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COMMENTARY

IgG: an emerging hallmark of aging

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During the physiological aging process of organisms, the immune system undergoes characteristic alterations marked by progressive functional decline and homeostatic imbalance[1-3]. These alterations encompass multifaceted pathophysiological changes, including diminished differentiation capacity of hematopoietic stem cells, dysregulated effector functions of mature immune cells, and disruption of chronic low-grade inflammatory homeostasis[4,5]. This systemic degenerative phenomenon is commonly defined as immunosenescence[6]. The pathological hallmarks of immunosenescence predominantly manifest as thymic parenchymal atrophy-induced reduction in T-cell output, dysregulated the ratio of naïve to memory T-cell subsets, mitochondrial dysfunction-associated metabolic disturbances, and epigenetic modifications characterized by aberrant DNA methylation patterns[7,8]. Notably, emerging research evidence identifies immunoglobulin superfamily members, particularly immunoglobulin G (IgG), as novel biomarkers for evaluating aging trajectories and as participants in the process of immunosenescence.

Immunoglobulins, also known as antibodies, are glycoprotein molecules with specific recognition functions. They are synthesized and secreted by B lymphocytes (B cells). As key effector molecules of the adaptive immune system, immunoglobulins specifically recognize and bind to foreign antigens through their antigen-binding sites. They play critical roles in the host defense mechanism, including antigen recognition and binding, immune effector activation, pathogen neutralization, and the formation of immune memory. Immunoglobulins are classified into five isotypes—IgG, IgA, IgM, IgE, and IgD—based on structural differences in their heavy chain constant regions. These isotypes exhibit distinct molecular structures, tissue distributions, and immune functions, which contribute to the construction and regulation of the immune defense network through their synergistic effects[9,10]. Among them, IgG is the most abundant immunoglobulin isotype in serum, accounting for approximately 10%-20% of total serum proteins[11]. IgG plays a central role in the humoral immune response. It not only demonstrates efficient neutralizing activity but also mediates complement activation and antibody-dependent cell-mediated cytotoxicity via its Fc region, thereby aiding in pathogen clearance[12]. However, recent studies suggest that the function of IgG may extend beyond the traditional domain of immune defense. Increasing evidence points to its potential involvement in physiological processes such as aging and metabolic regulation. While these findings highlight novel roles of IgG, the underlying molecular mechanisms remain to be fully elucidated.

In a recent study, Ma et al. constructed a multi-organ aging atlas in mice using spatial transcriptomics technology and identified IgG as a novel aging biomarker involved in the multi-organ aging process[13]. Ma et al. selected mice aged 2 and 25 months as research models and mapped the spatiotemporal aging atlas of nine tissues, including the hippocampus, spinal cord, heart, lung, liver, small intestine, spleen, lymph node, and testis. They analyzed changes in over 70 different cell types across these organs during aging. Histological analysis of aging tissues typically reveals damage to previously well-ordered structures. To quantify this phenomenon, Ma et al. established a novel computational method for spatial transcriptome analysis to assess the degree of tissue disorder, introducing the concept of "organizational structural entropy" (OSE). They found that the hippocampus, spleen, lymph nodes, and liver exhibited the highest OSE levels, with immune cells—including microglia, macrophages, and plasmocytes—being preferentially enriched in the aging tissue areas with high OSE. Using algorithmic modeling, the researchers identified the most senescence-sensitive spots (SSS) in each organ. They observed a clear distance-dependent gene expression pattern in the SSS regions: the core of the SSS showed enrichment in genes related to humoral immunity and complement activation; the adjacent areas expressed genes associated with the senescence-associated secretory phenotype (SASP); and the distal areas exhibited restored expression of genes involved in ATP biosynthesis and the cell cycle. These findings suggest that SSS, acting as a center of intensified inflammation, causes damage to surrounding cells in a distance-dependent manner. Notably, immunoglobulin-related genes were specifically localized within the SSS microenvironment, driving the aging process in organs such as the lymph nodes and spleen. This IgG-mediated aging phenotype appears evolutionarily conserved, with similar age-dependent accumulation patterns observed across a variety of human tissues, such as the liver and lymph node.

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Mechanistic studies demonstrate that IgG can directly induce senescence in macrophages and microglia from human and mouse, promote the release of inflammatory factors, and potentially induce senescence in neighboring cells through paracrine signaling. These results suggest that IgG may act as a "source of infection", mediating aging between cells. *In vivo* experiments further corroborated the pro-aging effects of IgG. Direct injection of IgG into young mice induced aging in multiple tissues and organs throughout the body. Moreover, targeted reduction of IgG levels through antisense oligonucleotides (ASOs) delayed aging across various tissues and organs, indicating that IgG is a promising new target for aging intervention. Based on these findings, Ma et al. proposed the immunoglobulin-associated senescence phenotype (IASP), which not only expands the field of aging research but also opens new avenues for delaying aging and preventing or treating age-related diseases (**Fig. 1**).

Complementary investigations by Yu et al. revealed conserved IgG accumulation patterns in adipose tissue microenvironments, further substantiating its role as a hallmark of mammalian aging[14]. They compared the quantitative proteome of white adipose tissue from young (3 months old) and old (33 months old) mice and found that 93 proteins were significantly enriched (by more than two-fold) in the aging group, particularly within the 35 to 60 kDa size range. Notably, 45 of these proteins were immunoglobulins, with IgG showing the most significant age-related upregulation. Further tissue-specific analysis revealed that IgG accumulation in white adipose tissue exhibited a clear time-dependent pattern: a significant increase was detectable as early as 4 months of age, becoming more pronounced at 6 months, peaking at 18 months, and accumulating at levels considerably higher than in other tissues. This age-dependent IgG accumulation pattern was also confirmed in human adipose tissue. Caloric restriction (CR), a well-established and effective anti-aging intervention, was shown by Yu et al. to not only improve insulin sensitivity but also reduce circulating IgG levels by approximately 60%. Additionally, CR significantly inhibited IgG accumulation in white adipose tissue. However, supplementation with exogenous IgG reversed the metabolic benefits of CR, as evidenced by increased levels of inflammatory markers, upregulated senescence genes, and reduced insulin sensitivity. These findings suggest that IgG may act as an early-appearing, aging-related factor that contributes to metabolic dysfunction. Subsequent *in vivo* and *in vitro* mechanistic studies revealed that IgG activates the Ras/MEK/ERK signaling pathway, promoting macrophage secretion of TGF-β, which in turn induces adipose tissue fibrosis, ultimately leading to metabolic dysfunction. To further validate this observation, the researchers used a B cell-deficient (B^{null}) mouse model, which exhibited significantly reduced adipose tissue fibrosis and improved metabolic function during aging. However, because B^{null} mice lack all antibody subtypes, the specific role of IgG could not be assessed. Therefore, the researchers constructed a macrophage-specific FcRn (IgG receptor) knockout mouse model, which successfully blocked the age-dependent accumulation of IgG, significantly improved metabolic function, and extended the lifespan of the mice by approximately 12%. Building on these results, the researchers developed an antisense ASO strategy targeting FcRn, which effectively decreased IgG levels in the plasma, adipose tissue and liver, reversed white adipose tissue fibrosis in aged mice, and ameliorated metabolic dysfunction. These pioneering studies establish IgG as a key regulator of aging for the first time, offering a novel intervention strategy for the restoration of metabolic health (**Fig. 1**).

As the core effector molecule in the humoral immune response, IgG plays a crucial role in antimicrobial immunity. Consequently, previous studies focused on the diagnostic value and therapeutic applications of IgG in chronic infections and immunodeficiency disorders[15]. Notably, while significant increases in circulating IgG levels have been observed in elderly individuals and aging model animals for decades[16], systematic research on the accumulation pattern of IgG in tissues and its specific mechanisms in aging remains limited. Recent breakthrough studies, however, have for

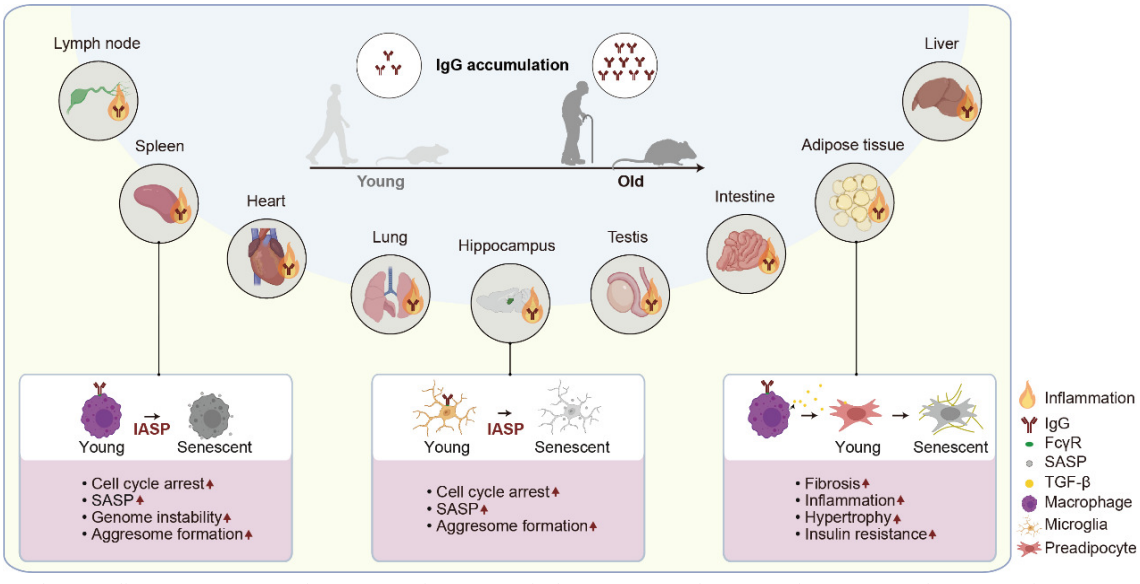

Figure 1 The schematic illustrates age-associated IgG accumulation in multiple tissues across humans and mice. IgG induces a novel senescent phenotype in macrophages and microglia, termed IASP. Furthermore, IgG indirectly promotes adipose tissue senescence through a macrophage-mediated mechanism, wherein IgG-stimulated macrophages secrete TGF-β, leading to adipose tissue fibrosis and subsequent metabolic dysregulation. IgG, Immunoglobulin G. FcγR, Fc gamma receptor. SASP, senescence-associated secretory phenotype. TGF-β, Transforming Growth factor β. IASP, Immunoglobin-associated senescence phenotype. This figure was created by Biorender.

the first time systematically elucidated the potential of IgG as a new biomarker of aging at the molecular level and provided preclinical evidence for its targetability as a target for aging intervention through experimental validation[13,14]. Moreover, IgG glycosylation has been linked to various clinical parameters such as triglycerides, total cholesterol, uric acid, creatinine, and C-reactive protein. The glycosylation level of IgG also holds promise as an aging biomarker[17]. Although IgG has been extensively studied and applied in the diagnosis, prognosis assessment, and treatment monitoring of aging-related diseases such as inflammatory disorders, autoimmune diseases, and cancers[18], further large-sample, multi-center clinical studies are required to fully assess its safety and therapeutic efficacy as a target for aging intervention.

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Data available statement

Not applicable.

Author contribution

G.-H.L. and J.Q. designed the work. H.Y. and M.J. wrote the initial draft of this paper. All the authors participated in editing the content of this paper and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflicts of interest

Author Guang-Hui Liu is an associate editor of this journal, but he is not involved in the peer-review or decision of this article.

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