SCIENCE HUB REVIEW
2026
Volume 1
Issue 4
www.sciencehubreview.uz
ILMIY ELEKTRON JURNAL

IMMUNOSENESCENCE AND CHRONIC LOW-GRADE INFLAMMATION: MOLECULAR MECHANISMS, BIDIRECTIONAL INTERACTIONS, AND CLINICAL IMPLICATIONS

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Introduction. Aging is associated with progressive remodeling of the immune system and changes in inflammatory regulation. Immunosenescence describes age-related alterations in immune cell composition and function, whereas inflammaging refers to persistent, low-grade systemic inflammation that develops with aging, often without overt acute infection [5,7].

Immunosenescence affects both innate and adaptive immunity. Reduced thymic output, altered lymphocyte differentiation, impaired antigen-specific responses, and changes in innate immune activity may compromise host defense. Inflammaging, in contrast, involves sustained inflammatory signaling that can disrupt tissue homeostasis and contribute to organ dysfunction [12].

These processes are biologically interconnected. Cellular senescence, mitochondrial stress, altered nutrient sensing, and impaired clearance of damaged cellular components provide potential mechanistic links between them. Persistent inflammatory mediators may aggravate immune dysfunction, while impaired immune surveillance may allow senescent cells and inflammatory stimuli to accumulate [4,6,16].

Chronic inflammation has been associated with cardiovascular disease, metabolic disorders, frailty, and neurodegenerative conditions. However, the direction and strength

of these relationships vary across diseases and individuals [9]. Understanding the mechanisms connecting immunosenescence and inflammaging is therefore essential for distinguishing causal pathways from associated biomarkers.

This review examines the principal cellular and molecular mechanisms linking immunosenescence with chronic low-grade inflammation and discusses their clinical implications.

Methods. A narrative literature review was conducted using peer-reviewed publications on immunosenescence, inflammaging, cellular senescence, inflammatory signaling, mitochondrial dysfunction, and age-related diseases.

Relevant publications were identified through biomedical databases and scientific journal platforms, including PubMed and publisher databases. Foundational studies and reviews addressing the biological mechanisms of immune aging were considered alongside more recent publications.

The literature was organized into five thematic categories:

1. Age-associated changes in innate and adaptive immunity.
2. Cellular and molecular mechanisms of chronic inflammation.
3. Bidirectional interactions between immune dysfunction and cellular senescence.
4. Biomarkers and clinical consequences.
5. Potential therapeutic approaches and research priorities.

The findings were synthesized qualitatively. No formal systematic-review protocol, quantitative risk-of-bias assessment, or meta-analysis was performed. Accordingly, this article represents a narrative synthesis rather than an exhaustive systematic review.

Results. Immunosenescence involves structural, cellular, and functional changes in innate and adaptive immunity. It should not be interpreted as uniform immunosuppression; instead, it reflects an altered balance between protective immune responses, immune regulation, and inflammatory activity [7,8,12].

Adaptive immunity. Thymic involution reduces the output of naïve T lymphocytes and limits T-cell receptor diversity. Repeated antigenic stimulation contributes to changes in T-cell differentiation and the accumulation of highly differentiated T cells with altered

proliferative capacity. B-cell aging may impair antibody production, affinity maturation, and responses to novel antigens and vaccination.

Innate immunity. Aging is associated with functional changes in monocytes, macrophages, neutrophils, and natural killer cells. Alterations in chemotaxis, phagocytosis, antigen presentation, and inflammatory regulation may compromise pathogen clearance and the resolution of inflammation.

Immune surveillance. The accumulation of senescent cells and damaged cellular components may reflect an imbalance between cellular damage and immune-mediated clearance. Insufficient clearance can facilitate persistent inflammatory signaling, although the magnitude of these effects varies among tissues and individuals [12].

Consequently, immunosenescence may simultaneously reduce the effectiveness of selected protective immune responses and contribute to dysregulated inflammation.

Inflammaging is maintained by interacting cellular processes rather than a single inflammatory pathway. The principal mechanisms are summarized below.

Cellular senescence is a state of stable proliferative arrest accompanied by changes in cellular metabolism, gene expression, and secretory activity. Senescent cells may release a senescence-associated secretory phenotype comprising inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes.

SASP components, including IL-6, IL-1 family mediators, and chemokines, can modify the surrounding tissue environment and promote secondary senescence in neighboring cells. Although cellular senescence contributes to tumor suppression, tissue repair, and normal development, persistent accumulation of senescent cells may become detrimental [3,17].

Mitochondrial dysfunction contributes to altered energy metabolism, oxidative stress, and inflammatory signaling. Mitochondrial components released into the cytoplasm or extracellular environment can act as damage-associated molecular patterns (DAMPs), activating innate immune pathways.

Mitochondrial stress and mitokines may also influence immune cell function and systemic metabolic regulation. These mechanisms provide a potential connection between cellular energy imbalance, immunosenescence, and inflammaging [2].

Nuclear factor-kappa B (NF-κB) regulates the expression of numerous inflammatory mediators. Persistent activation of this pathway can promote cytokine and chemokine production, thereby sustaining inflammatory activity.

Inflammasomes, particularly the NLRP3 inflammasome, contribute to caspase-1 activation and the maturation of IL-1β and IL-18. Age-associated cellular stress and metabolic dysfunction may favor inflammasome activation in susceptible biological contexts. However, the contribution of individual pathways differs among tissues and diseases [12].

Autophagy facilitates the removal and recycling of damaged proteins and organelles. Insufficient autophagic activity can allow dysfunctional mitochondria and other cellular components to accumulate, promoting inflammatory signaling.

Impaired clearance of senescent cells and cellular debris may further prolong inflammatory stimulation. These processes interact with altered nutrient sensing and other biological hallmarks of aging, reinforcing the relationship between cellular dysfunction and chronic inflammation [13,17].

The relationship between immunosenescence and inflammaging is bidirectional and involves three interconnected mechanisms.

First, immune dysfunction can reduce the efficient elimination of pathogens, damaged cells, and senescent cells. Persistent biological stimuli may consequently maintain innate immune activation and inflammatory mediator production.

Second, prolonged exposure to inflammatory cytokines and other stress signals can alter immune cell metabolism, differentiation, and functional responses. These changes may further compromise immune regulation and the resolution of inflammation.

Third, senescent immune and non-immune cells can release SASP factors that modify the local tissue environment. These factors may recruit inflammatory cells, induce secondary senescence, and extend inflammatory signaling beyond the original site of damage [3,16].

The interaction can be represented conceptually as follows:

Age-associated cellular damage → immune dysfunction and senescent cell accumulation → persistent inflammatory signaling → further immune and tissue dysfunction.

This model describes a potential self-reinforcing cycle rather than a universal sequence. Immunosenescence and inflammaging are influenced by genetic factors, infection history, metabolic health, environmental exposures, and lifestyle [6,7]. Their severity and interaction therefore differ among individuals.

Several biomarkers are used to investigate inflammaging and immune aging. However, no single biomarker reliably distinguishes these processes.

Biomarker or parameter	**Biological relevance**	**Important limitation**
C-reactive protein (CRP)	Systemic inflammatory activity	Nonspecific; affected by infection and other inflammatory conditions
Interleukin-6 (IL-6)	Inflammatory signaling and systemic responses	Influenced by acute illness and metabolic status
Interleukin-1β (IL-1β)	Inflammasome-associated signaling	Circulating levels may not reflect tissue-level activity
Tumor necrosis factor-alpha (TNF-α)	Inflammatory signaling and tissue regulation	Not specific to aging
Naïve and memory T-cell subsets	Adaptive immune remodeling	Requires standardized immunophenotyping
Senescence-associated markers	Cellular senescence and associated pathways	No single marker identifies all senescent cells reliably

Elevated inflammatory markers have been associated with cardiovascular disease, type 2 diabetes, frailty, neurodegenerative disorders, and other chronic conditions. Persistent inflammation may contribute to disease progression, but these associations do not establish inflammaging as the sole cause of these conditions [4,9].

Age-related immune dysfunction is also relevant to infection susceptibility and vaccine responsiveness. Nevertheless, immune aging is heterogeneous, and chronological age alone does not adequately characterize individual immune function.

Discussion. The reviewed literature supports a close biological relationship between immunosenescence and inflammaging. Although they represent different aspects of aging, their underlying mechanisms overlap through cellular senescence, mitochondrial dysfunction, altered innate immune activation, and impaired clearance of damaged cells [2,3,7].

A central feature of this relationship is the coexistence of diminished protective immunity and increased basal inflammatory activity. This apparent paradox reflects the complexity of the aging immune system: selected immune responses become less effective, while other pathways remain chronically activated. Persistent inflammation may therefore coexist with impaired pathogen clearance, altered antigen-specific responses, and insufficient immune surveillance.

The distinction between immunosenescence and inflammaging is clinically important. Immunosenescence primarily describes age-associated changes in immune competence, whereas inflammaging describes persistent inflammatory activity. Neither process should be inferred solely from an isolated increase in CRP or a single cytokine measurement.

Several limitations of the current evidence must be acknowledged. First, much of the mechanistic evidence comes from experimental models, while human studies frequently establish associations rather than causation. Second, inflammatory markers are influenced by comorbidities, body composition, medication use, and environmental exposures. Third, senescence markers are not entirely specific, and immune aging varies substantially among individuals [9,12,13].

Future studies should integrate longitudinal inflammatory measurements, immune cell phenotyping, functional immune assays, and clinical outcomes. Standardized definitions

of immunosenescence and inflammaging would improve comparability across studies. Research should also distinguish beneficial, transient inflammatory responses from persistent inflammation that contributes to tissue damage.

Conclusion. Immunosenescence and chronic low-grade inflammation are distinct but interconnected processes in biological aging. Age-associated changes in immune cell function, cellular senescence, mitochondrial dysfunction, inflammatory pathway activation, and impaired cellular clearance provide plausible mechanisms linking them. Their interaction may sustain inflammatory activity while reducing the effectiveness of protective immune responses, contributing to age-related disease susceptibility. However, causal relationships and the clinical value of individual biomarkers require further validation. Future research should prioritize longitudinal human studies and targeted interventions that preserve immune competence while limiting persistent, maladaptive inflammation.

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