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Immunosenescence and Chronic Low-Grade Inflammation: Molecular Mechanisms, Bidirectional Interactions, and Clinical Implications

Berdikulova Aziza Khaydarkul kizi

(Teacher at the Department of Medical Fundamental Sciences, Faculty of Medicine, Gulistan State University)

berdiqulovaaziza223@gmail.com

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Background. Immunosenescence and chronic low-grade inflammation, known as inflammaging, are interconnected biological processes associated with aging. Immunosenescence involves progressive alterations in innate and adaptive immunity, including reduced immune responsiveness, impaired immunological memory, and diminished immune surveillance. Inflammaging is characterized by persistent, low-grade systemic inflammation that occurs without an overt acute infectious stimulus. These processes interact bidirectionally and contribute to increased susceptibility to infections, reduced vaccine responsiveness, cardiovascular disease, metabolic disorders, neurodegeneration, and certain malignancies [1, 4, 5].

Materials and Methods. This thesis is based on a narrative review of scientific literature concerning immunosenescence, cellular senescence, inflammaging, and age-related inflammatory disorders. Relevant publications were identified through biomedical literature sources, including PubMed and peer-reviewed journals. The review focused on immune-cell alterations, inflammatory signaling pathways, cellular stress responses, disease associations, and emerging therapeutic approaches. No original experimental data were collected.

Results and Discussion. Immunosenescence is associated with thymic involution,

decreased production of naïve T lymphocytes, reduced T-cell receptor diversity, accumulation of highly differentiated lymphocytes, and impaired B-cell responses. Age-related changes in monocytes, macrophages, dendritic cells, and natural killer cells also affect pathogen recognition, antigen presentation, and immune surveillance. Consequently, older individuals may exhibit reduced immune responses to infections and vaccination despite increased basal inflammatory activity [4, 5].

At the molecular level, DNA damage, telomere attrition, mitochondrial dysfunction, oxidative stress, epigenetic alterations, and impaired autophagy contribute to cellular senescence and immune dysfunction. Senescent cells may develop a senescence-associated secretory phenotype (SASP), characterized by the release of pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodeling enzymes. Important mediators include interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α). Persistent production of these mediators can alter tissue homeostasis and promote inflammatory signaling in neighboring cells [2, 6, 7].

Several molecular pathways contribute to inflammaging, particularly nuclear factor kappa B (NF-κB), the NLRP3 inflammasome, and the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) pathway. Mitochondrial damage, cytosolic DNA accumulation, and other damage-associated molecular patterns can activate innate immune signaling. Persistent activation of these pathways sustains inflammatory responses and links cellular damage with age-related tissue dysfunction [1, 6, 7].

The relationship between immunosenescence and inflammaging is bidirectional. First, age-associated immune dysfunction may reduce the efficient clearance of senescent cells, damaged cellular components, and persistent pathogens, facilitating the accumulation of inflammatory mediators. Second, chronic inflammatory signaling can disrupt immune-cell metabolism, impair lymphocyte function, and promote further cellular senescence. This self-reinforcing cycle contributes to progressive immune dysregulation and tissue damage [1, 4, 5].

Clinically, immunosenescence and inflammaging are associated with increased

susceptibility to infections, impaired vaccine responses, atherosclerotic cardiovascular disease, type 2 diabetes, neurodegenerative disorders, and certain cancers. Nevertheless, the strength and nature of these associations vary across conditions. Genetic background, chronic infections, microbiome composition, nutritional status, physical activity, and comorbidities may influence the degree of immune aging and systemic inflammation [1, 4, 5].

Potential strategies for mitigating these processes include regular physical activity, balanced nutrition, vaccination, and effective management of chronic diseases. Senolytic agents, which aim to eliminate selected senescent cells, and senomorphic approaches, which aim to modify their harmful secretory activity, are promising research directions. However, their long-term safety, efficacy, and clinical benefits require further evaluation in well-designed human studies [2, 3, 7].

Conclusion. Immunosenescence and inflammaging are interdependent processes that contribute to age-associated immune dysfunction and chronic disease. Their interaction involves cellular senescence, SASP-mediated inflammation, mitochondrial dysfunction, DNA damage, altered immune-cell metabolism, and persistent activation of inflammatory signaling pathways. Understanding these mechanisms may support the development of targeted interventions to preserve immune competence, reduce chronic inflammatory burden, and improve healthspan. Further longitudinal and interventional studies are required to establish causal relationships, identify reliable biomarkers, and determine the clinical effectiveness of emerging therapeutic strategies.

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