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Commentary

Can inflammation regulate systemic aging?

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Senescence, at both the cellular and organismal levels, results from an accumulation of genetic and epigenetic changes that lead to progressive cell deterioration, impaired tissue function, homeostatic imbalance, declining resilience in response to stressors, and a subsequent vulnerability to age-induced disease development (Burton, 2009). While a single mechanism for the cause and progression of biological aging has not been established, among the most common theories include telomere attrition, endocrine disorders, and oxidative stress (Kirkwood, 1988). Despite these widely accepted models, however, the etiology of senescence at the cellular and molecular levels remains largely undefined.

Previous studies have suggested that chronic inflammation contributes to cellular senescence by propelling basic aging processes (Ren et al., 2009). While the immune response characteristic of acute inflammation dampens within days, chronic inflammation is characterized by elevated levels of pro-inflammatory cytokines in response to physiological and environmental stressors that essentially arrest the immune system in a state of low-level activation (Baylis et al., 2013). The chronically active immune system associated with advancing age, termed "inflammaging," eventually initiates immunosenescence, the functional decline of the immune system with age (Franceschi et al., 2007; Freund et al., 2010). Although definitive mechanisms are yet to be identified, the pro-inflammatory phenotype of senescent cells, coupled with the up-regulation of the inflammatory response with increasing age, has been found to play a role in the initiation and progression of age-related diseases such as type II diabetes, Alzheimer's disease, hypertension, atherosclerosis, and osteoporosis (Zhang et al., 2008; Cevenini et al., 2013).

The heightened vulnerability to such diseases with advancing age, along with the collective physiological decline induced by aging, has made the process of senescence a widely studied area in the scientific community. Moreover, whether this process can be delayed or even reversed in an attempt to control life span and delay the onset of age-related diseases is a topic of much speculation. A recent study by Zhang and colleagues at the Albert Einstein College of Medicine of Yeshiva University presents a novel hypothesis in which they suggest that aging is driven by the integration of both immune and hormonal responses, centering on the hypothalamus. The role of the hypothalamus in fundamental life functions such as growth, development, reproduction, and metabolism is well established. The hypothalamic gene *GNRH1* codes for gonadotropin releasing hormone, a neurohormone that indirectly controls reproductive competence through the anterior pituitary (Wierman et al., 1995). Zhang et al.'s integrative model has discovered not only a new key function of the hypothalamus in aging and lifespan control, but also a new role for GnRH in promoting neurogenesis (Fig. 1).

Zhang and colleagues' work elucidates a new link between the immune and neuroendocrine systems, suggesting a collaborative role in the regulation of inflammaging and immunosenescence (Zhang et al., 2013). Their study lends support to the concept that hypothalamic activity is directly influenced by the body's immune responses. At the core of their model lies the finding that the hypothalamus is capable of sensing inflammation by way of systemic signals in the blood. In response to this detection, the hypothalamic microglial cells, which are functionally analogous to macrophages in the immune system, produce their own inflammatory molecules, nuclear factor κB (NF-κB) and its upstream IκB kinase-β (IKK-β), hence stimulating further NF-κB activity in neighboring neurons through a cytokines-directed positive feedback mechanism. Conversely, upon the blocking of this hypothalamic NF-κB and IKK-β pathway in mouse models, the mice exhibited a decelerated aging process and an increased median longevity by nearly 20%, as compared to controls (Zhang et al., 2013).

Furthermore, Zhang and his group found that the microglia-neuron crosstalk via NF-κB and IKK-β negatively regulates GnRH production by attenuating the transcription of the hypothalamic *GNRH1* gene. In order to confirm the contribution of inhibited GnRH to whole-body senescence, the researchers administered daily GnRH into a hypothalamic ventricle of aged mice for a prolonged period. What they discovered was that the hormone exerted significant influence on brain activity by conferring resistance to aging-associated neurogenesis impairment and

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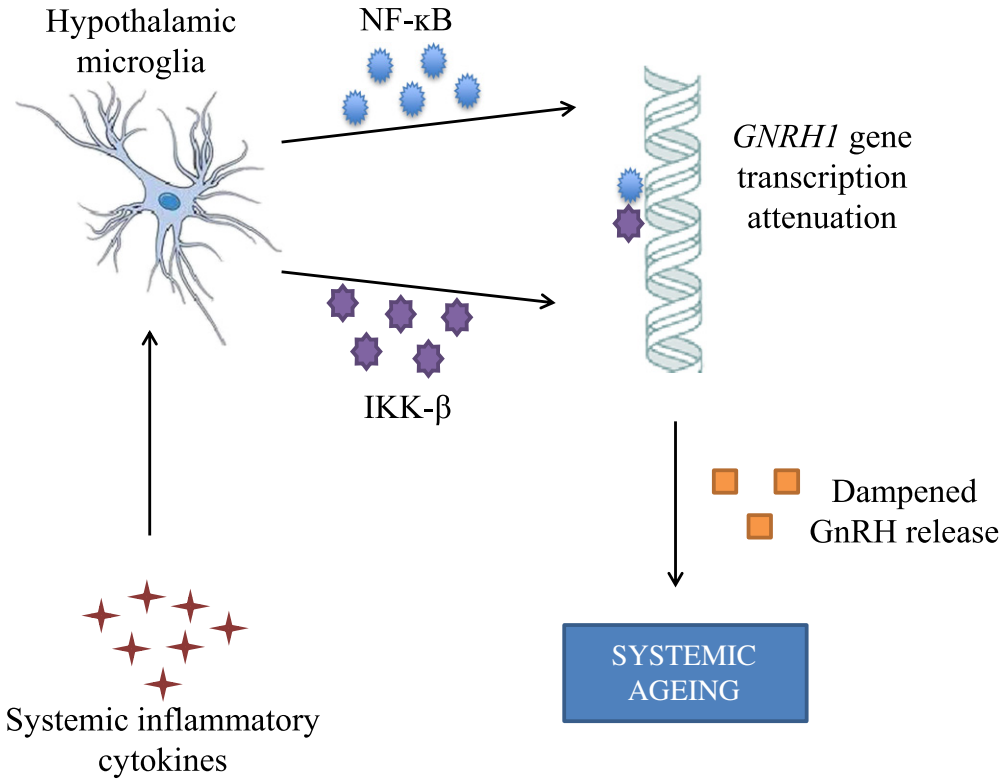

Fig. 1. Hypothalamic control of systemic aging. NF-κB mediated inflammation acts on the hypothalamus of the brain that leads to gonadotropin-releasing hormone (GnRH) and contributes to systemic aging.

ameliorating cognitive decline. Given these observations, Zhang and colleagues concluded that the inflammation-induced impairment of GnRH production, compounded with other defects in regulatory functions and neurogenesis in the hypothalamus, profoundly compromises the body's ability to cope with environmental insults. As the protective mechanisms involved in reducing inflammation are disrupted, the body becomes increasingly susceptible to accelerated aging and age-related conditions such as insulin resistance, metabolic disorders, and cardiovascular disease. The end result is a wide array of physiological, cognitive, and behavioral changes such as bone degeneration, skin atrophy, muscle deterioration, declined ability to learn, and memory impairment, all of which are direct indicators of systemic aging (Zhang et al., 2013).

Indeed, Zhang et al. present compelling evidence to demonstrate the pivotal role of the hypothalamus in programming aging development through the integration of NF-κB-directed immunity and GnRH-driven brain-wide neurogenesis. Their innovative immunoneuroendocrine model has far-reaching implications on the medicinal level. By establishing the hypothalamic NF-κB and IKK-β pathway as an endogenous mediator of the aging process, their results not only provide a more comprehensive understanding of the cellular and molecular basis of systemic aging, but also shed light on a new target for interventional strategies to combat age-induced disorders, especially those with an inflammatory pathogenesis. As a matter of fact, their findings hold significance for the field of aging studies at large. In essence, their findings lay the foundation for the exploration of therapeutic models to potentially ease the progression of a multitude of age-related and endocrinological diseases. NF-κB and IKK-β suppression and GnRH restoration now represent two promising methods of overcoming defects in immunological function in the aged, treating age-related diseases and disorders, decelerating aging, and ultimately granting genetic longevity and optimized lifespan.

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