the most consistent patterns across the available evidence is that aging may enhance IL-6 responses following inflammatory stimulation. In other words, age-related changes may become more apparent when the immune system is challenged than under basal conditions.

In aged rats, LPS produced higher IL-6 responses in several studies. Recent evidence also indicates that hindlimb suspension in 24-month-old Sprague-Dawley rats induced gastrointestinal inflammatory changes and increased IL-6, with responses varying across tissue segments (Al-Dwairi et al., 2025).

These findings suggest that inflammaging should not be understood solely as an increase in basal IL-6 levels, but also as an alteration in the capacity of the aging immune system to respond to inflammatory challenges.

IL-6 as a Component, Rather Than a Single Definition, of Inflammaging

The available evidence indicates that IL-6 has a strong biological association with age-related inflammation but cannot be considered a single biomarker that is consistently elevated in all aged rats. This concept is consistent with the hallmarks of aging framework, which places chronic inflammation within an interconnected network of aging mechanisms involving cellular senescence, mitochondrial dysfunction, altered intercellular communication, and dysbiosis (López-Otín et al., 2023). Therefore, changes in IL-6 are more likely to represent one component of a broader and more complex biological system.

Baechle et al. (2023) similarly emphasized the bidirectional relationship between chronic inflammation and multiple aging mechanisms. Tissue damage, metabolic alterations, immune dysfunction, and cellular senescence can generate inflammatory mediators, while chronic inflammation may further exacerbate tissue damage and accelerate age-related changes.

Why Is IL-6 Not Always Increased?

The heterogeneity of findings represents an important observation of this review. One possible explanation is that aging involves two concurrent processes: chronic low-grade inflammation and immunosenescence.

On the one hand, senescent cells and stressed tissues can produce pro-inflammatory mediators such as IL-6. On the other hand, the aging immune

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system undergoes functional alterations that may reduce its capacity to generate certain inflammatory responses. Consequently, the measured IL-6 response may depend on the balance between inflammatory mediator production and the functional capacity of the aging immune system.

This interaction may explain why some studies report increased IL-6 in aged rats, whereas others observe unchanged levels or even reduced expression in specific tissues.

Basal Inflammaging versus Stimulus-Induced Inflammation in Aged Animals

One of the most important interpretations of the available evidence is the need to distinguish between basal inflammaging and stimulus-induced inflammatory responses in aged animals.

An increase in IL-6 following LPS administration in aged rats does not necessarily indicate that IL-6 is consistently elevated under basal conditions. Rather, aging may alter the response threshold and dynamics of inflammatory responses.

In this context, the findings of Foster et al. (1992) and Terrazzino et al. (1997) are important because they demonstrated altered IL-6 responses following inflammatory stimulation. Conversely, studies that did not detect increased plasma IL-6 under specific conditions indicate that inflammaging should not be equated with a persistent elevation of circulating biomarkers.

Therefore, IL-6 in aged rats may be more appropriately regarded as an indicator of altered inflammatory responsiveness rather than merely an indicator of chronological age.

Biological Compartment Determines Interpretation

Differences between plasma and tissue compartments are important for understanding IL-6 responses. Increased hypothalamic IL-6 mRNA expression in the absence of a corresponding change in plasma IL-6 indicates that age-related inflammation may be tissue-specific. This finding is particularly relevant to studies of neuroinflammation because circulating biomarkers may have limited sensitivity for detecting inflammatory changes occurring within the central nervous system.

Similarly, alterations in IL-6 within adipose or gastrointestinal tissues may reflect local inflammatory processes that do not necessarily produce circulating changes of comparable magnitude.

Therefore, future studies should not rely exclusively on serum or plasma IL-6 but should consider assessment of tissues relevant to the underlying biological hypothesis.

Role of Adipose Tissue and Metabolism

Adipose tissue is an important source of inflammatory mediators. During aging, increased adiposity may enhance the pro-inflammatory environment through interactions among adipocytes, macrophages, and cytokine mediators.

Carter et al. (2007) provided important evidence that caloric restriction in aged rats reduced IL-6 secretion from adipose tissue and improved physical performance-related parameters. These findings suggest that the relationship between aging and IL-6 may be mediated, at least partly, by changes in body composition.

Accordingly, studies comparing young and aged rats should consider body weight, fat mass, diet, and metabolic status as potential confounding factors.

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Strain as a Source of Heterogeneity

Differences among rat strains represent an important reason why findings from animal aging studies cannot always be directly combined.

Stanojević et al. (2016) demonstrated different inflammatory responses between Dark Agouti and Albino Oxford rats despite comparable age-related conditions. These findings suggest that genetic background may influence basal inflammation, macrophage phenotype, and responses to LPS.

The implication for systematic reviews is that IL-6 findings should be analyzed according to strain. Treating all strains as a homogeneous population may lead to overly simplified conclusions.

IL-6 and Cellular Senescence

IL-6 is closely associated with the senescence-associated secretory phenotype (SASP). When cells enter a senescent state, alterations in their secretory phenotype can generate various inflammatory mediators that influence the surrounding tissue environment.

This relationship may help explain how cellular senescence contributes to inflammaging. However, increased IL-6 alone is insufficient to demonstrate the presence of cellular senescence. Establishing this mechanism would ideally require concurrent assessment of senescence markers such as p16^INK4a, p21^CIP1, SA-β-gal, or other SASP components.

Therefore, future studies should integrate IL-6 measurements with senescence markers and tissue functional parameters to establish more robust relationships between inflammation and biological aging.

IL-6 in the Context of Allostatic Load

The study by Chen et al. (2024) provides a broader perspective by positioning IL-6 within a larger biomarker system. In this longitudinal study, naturally aging rats aged 5–21 months were assessed for IL-6 together with CRP, corticosterone, lipid parameters, vitamin D, and immune-related variables to construct an allostatic load measure.

The allostatic load score progressively increased with age. These findings support the concept that biological aging represents the cumulative burden of multisystem stress and that IL-6 should therefore be interpreted as one component of this interconnected network rather than as a single surrogate marker of biological age.

Methodological Implications

The heterogeneity of the available evidence also indicates the need for more standardized reporting in animal aging research. ARRIVE 2.0 emphasizes comprehensive reporting of animal characteristics, experimental design, sample size, outcomes, and statistical methods to facilitate evaluation and reproducibility (Percie du Sert et al., 2020).

Within a systematic review, variables such as strain, sex, age, housing conditions, diet, measurement methods, and inflammatory stimuli should be systematically extracted because these factors may contribute substantially to biological heterogeneity.

In addition, application of the SYRCLE Risk of Bias Tool is important for systematically assessing the risk of bias in animal studies (Hooijmans et al., 2014).

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CONCEPTUAL MODEL

Based on the available evidence, the relationship between aging and IL-6 can be conceptualized as follows:
Aging → altered inflammatory responsiveness → compartment- and stimulus-dependent IL-6 response

LIMITATIONS

This review has several methodological limitations. First, the available primary studies used heterogeneous rat strains, ages, sexes, tissues, and experimental conditions, limiting direct comparisons across studies. Second, some studies assessed IL-6 as a secondary outcome; consequently, information on effect sizes and data variability was not always reported comprehensively.Third, differences in IL-6 measurement methods, including protein-based assays, bioassays, and mRNA analyses, may produce outcomes that are not fully biologically equivalent. Fourth, animal studies often provide limited reporting of randomization, allocation concealment, and blinding, which may result in an "unclear" risk-of-bias judgment for several domains. Fifth, the final PRISMA flow numbers and the number of studies meeting all eligibility criteria cannot yet be determined in this draft because the final searches across all databases and full-text screening have not been completed. Therefore, the findings presented here should be regarded as a provisional evidence synthesis based on verified studies, rather than a definitive representation of the entire available literature.

CONCLUSIONS

IL-6 is an important mediator of age-related inflammation in Rattus norvegicus models; however, the available evidence does not support the conclusion that IL-6 is consistently elevated in all aged rats. Some studies have demonstrated increased IL-6 levels in aged rats, particularly following inflammatory stimuli such as lipopolysaccharide, whereas others have reported relatively unchanged circulating IL-6 levels despite increased IL-6 expression in specific tissues.

This heterogeneity suggests that inflammaging in rats is more appropriately understood as an alteration in inflammatory regulation and responsiveness influenced by biological compartment, strain, age, metabolic status, and inflammatory stimuli. Thus, IL-6 may serve as one biomarker of inflammaging, but should not be used as a single biomarker for determining biological aging.

Interpretation of IL-6 in aging research should consider the sample source, measurement method, metabolic status, and other inflammatory or senescence markers. Integrating IL-6 with CRP, TNF-α, IL-1β, NF-κB, p16, p21, SA-β-gal, and SASP markers may provide a more comprehensive assessment of the inflammaging process.

RECOMMENDATIONS

Future studies should employ longitudinal designs with multiple age points to distinguish changes attributable to chronological aging from those resulting from disease or experimental stimuli. The inclusion of multiple rat

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strains and both sexes is also warranted to determine the generalizability of IL-6 responses.

Experimental studies should simultaneously assess IL-6 in serum/plasma and relevant target tissues to better characterize the relationship between systemic and tissue-specific inflammation. IL-6 measurements should also be combined with markers of cellular senescence and the senescence-associated secretory phenotype (SASP) to strengthen the mechanistic understanding of the relationship between senescence and inflammaging.

Furthermore, future studies should comprehensively report animal characteristics, randomization, blinding, sample size, and analytical methods in accordance with ARRIVE 2.0. Improved reporting quality would strengthen the evidence base for animal research and facilitate the inclusion and interpretation of findings in future systematic reviews.

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