

Inflammation in Aging and Age-related Diseases

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Editorial

Aging is a result of gradual and overall functional deterioration of the body derived from the interaction between genetic and environmental factors and lifestyle. Many studies have analyzed the biological events involved in the progressive deterioration that occurs in aging. Although there is an increasing awareness that age-associated changes in immunity might contribute to several disease processes, the role of immunity remains controversial.

It is not clear whether inflammation causes age-related processes, results from these processes, or both. In fact, inflammation is the basis for a wide spectrum of age-related diseases that affect different organs, such as diabetes type 2, Alzheimer's disease (AD), Parkinson's disease (PD), atherosclerosis and other cardiovascular diseases [1-3]. 'Inflamm-aging' is the term that describes the close relationship between low-grade chronic inflammation and ageing [4,5].

Multiple inter-related and complex mechanisms contribute to inflammation in aging. Currently, the most accredited hypothesis is that upregulation of pro-inflammatory mediators is induced during the aging process due to an age-related redox imbalance. Genetic and environmental factors that promote inflammation or disrupt the mechanisms involved in reducing inflammation seem to confer increased susceptibility to 'accelerated ageing' and age-related disorders.

The age-related redox imbalance is likely caused by the unregulated and overproduced reactive species (ROS), such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($\cdot OH$), reactive nitric oxide (NO) and peroxynitrite ($ONOO^-$), and by reduced anti-oxidative defense systems [6]. The interaction between oxidative stress and inflammation is closely related to the pathway of prostaglandins (PG). COX is a key enzyme in the PG pathway that induces ROS production and exacerbates inflammation. Oxidative stimuli activates the NF- κ B transcription factor that during aging regulates chronically the transcription of pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-2, and IL-6, chemokines such as IL-8 and RANTES, adhesion molecules such as ICAM-1, VCAM and E-selectin [7]. Although elevated levels of IL-1 and TNF α , have been associated with aging, and high plasma levels of IL-6, IL-1 and TNF α are correlated with diseases such as atherosclerosis, cardiovascular, diabetes type 2, AD and PD, the strongest evidence is for IL-6, that has been shown to be important for CD4+ T-cell helper differentiation in Th17 cells that release the inflammatory cytokine IL-17. Studying the effect of aging on T-cell function, proportions and T-cell subset functions appeared modified. In aging, the frequency of naive CD4+ and CD8+ T cells decreases, whereas the frequency of memory CD4+ and CD8+ T cells increases. The studies to evaluate the effect of aging on Th1 and Th2 responses are inconsistent, showing both increases or no change in IFN- γ or IL-4 producing T cells [8,9].

Adhesion molecules (AM) are proinflammatory proteins that regulate different steps of leukocyte infiltration and contribute to immune response and inflammatory processes. Increased levels of AM, which were correlated with increased oxidative stress, may represent markers for many diseases such as atherosclerosis, AD, and conditions such as inflammation and vascular diseases that are closely related to the aging process [10].

At the molecular level, attention has focused on how the interplay between several cellular processes including mitochondrial function, autophagy and activation of the NLRP3 inflammasome, drives age-dependent inflammatory conditions. It has been observed that aging causes a decline of autophagic capacity which impairs cellular housekeeping, leading to protein aggregation and accumulation of dysfunctional mitochondria which stimulates ROS production, oxidative stress and consequently NLRP3 activation. NLRP3 activates inflammatory caspases, which cleave the inactive precursors of IL-1 β and IL-18 increasing inflammatory responses and accelerating the aging process [11]. Inflammation and oxidative stresses stimulate NF- κ B transcription factors, therefore NF- κ B plays a key role in the aging process, and in age-associated diseases an altered NF- κ B signaling has been observed. The up-regulation of NF- κ B signaling and cytokines production was observed in neurodegeneration, cardiovascular disease and osteoporosis [12]. During aging, the DNA methylation pattern can change, and many studies have characterized the genes or genomic regions that either get hypermethylated or hypomethylated with age [13,14]. A number of studies suggest that a higher risk of carcinogenesis in aged individuals may be related to aging-associated DNA methylation changes that direct cells into a "stem-like" state predisposing to cancer [15,16]. Recently, some miRNAs have been linked to human aging-related disorders such as heart, muscle, and neurodegenerative diseases, although, not all miRNAs that are up- or down-regulated during aging necessarily play crucial roles during aging [17-19].

There is no single theory to explain all aspects of aging, but a number of theories, that are not mutually exclusive, try to explain how and why aging occurs [20]. The evidence accumulated over the years indicate that the pro-inflammatory molecules and molecular mechanisms of inflammation are the basis of aging and many age-related diseases. The understanding of the mechanisms that regulate biological processes related to inflammation in aging, is a very promising frontier for the development of therapeutic tools extraordinarily important to human longevity.

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