

The Phenomenon of Senile Resistance: The Role of Chronic Inflammation in Elderly Patients

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Abstract

Population aging increases the risk of disease, polypharmacy, and functional decline. However, older adults differ greatly in their ability to maintain health despite similar medication burdens. This phenomenon, known as senile resistance, may be influenced by chronic low-grade inflammation, immunosenescence, and inflammaging. These processes can affect hepatic drug metabolism and blood-brain barrier function, altering individual responses to medications. Understanding these mechanisms may support more personalized and safer pharmacotherapy in older adults.

Key Words: senile resistance; immunosenescence; inflammaging; polypharmacy; cytochrome P450; CYP3A4; P-glycoprotein; neutrophil-to-lymphocyte ratio; interleukin-6; geriatrics

Introduction

Population aging is one of the key medical and social challenges of our time [1]. According to projections, by 2050 the number of people aged 60 years and older will reach 2 billion, accounting for more than 20% of the total population [1].

In clinical practice, there is a well-known phenomenon observed: some elderly patients retain functional independence despite taking five or more medications, while others experience decompensation even with minimal drug burden (two to three drugs) [6, 12]. In gerontology, the term senile resistance is used to describe this phenomenon—the ability of the organism to resist the accumulation of age-related pathological changes and maintain systemic homeostasis under conditions of external and internal stressors [6]. However, the molecular and physiological mechanisms underlying this phenomenon remain the subject of active investigation [7, 9].

A key modifiable factor determining individual resistance to stress, including drug therapy, is the state of low-grade chronic inflammation [7, 16]. This phenomenon develops as a result of immunosenescence – an age-related dysfunction of the immune system characterized by T-cell exhaustion and accumulation of senescent cells with a proinflammatory secretory phenotype [8, 20]. Inflammaging exerts systemic effects, particularly on the liver and the blood-brain barrier, accompanied by alterations in the activity of xenobiotic-metabolizing enzymes and the function of transport proteins [6, 10].

Immunosenescence and Inflammaging: Pathogenetic Mechanisms

Immunosenescence is a progressive dysfunction of the immune system that develops with age [1, 16]. Key mechanisms of this process include thymic involution, leading to reduced production of naïve T-cells, as well as the accumulation of terminally differentiated effector cells [8, 16]. Persistent cytomegalovirus infection plays a particular role in accelerating immunosenescence; it persists lifelong in the organism and continuously stimulates specific T-cells, accelerating their exhaustion [7, 18].

Concurrently with immunosenescence, chronic sterile low-grade inflammation develops [3, 9]. It is based on three key pathogenetic mechanisms [9, 16].

The first mechanism is associated with senescent cells and their secretory phenotype [2, 7]. Cells that have reached the state of senescence (irreversible cell cycle arrest) acquire the SASP (senescence-associated secretory phenotype) and actively secrete proinflammatory cytokines – IL-6, IL-8, TNF- α [2, 7, 16]. According to data published in *Nature Aging* in 2025, senescent cells evade immune surveillance by increasing the expression of ganglioside GD3 on their surface, which suppresses NK-cell activity and allows aging cells to accumulate in tissues, including the liver, lungs, kidneys, and bone tissue [2].

The second mechanism is driven by mitochondrial dysfunction [18-21]. Mitochondrial damage accumulates with age [9]. Reduced efficiency of mitochondrial quality control leads to mitochondrial components entering the cytoplasm and triggering inflammatory signals through pattern-recognition receptors [9, 16].

The third mechanism is associated with energy imbalance [3, 16]. According to the modern Brain-Body Energy Conservation model, the relationship between immunosenescence and inflammation is mediated by an adaptive response: chronic inflammation requires significant energy resources, leading to reduced immune system activity [3]. This mechanism provides short-term adaptation; however, in the long term, it contributes to increased susceptibility to infections and accelerates the development of age-associated diseases [3, 7].

The energy conservation hypothesis has recently received confirmation in large population studies [3]. Analysis of data from the US Health and Retirement Study and the UK Biobank showed that the key inflammatory marker TNFR1 mediates age-related increases in the levels of immunosuppressive proteins IL-10 and GDF-15, which suppress the immune response to infections, and also contributes to the reduction of naïve T-cell counts [3]. These data confirm that immunosenescence is an adaptive response aimed at redistributing energy resources under conditions of chronic inflammation, with the long-term cost of such adaptation being increased susceptibility to infections and accelerated development of age-associated diseases [3, 7].

Thus, immunosenescence and inflammation form a pathophysiological vicious cycle: senescent cells sustain chronic inflammation, which in turn accelerates the exhaustion of the naïve T-cell pool, while reduced immune surveillance increases the organism's vulnerability to infectious agents and stressors, including drug therapy [7, 9, 16]. It is this balance that determines sensitivity to drug therapy and underlies the phenomenon of senile resistance [6, 16].

Impact of Chronic Inflammation on Drug Metabolism and Transport

The key mechanism linking immunosenescence with polypharmacy is the modulation of drug-metabolizing enzyme activity under the influence of proinflammatory cytokines [15, 19]. Chronic inflammation is a powerful regulator of enzyme systems involved in xenobiotic metabolism [4-11]. It is this effect that determines whether polypharmacy will be safe or lead to toxic complications [7-12].

Suppression of cytochrome P450. The most well-studied effect is the influence of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) on cytochrome P450 enzymes, primarily CYP3A4—the major hepatic enzyme metabolizing more than 50% of all drugs [10, 12]. Proinflammatory cytokines suppress CYP3A4 expression by 5- to 8-fold through reducing mRNA levels of the nuclear receptors PXR and CAR in hepatocytes [10-14].

In recent years, an important role of microRNAs in the regulation of CYP450 during inflammation has been established [15]. Proinflammatory cytokines induce the expression of miR-155, which directly binds to the 3'-untranslated region of CYP3A4 mRNA and suppresses its translation [15]. This post-transcriptional mechanism represents an important addition to previously described transcriptional effects and explains the persistence of enzyme suppression even after normalization of cytokine levels [15].

Impairment of transport protein function. Along with biotransformation enzymes, P-glycoprotein (P-gp) – a transporter expressed in the liver, kidneys, and on the apical membrane of blood-brain barrier endothelial cells – is a target of proinflammatory cytokines [11-14]. During inflammation, P-glycoprotein function declines as the protein is internalized from the cell surface [11]. This leads to two important consequences: drugs are less efficiently eliminated from the liver and kidneys, and they penetrate more readily across the blood-brain barrier into the brain [13-21].

Clinical Markers for Assessing Senile Resistance

The theoretical mechanisms outlined above require verification in clinical practice [6, 12]. In this regard, the search for accessible markers reflecting

immune-inflammatory status and enabling prediction of individual tolerance to polypharmacy in elderly patients is of considerable importance [7, 17].

Neutrophil-to-lymphocyte ratio (NLR). The most accessible and informative marker of systemic inflammation in older adults is the ratio of neutrophils to lymphocytes in the complete blood count [17-21]. NLR reflects the balance between innate (neutrophils) and adaptive (lymphocytes) immunity and is regarded as a universal marker of stress and inflammation [4, 20]. In geriatric practice, elevated NLR is associated with adverse outcomes [9, 19]. For instance, NLR > 2.8 significantly increases mortality risk in patients with sarcopenia [21].

Recent studies have refined the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in geriatric patients [4, 5]. In a cohort study of hospitalized elderly patients (mean age 87 years), elevated NLR was an independent predictor of 90-day mortality, with an optimal threshold value for risk stratification of 12.63 [4]. Interestingly, this association was significantly stronger in women (adjusted HR 2.50 vs. 1.34 in men), indicating gender differences in the immune-inflammatory response and highlighting the need to consider sex when stratifying risk in elderly patients [4-10]. Moreover, studies of long-lived populations show that lower NLR values are associated with successful aging, particularly in women, likely reflecting more effective immune regulation and less pronounced chronic inflammation [5, 19].

C-reactive protein and interleukin-6. More precise markers include CRP and interleukin-6 [17, 18]. IL-6 is a key proinflammatory cytokine that directly suppresses CYP3A4 activity [3, 14]. CRP > 3 mg/L is a marker of elevated cardiovascular risk and chronic inflammation [17, 18].

The Charlson Comorbidity Index is a widely used tool for assessing the severity of comorbid conditions [2, 16]. A number of studies demonstrate that high index values (e.g., >4) are associated with elevated levels of systemic inflammatory markers such as interleukin-6 and CRP, allowing it to be considered an indirect indicator of the inflammatory background in patients with significant multimorbidity [6, 12].

The Barthel Index is used to assess patients' activities of daily living [17]. A decrease in its score indicates functional decompensation, which may be caused by adverse effects of drug therapy [6, 17].

Conclusion

Thus, senile resistance is a multifactorial phenomenon underpinned by the balance between proinflammatory and anti-inflammatory components of immunosenescence [7, 9, 16]. Chronic inflammation, induced by the accumulation of senescent cells, acts as a systemic modulator of xenobiotic biotransformation [6, 10, 19].

It has been demonstrated that proinflammatory cytokines (IL-6, TNF- α , and IL-1 β) suppress CYP3A4 expression by 5- to 8-fold, attenuate P-glycoprotein activity at the blood-brain barrier, and reduce drug elimination from cells through inhibition of transporter proteins [8-14]. This creates conditions for drug accumulation and toxic reactions even at standard dosages [9, 15]. A vicious cycle emerges: inflammation driven by immunosenescence impairs pharmacokinetics, necessitating the prescription of new drugs to manage complications, which in turn exacerbates the inflammatory burden and polypharmacy [6-12].

In clinical practice, accessible markers of inflammation that may serve to assess the risk of adverse outcomes of polypharmacy include the neutrophil-to-lymphocyte ratio (NLR > 3.0), C-reactive protein (>5 mg/L), and interleukin-6 (>5 pg/mL) [5, 17, 20]. Integration of these indicators into geriatric protocols opens opportunities for safer personalized pharmacotherapy [7,12].

At the same time, the majority of available data have been obtained from models of acute inflammation or in specific conditions (rheumatoid arthritis, inflammatory bowel disease) [6-14]. Threshold cytokine levels at which clinically significant alterations in enzyme activity develop during physiological aging remain to be determined [11, 20].

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