Inflammaging: should this term be suitable for age related macular degeneration too?

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COMMENTARY

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Abstract
Introduction Inflammaging is a phenomenon triggered by the conjunction of chronic repetitive and subclinical inflammation from external aggressors and internal inflammatory mechanisms due to the progressive degradation of systems such as the mitochondrial function. Age-related macular degeneration is the leading cause of blindness and visual impairment in patients older than 60 years in developed countries.
Discussion Remarkable correlations have been documented between common or rare immunological/inflammatory gene polymorphisms and AMD, unequivocally indicating the involvement of inflammation and immune-mediated processes (complement activation) in the pathogenesis of this disease.
Conclusion Altogether these factors also drive this pathologic condition under the general heading of "Inflammaging".

Keywords Inflammaging · Age related macular degeneration · Cytokines · Complement

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Introduction

Aging is accompanied by the development of low-grade systemic inflammation, termed 'inflammaging', characterized by increased serum levels of pro-inflammatory cytokines and by a concomitant decrease of cytokines counteracting the inflammatory state [1, 2]. According to Franceschi et al. [1, 3], inflammaging may be defined as the condition in which occurs a low-grade, controlled, asymptomatic and not pathological; but chronic, systemic inflammatory state. It has beneficial effects in early life but detrimental effects in later life for individuals [4, 5]. These attributes correspond to the Celsus inflammation signs: calor, rubor, tumor, dolor et function laesa and fits with the antagonistic pleiotropy theory on the evolution of aging postulating that senescence is the late deleterious effect of genes (pro-inflammatory versus anti-inflammatory) that are beneficial in early life. Evolutionary programming of the innate immune system may act via selection on these genetic traits [5]. According to the inflammaging theory, aging, either physiologically or pathologically, can be driven by the pro-inflammatory cytokines and substances produced by the innate immune system. Mammals maintain homeostasis as they age despite incessant attack from both intrinsic and extrinsic stimuli/antigens.

Inflammation and aging

Recent studies performed on populations resident in high-income nations with low levels of infectious disease and high levels of overweight/obesity have stressed the link between low-grade inflammation and a wide range of chronic degenerative diseases, indicating that there is a common factor among these pathologies even if they differ

in etiology and physiology [6]. Although inflammation has long been recognized as a critical line of defence against infectious disease, chronic low grade inflammation has been now recognized as a pathogenic trigger in the development of several age-related pathologies like atherosclerosis and type 2 diabetes [7, 8]. At a certain stage of each of these diseases, while the chronic inflammation proceeds, some key players of the immune system become immunosuppressed. The suppressive environment induced during chronic inflammation is governed by a complex process characterized by the accumulation and activation of immune suppressor cells, pro-inflammatory cytokines, chemokines, growth and angiogenic factors, and by the activation of several inflammatory signaling pathways mediated predominantly by NFkB and STAT3 transcription factors [9]. Different types of chronic pathologies share a chronic inflammatory response, which induce in affected tissues an immunosuppressive environment responsible for disease progression and a further tissue destruction and abnormal organ homeostasis.

Age related macular degeneration and inflammation

Age-related macular degeneration (AMD) is a multifactorial disease with progressive evolution affecting the macular area. It is responsible for central high resolution visual acuity. AMD is the leading cause of blindness and visual impairment in patients older than 60 years in Europe and North America [10]. Remarkable correlations have been documented between common or rare immunological/inflammatory gene polymorphisms and AMD, unequivocally indicating the involvement of inflammation and immune-mediated processes (complement activation) in the pathogenesis of this disease [11]. Albeit AMD is not considered a classic inflammatory disease, immunocompetent cells, such as macrophages and lymphocytes, are present in the chorioretinal tissues affected by AMD. Moreover, proteomic studies have revealed in the primary culture of human retinal pigment epithelial cells the presence of proteins associated with the immune response and inflammation; among these, transcription factors (such as NF-κB and STAT3), inflammatory cytokines and chemokines (TNF-α, IL-1, IL-6, IL-8, and monocyte chemotactic protein 1), proinflammatory enzymes (such as COX-2, 5-LOX, 12-LOX, and matrix metalloproteinases), C-reactive protein, adhesion molecules, vascular endothelial growth factor (VEGF), and adiponectin are the most common. These molecules strongly suggest an inflammatory process associated with AMD, but whether they are the cause or the effect of this low grade inflammation is not yet clarified [12]. Clinically, the therapeutic approach with anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) further confirm the role of inflammation in the pathogenesis of the disease, providing evidence that topical NSAIDs act synergistically with intravitreal anti-VEGFs in the prognosis of AMD [13]. Reactive oxygen species generated from phagocytosis, lipid peroxidation, and photic stress, together with the high oxygen tension in the choroid and in the macular region, contribute to the particular susceptibility to oxidative stress demonstrated in retinal pigment epithelial (RPE) cells in the macular region. Free radicals and oxidants play a key role in the pathogenesis of AMD. They are produced either from normal cell metabolisms in situ or from external sources (pollution, cigarette smoke, radiation, medication). The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Interactions between genetic (genome) and environmental factors (epigenome) operate during a person's entire lifespan. The aging process is associated with several cellular and organic functional alterations that, at the end, cause multi-organic cell failure. Epigenetic mechanisms of aging are modifiable by appropriate preventive actions like diet components, lifestyle and physical activity. Thus, some dietary components, such as olive oil, antioxidants, omega-3 and omega-6 polyunsaturated acids, polyphenols and flavonoids, mediate beneficial anti-aging effects [14]. These findings have been confirmed by the Age-Related Eye Disease Study 1 and 2 which have shown that supplementation with high levels of antioxidants significantly reduce the risk of AMD progression and its associated vision loss [15].

AMD, as well as the major chronic diseases (i.e,. cancer, rheumatoid arthritis, atherosclerosis and other cardiovascular disease, diabetes, pulmonary disease, and neurological disease including Alzheimers, Parkinson, and other neurodegenerative disorders), is associated with aging and inflammation. Extensive observations and experiments have demonstrated that most of these chronic pathologic conditions are preceded by a chronic low level of inflammation. Molecular studies on the causes of inflammation have shown that numerous biomarkers are involved in the process of inflammation. On the other hand, aging results in an increase of inflammatory cytokines that contribute to the progression of many degenerative diseases [16, 17]. Understanding the mechanisms underlying the function of key players in such an intricate environment, could lead to the discovery of attractive therapeutic targets in the inflammatory environment. Therefore, treatment of patients suffering from chronic inflammatory diseases such as AMD remains a major challenge in the clinic.

Conclusion

Age related diseases are not the simple result of a linear process where cumulative insults lead to chronic inflammation, against which there is little to do, as reported with barely concealed acknowledgment in the latin sentence "senectus ipsa morbus est" ("old age is itself a disease", P. Terentius Afer, 160 BC, Phormio comedy). Multiple processes form a conundrum where loss of functions, environmental insults and/or natural programmed phenomena, lead to inflammatory responses, which results in what is defined as age related disease [18]. Altogether these factors may be also applied to AMD, where aging, a genetic-genomic pattern and chronic subclinical inflammation with release of mediators connected to the development of neovascular process, drives this pathologic condition under the general heading of "Inflammaging".

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