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Inflammation links ageing to the brain

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One of the least understood aspects of aging is its coordinated and stereotyped progression in all organ systems. Although the brain has been long suspected of orchestrating systemic aging, compelling evidence of this in mammalian systems has been lacking. Nor has there been a clear understanding of how aging is affected by inflammation, a hallmark of age-related diseases such as diabetes, cardiovascular disease, arthritis, and Alzheimer's disease. On page 211 in this issue of *Nature* (May 9 2013), Zhang et al.¹ provide evidence for the integration of inflammatory responses with systemic control of aging by the hypothalamus, a part of the brain that controls growth, reproduction and metabolism.

Studies in invertebrate model systems of aging, such as *C. elegans* and *Drosophila*, suggest that neurons which sense nutrients and environmental stresses can regulate aging of the entire organism²⁻⁴. Zhang and colleagues now suggest that the hypothalamus, which subserves similar functions in the mammalian brain, may also exert broad control over the physiological changes we call aging. The new findings show that signaling through NF-kappa B increases in many regions of the brain in aging mice but is greatest in the hypothalamus. NF-kappa B is a centrally important regulator of transcription that mediates immune cell communication and inflammatory responses, and has been implicated previously in the control of gene expression during aging⁵. The present report indicates that NF-kappa B is activated in the resident macrophage cells of the brain, the microglia, stimulating secretion of the pro-inflammatory cytokine TNF α which, in turn, stimulates NF-kappa B signaling in neurons of the medial basal hypothalamus. This feed-forward loop sets up a new homeostatic state in the aging hypothalamus, leading to epigenetic changes in neuroendocrine genes. A focus of this report is NF-kappa B-mediated epigenetic repression of the gonadotropin-releasing hormone (GnRH) gene. Zhang et al. provide evidence that reduced hypothalamic release of GnRH may contribute to multiple systemic attributes of aging, including declining muscle strength, skin atrophy, bone loss, reduced neurogenesis, and memory impairment. If validated, this new paradigm could have potentially important implications for understanding and treating age-related diseases, particularly those linked to chronic inflammation.

Inflammaging is a term used to describe the close relationship between low-grade chronic inflammation and aging, which has been linked to a wide spectrum of age-related disorders in various organs including the brain⁶. Healthy aging and longevity may relate in part to lower levels of inflammation or stronger protective mechanisms that guard against adverse effects of chronic inflammation. Conversely, genetic and environmental factors that promote inflammation or disrupt homeostatic mechanisms involved in downregulating inflammation (e.g., mutations in certain genes that mediate innate immune responses, effects of chronic

stress on glucocorticoid-mediated anti-inflammatory responses) appear to confer increased susceptibility to “accelerated aging” along with age-related disorders such as insulin resistance, metabolic disorders, and cardiovascular disease⁷. This accelerated aging typically involves multiple organ systems, though effects in some organs can be subclinical. At the molecular level, recent attention has focused on the interplay between age-dependent alterations in inflammation, mitochondrial function, and autophagy (the cellular process mediating turnover/recycling of damaged cellular organelles), and role of decreased autophagy, accumulation of damaged mitochondria, increased generation of reactive oxygen species (ROS), and activation of the NLRP3 “inflammasome” in driving age-dependent inflammatory pathologies^{8–10}. Zhang et al provide a new paradigm for the inflammaging model at the whole-organism level through a mechanism in which immune and endocrine responses are integrated in the hypothalamus to drive mechanisms involved in accelerated aging. NF-kappa B signaling in the hypothalamus, and subsequent decline in GnRH production, could be activated locally in response to increased inflammatory cytokines such as TNF α and IL-1 or other activating mediators produced by microglia within the hypothalamus. Alternatively, the hypothalamus may respond to systemic signals since dendrites of GnRH-producing neurons extend through regions of the blood-brain barrier so they are positioned to sense pro-inflammatory and metabolic signals in the blood¹¹.

Although the classical function of GnRH is to regulate release of sex steroids involved in development and reproduction (estrogens and progesterone in females and androgens in males), GnRH may also mediate other functions independent of reproduction¹². Notably, GnRH administration abrogated the aging phenotype and increased neurogenesis in the hypothalamus and hippocampus in the mice studied by Zhang et al, whereas sex steroids did not have these anti-aging effects. A decrease in gonadal sex steroids is one of the most well-established markers of aging, but many other endocrine changes also accompany aging, including alterations in adrenal steroids (e.g., decreased pregnenolone, DHEA) and the insulin/IGF axis. Some of these age-regulated hormones, including sex steroids and DHEA, regulate inflammation and other immune responses. The inter-play and cross-talk between endocrine and immune functions therefore occurs at multiple levels.

A considerable body of literature suggests that early life adversity, such as childhood neglect or nutritional deprivation, can influence late life health giving rise to age-related disorders, including type-2 diabetes, obesity and cardiovascular disease¹³. NF-kappa B signaling may serve as a central integrator of these various environmental and life experience related stressors, as well as inflammation, to bring about changes in the hypothalamic-pituitary axis. This may be mediated by epigenetic reprogramming of key stress response genes in the brain that persists throughout adult life. One such gene is the glucocorticoid receptor, which mediates stress responses through a hippocampal-hypothalamic feedback loop in which glucocorticoid receptor activation in the hippocampus inhibits neuronal activity in the hypothalamus. Early life deprivation in rats or a history of early life abuse in humans is associated with methylation and silencing of the glucocorticoid receptor gene NR3C1¹⁴. This alters the stress responsiveness of the hypothalamic-pituitary axis, resulting in a permanent state of heightened sensitivity with elevated release of stress hormones. Although glucocorticoids are typically anti-inflammatory and inhibit NF-kappa B signaling outside the brain, recent findings suggest that glucocorticoids can have the opposite effect in the brain, triggering inflammatory changes and stimulating NF-kappa B signaling¹⁵. As such, NF-kappa B signaling may integrate diverse inputs related to stress and inflammation to regulate aging through changes in hypothalamic function as well as other target organ systems.

How might hypothalamic regulation of aging have evolved? Chronic inflammation is a marker of the aging process that arises from many different kinds of insults, from acute infection to genomic instability. The ability of the hypothalamus to sense inflammation

through immune signaling pathways is a novel concept, and just as the hypothalamus responds to nutrient status, the response to inflammation may enable the organism to adapt rapidly to physiological perturbations. Turning down hypothalamic release of GnRH and other modulators to prevent reproduction and reduce growth may be adaptive during times of acute infection, injury, or deprivation. While adaptive for our shorter lived ancestors, this may accelerate aging in older individuals once the species became longer-lived. It raises the intriguing possibility, however, that hypothalamic regulation could be therapeutically manipulated to broadly impact the aging process and age-related pathology.

Acknowledgments

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Figure 1. Hypothalamic inflammation and control of systemic aging

Zhang et al¹ report that inflammation and activation of NF-kappa B in the hypothalamus of the brain (boxed region) control systemic aging in part through a decline in expression and release of gonadotropin-releasing hormone (GnRH). NF-kappa B activation in microglia, as part of an age-related inflammatory response in the brain, results in production of TNF α , which stimulates NF-kappa B signaling and local neurons. In hypothalamic neurons, NF-kappa B signaling results in epigenetic repression of the GnRH gene, leading to reduced GnRH release and multiple physiological changes related to aging. Abbreviations: ROS, reactive oxygen species; LH, luteinizing hormone; FSH, follicle-stimulating hormone. Reprinted by permission from Macmillan Publishers Ltd: Nature, Gabuzda, D. & Yankner, B.A. 497, 197–198 (2013), copyright 2013.