Inflammation and aging: Unraveling cellular signals and innovative therapies

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Abstract

As we grow older, our body starts to experience persistent, low grade inflammation- referred to as inflammaging. Unlike the acute responses which promotes healing, this chronic inflammation acts as a wildfire which leads to initiation and progression of various age-related disorders including cardiovascular disease, metabolic and neurological disorders. Inflammaging arises as a result of combination of complex overlapping processes- cellular senescence, gradual weakening of the immune system (immunosenescence) and build up of cellular stress and damage. These process together create a self-reinforcing cycle that along with driving aging at cellular level also contributes in overall physical and mental decline. The article explores how inflammaging impacts different organs and tissues in the body. Additionally, it highlights the promising therapeutic strategies such as senolytic drugs, anti-inflammatory compounds, life-style modification, which aims at restoring healthy body and support resilient aging.

Keywords: Aging, cellular senescence, inflammation, immunosenescence, therapeutic strategies

1. Introduction

Aging refers to a complex biological process shaped by various factors including genetic suspectibility, lifestyle, metabolic alterations and enviromental contact. These factors gradually accumulates worsening the body system over the years and lead to functional decline of the tissues and organs. Among the many changes that occur due to aging, inflammaging has come out as a key contributor to age-related functional decline (1,2). Inflammaging refers to a state of persistent low-level chronic inflammation which acts as a menace for the body. This chronic response is fueled by variouss overlapping process, one among which is cellular senescence. In this phenomenon the cells permanently lose their ability to divide

because of DNA damage, telomerase shortening or oxidative stress- all of these acts as a stressor. The senescent cells then release a mix of bioactive compounds including cytokines, proteases, growth factors and chemokines collectively known as Senescence-associated secretory phenotype (SASP), which spreadout the inflammation and hinders the tissue repair process.

Another process contributing to inflammaging is immunosenescence, which refers to the gradual decline or weakning of immune response with aging. As individual grows older, the adaptive immune response weakens, losing its potential to fight pathogens or respond actively to vaccines, while the innate immune response becomes erratic, often hyperactive contributing to chronic inflammation. This imbalance is responsible for worsening the balanced state of body, increasing vulnerability to chronic diseases and infections (3).

These overlapping processes which includes cellular senescence, immunosenescence and molecular damage fuel a vicious cycle of inflammation, that accelarates aging, contributing to the intiation of age-related disorders including cardiovascular disorders, diabetes, cancer, neurodegeneration and sarcopenia (figure 1).

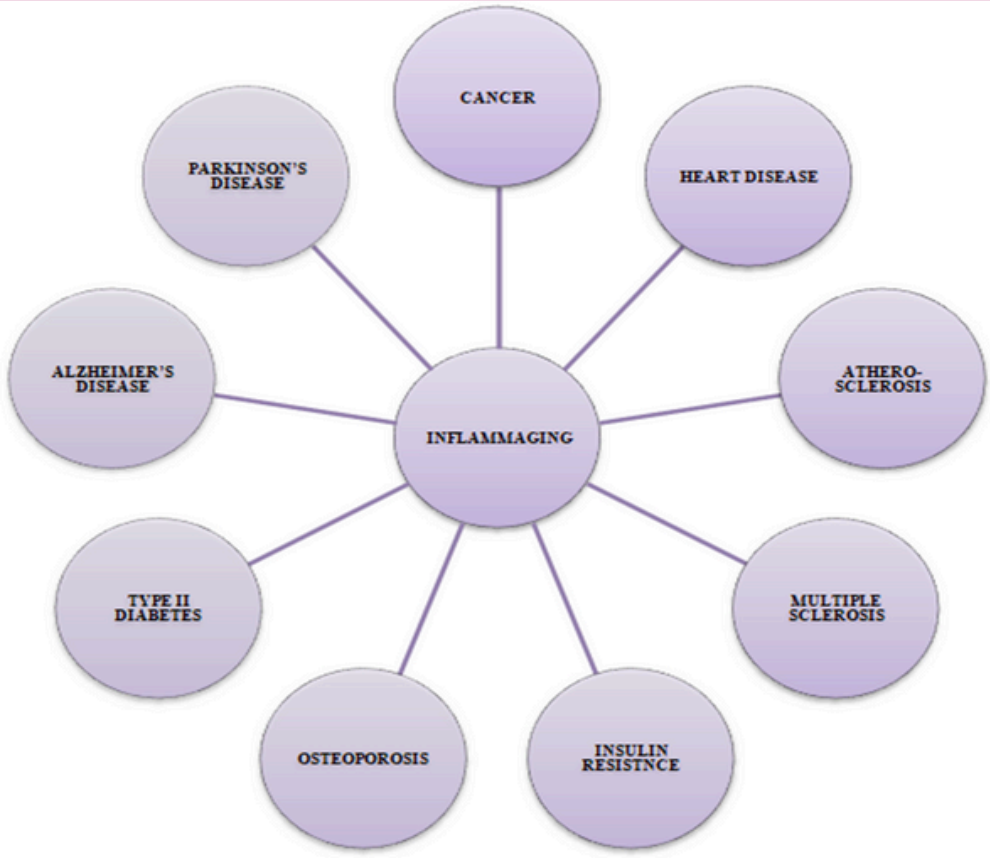

Figure 1. Spectrum of age-related diseases linked to chronic inflammation

Inflammaging has become a key focus area, with widespread growing interest in healthy aging. Researchers are exploring novel therapeutics such as senolytics, immuno-modulators in order to slow down or reduce the aging process, opening doors for resilient aging and improving quality of life of people.

2. Inflammaging at the cellular level

2.1. Senescence-associated secretory phenotype (SASP)

Cellular senescence refers to a state where the cells permanently lose their ability to divide, but remain active in terms of signalling and metabolism. Instead of becoming dormant, these cells begin to release wide range of biologically active substances collectively termed as SASP (Senescence-associated secretory phenotype). These bioactive compounds include pro-inflammatory cytokines like

(IL-1, IL-6, TNF-α), growth factors, chemokines and enzymes such as matrix metalloproteinases (MMPs), that are responsible for degrading matrix enzymes. SASP displays positive role by helping in wound healing and preventing cancer by halting damaged cells growth. But when the senescent cells keep on accumulating over time, the continuous release of SASP factors lead to chronic inflammation, disrupting normal tissue structure. These signals further spread to healthy cells inducing them to also undergo senescence. This further creates a dominant effect worsening situation by weakening the tissue functionality intensifying inflammation. This chain plays a key role in inflammaging, therefore understanding and exploring ways to suppress harmful effects of SASP and target the senescent cells is now the major focus area in order to promote healthy aging (4).

2.2. Hematopoietic stem cell (HSC) dysfunction

As one grows older, Hematopoietic stem cells (HSCs), the cells tasked with maintaining body's blood and immune cells beings to lose their efficiency. They lose their ability to self renew and forms more myeloid cells- cells of the innate immune system, at the expense of the lymphoid cells, which are important for adaptive immunity, with a resulting distorted immune response. This age-induced alteration is attributed to elevated amounts of pro-inflammatory signals including Interleukin (IL-1) and granulate colony stimulating factor (G-CSF). Second, the maintenance of the integrity of the milieu surrounding HSC's within bone marrow via signalling pathway CXCL12/CXCR4 fails with advancing age. Also, increased ROS and enhanced genomic instability, which deteriorates the ability of HSC's further are generated through aging. The overall impact of these alternations is a weakened immune system with an inflammatory bias. Inflammaging is a low grade chronic inflammation that is characteristic of aging and contributes significantly to the pathogenesis of age-related disease (5).

2.3. Immune cell aging

Various elements of the immune system face functional decline with growing age, with further leads to immunoscence. They are as follows:

- **2.3.1. Neutrophils:** Although their numbers remain relatively stable, aged neutrophils show reduced chemotaxis, phagocytic activity, and oxidative burst, impairing their ability to eliminate pathogens (6).
- **2.3.2. Monocytes/macrophages:** With aging, their characteristics shift toward a more pro-inflammatory state marked by elevated SASP secretion, while reduced autophagic activity results in the buildup of cellular debris and exacerbates inflammation (7).
- **2.3.3. Natural killer (NK) cells:** These cells experience a reduction in cytotoxic granule release and diminished cytokine production, weakening the response to tumors and viral infections (8).
- **2.3.4. B and T Lymphocytes:** Advancing age leads to a decline in lymphocyte diversity, diminished proliferative capacity, and weakened responsiveness to antigens. Moreover, there is a tendency toward pro-inflammatory memory cell phenotypes, which sustains chronic systemic inflammation (9).

3. Inflammaging at the organ level

3.1. Lymphoid organs

- **3.1.1. Bone marrow:** With age, both hematopoietic stem cells and mesenchymal stem cells (MSCs) exhibit senescence, reducing regenerative capacity and favoring myeloid-biased hematopoiesis.
- **3.1.2. Thymus:** Undergoes age-associated involution, leading to decreased production of naive T cells and impaired adaptive immunity.
- **3.1.3. Spleen and lymph nodes:** Structural changes such as fibrosis and disrupted architecture result in reduced lymphocyte trafficking and diminished antigen presentation, contributing to immune inefficiency (10).

3.2. Sterile organs

Inflammaging extends beyond the immune system and affects "sterile" organs—those not typically exposed to external pathogens:

3.2.1. Brain: Microglia and astrocytes become activated and senescent, releasing SASP factors that contribute to neuroinflammation, a key feature of neurodegenerative diseases such as Alzheimer's.

3.2.2. Heart:: Senescent cardiac fibroblasts and macrophage polarization toward an M1 phenotype promote fibrosis and impair contractility.

3.2.3. Kidneys: Age-related mitochondrial dysfunction, oxidative stress, and immune activation increase susceptibility to acute kidney injury and chronic kidney disease.

3.2.4. Liver: Senescent hepatocytes and activated hepatic stellate cells drive fibrogenesis, compromising liver function and promoting systemic inflammation.

3.2.5. Skin and lungs: Barrier integrity declines due to senescence and inflammation, with increased infiltration of immune cells and SASP-driven damage accelerating epidermal thinning, wrinkling, and pulmonary inflammation.

4. Mechanisms and triggers of inflammaging

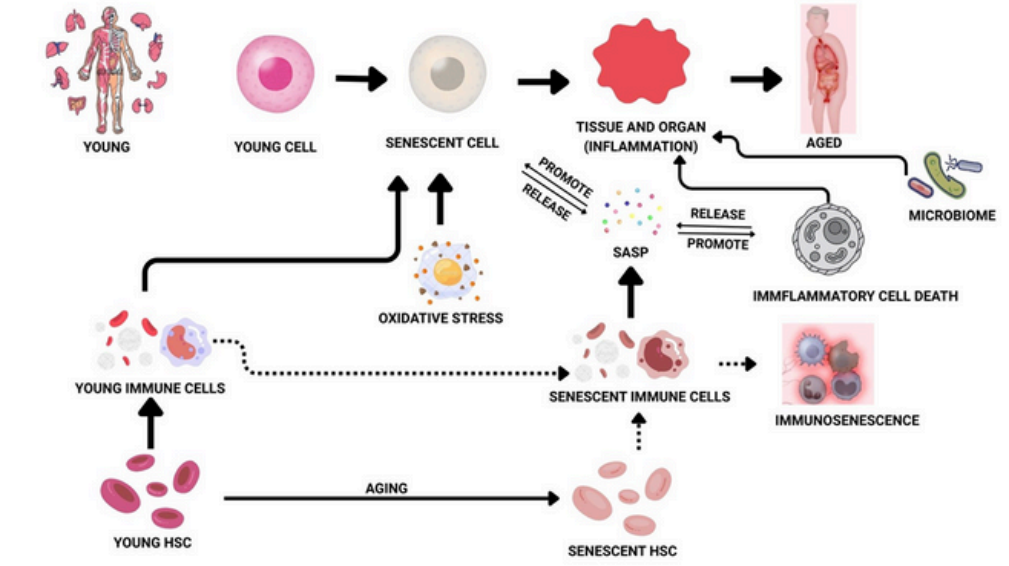

Figure 2. Inflammation at molecular, cellular, and organ levels, its triggers and mechanism of action

4.1. Oxidative stress and DNA damage

Prolonged oxidative stress results in the gradual accumulation of DNA damage, mitochondrial impairment, and activation of DNA damage response (DDR) mechanisms. A key pathway in this process involves NF-κB, a transcription factor that regulates the expression of numerous pro-inflammatory SASP elements. Continuous DDR activity helps maintain a persistent inflammatory milieu and sustains SASP expression, thereby reinforcing the cycle of Inflammaging (12).

4.2. Microbiome dysbiosis

Aging brings about notable shifts in the gut microbiome, characterized by decreased microbial diversity and a rise in pro-inflammatory bacterial populations. This imbalance, referred to as dysbiosis, compromises the gut barrier, enabling bacterial components like lipopolysaccharides to enter the bloodstream and initiate systemic inflammation. Additionally, age-related changes in the microbiota reduce the production of immune-regulating metabolites such as short-chain fatty acids (SCFAs), further impairing immune homeostasis (13).

4.3.Inflammatory cell death

Several forms of programmed cell death contribute to inflammaging (2):

4.3.1. Necroptosis: A form of lytic cell death that releases DAMPs and activates immune responses.

4.3.2. **Pyroptosis:** A form of programmed inflammatory cell death characterized by the activation of caspase-1 and gasdermin-D, leading to cell membrane pore formation and the release of pro-inflammatory cytokines such as IL-1β and IL-18.

4.3.3. **Ferroptosis:** Iron-dependent oxidative cell death, closely linked to lipid peroxidation.

4.3.4. **NETosis:** In neutrophils, the release of neutrophil extracellular traps (NETs) can promote chronic inflammation and tissue injury.

5. Therapeutic strategies targeting inflammaging

5.1. Senolytics and senomorphics

Senolytics are drugs that selectively induce apoptosis in senescent cells. Examples include dasatinib, quercetin, and navitoclax, which have shown promising results in animal models by improving physical function and reducing inflammation (14,15). Senomorphics modulate the SASP without killing the cells. Agents like rapamycin and metformin suppress mTOR signaling and SASP production, providing anti-inflammatory benefits (14,15).

5.2. Anti-inflammatory agents

NSAIDs inhibit cyclooxygenase enzymes but may cause gastrointestinal and cardiovascular side effects with long-term use. Cytokine inhibitors such as IL-1 (anakinra) and IL-6 (tocilizumab) blockers, show potential in modulating chronic inflammation but require careful monitoring (16).

5.3. Immunomodulation and stem cell therapies

Hematopoietic Stem cell transplantation (HSCT) has been investigated as a strategy for rejuvenating the aging immune system (17). Mesenchymal stem cells (MSCs) exhibit strong anti-inflammatory and immunomodulatory capabilities, demonstrating promise in preclinical studies for repairing tissue damage and enhancing immune responses (17).

5.4. Microbiome interventions

Restoring microbiome homeostasis can significantly reduce systemic inflammation. Strategies include (18)**:**

- Probiotics and prebiotics to enhance beneficial bacteria.
- Fecal microbiota transplantation (FMT) to reintroduce a healthy microbiome.
- Dietary fibers to boost SCFA production, reducing gut inflammation.

5.5. Lifestyle modifications

Aging and inflammation are greatly influenced by lifestyle choices (18):

- **Mediterranean diet:** Rich in anti-inflammatory compounds such as omega-3 fatty acids, polyphenols, and fiber.
- **Caloric restriction:** Extends lifespan in various species and reduces inflammatory markers.
- **Exercise:** Enhances anti-inflammatory cytokine production and improves immune surveillance.
- **Sleep hygiene and stress management:** Critical for maintaining circadian rhythm and hormonal balance, reducing systemic inflammation.

6. Conclusion

Inflammaging, that is referred to as low-grade chronic inflammation is recognized as the key hallmark of aging. It is closely linked with complex processes i.e. cellular senescence, immunosenescence and gradual organ deterioration. This chronic inflammation plays a central role in initiation and progression of various age-related disorders including cardiovascular, neurodegeneration and metabolic disorders. Understanding and research into the molecular drivers of inflammaging provides insights into potential therapeutic target for therapy. Promising interventions such as senolytics, gut-microbiome based therapies have helped regulate immune response, reducing systemic inflammation. These treatments when combined with life-style modifications such as having healthy diet, performing regular physical

exercise and taking adequate sleep has shown significant effective results. The target is not just expansion of lifespan but also healthspan- i.e. the years being lived in good health By delving deep into inflammaging, the Quality of life can be improved.

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