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Review

Interaction of aging-associated signaling cascades: Inhibition of NF-κB signaling by longevity factors FoxOs and SIRT1

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Abstract. Research on aging in model organisms has revealed different molecular mechanisms involved in the regulation of the lifespan. Studies on *Saccharomyces cerevisiae* have highlighted the role of the Sir2 family of genes, human Sirtuin homologs, as the longevity factors. In *Caenorhabditis elegans*, the daf-16 gene, a mammalian homolog of FoxO genes, was shown to function as a longevity gene. A wide array of studies has provided evidence for a role of the activation of innate immunity during aging process in mammals. This process has been called inflamm-aging. The master regulator of innate immunity is the NF-κB system. In this review, we focus on the several interactions of aging-associated signaling cascades regulated either by Sirtuins and FoxOs or NF-κB signaling pathways. We provide evidence that signaling *via* the longevity factors of FoxOs and SIRT1 can inhibit NF-κB signaling and simultaneously protect against inflamm-aging process.

Keywords. Aging, FoxO, NF-κB, sirtuins, inflamm-aging, inflammation.

Introduction

Traditionally, aging research has attempted to devise plausible mechanisms to explain the aging process. During the last decade, molecular research has focused on the aging mechanisms of several model organisms, such as the budding yeast *Saccharomyces cerevisiae* and the nematode *Caenorhabditis elegans*. This approach has been profitable in unraveling the complex molecular mechanisms behind the aging process in these model organisms. The Sir2 family of genes governs the budding exhaustion in *S. cerevisiae* [1, 2] and the daf-16 gene regulates lifespan extension in *C. elegans* [3, 4]. Both of those genes are conserved during evolution and several homologs of Sirtuins and FoxOs (daf-16 homologs) have been cloned in mammals. The relevance of these models for illustrating mammalian aging has been criticized [5–7]. For instance, the yeast model seems to mimic better cellular senescence rather than organism aging. Since *C. elegans* is a continuously growing organism, it may be more useful in elucidating the role of signaling pathways specialized in growth and cellular resistance, such as insulin/IGF/PI3K pathway. Furthermore, germline signaling occurs in *C. elegans* [8], but this does not probably take place in mammals.

Several studies have highlighted the direct correlation between cellular resistance and lifespan of lower organisms [9–12]. This is attributable to hormesis and

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resistance to age-related stress. Effective defense mechanisms against inherent cellular stress and environmental attacks are essential for successful aging process and long lifespan. Innate and adaptive immunity are the major defense mechanisms in the higher organisms. Innate immunity is already present in unicellular organisms but novel mechanisms of adaptive immunity have developed during evolution in the defense capabilities of multicellular organisms [13]. The pattern recognition receptors and signaling pathways involved in innate immunity have been highly conserved during evolution. The master regulator of innate immunity is the evolutionary ancient NF-κB signaling system [14]. Interestingly, the efficiency of adaptive immunity significantly declines during aging, whereas innate immunity is clearly activated. This induces a pro-inflammatory condition called inflamm-aging [15–17]. The role of NF-κB signaling is important in organism defense since it links the inherent system with that devoted to responding to environmental danger signals and in that way organizes the cellular defense [18–20].

Simultaneously with the discoveries in molecular aging mechanisms, enormous progress has been made in our understanding about cellular signaling cascades and interactions of different pathways in the regulation of gene expression. Several key players have been discovered in aging research that are important participants in signaling networks: FoxOs and NF-κB are transcription factors, and Sirtuins are the protein deacetylases that regulate the activity of FoxOs and NF-κB (Fig. 1). In this review, we postulate that the aging-associated signaling cascades regulate each other and all interactions affect the final outcome of the signaling network. Aging-associated signaling may represent the lifespan extending, longevity regulation, or the age-related degenerative, pro-aging signaling. We propose that the signaling cascades mediated *via* Sirtuins and FoxO represent the lifespan extending, anti-aging type of regulation. Conversely, NF-κB signaling enhances the tissue atrophy and inflammation and supports inflamm-aging. We also provide evidence that the signaling *via* longevity factors FoxOs and SIRT1 can inhibit the NF-κB signaling and simultaneously protect against inflamm-aging.

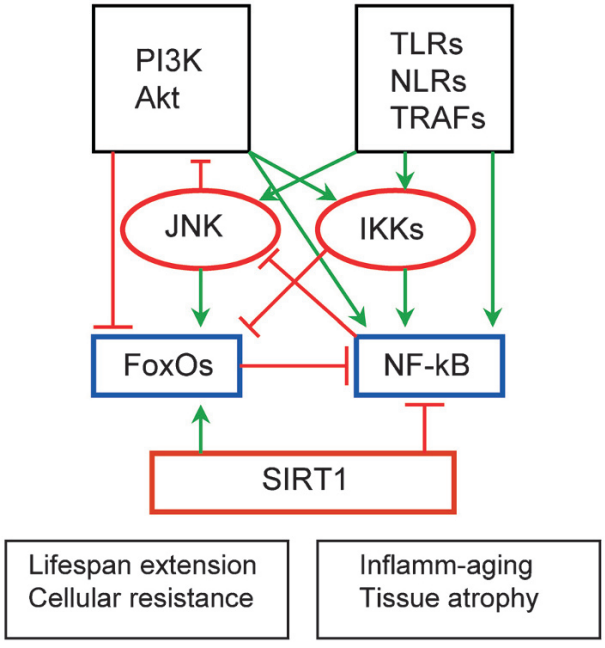

Figure 1. Schematic representation of the molecular interactions between longevity signaling mediated by FoxOs and inflamm-aging signaling involving NF-κB system. More details are presented in the text.

Longevity regulation: Signaling *via* FoxOs and Sirtuins

Daf-16/FoxO family of *C. elegans* longevity genes

C. elegans is a nematode that has been extensively studied in aging paradigms [21]. *C. elegans* has a short lifespan and it is able to enter a developmental diapause state, *i.e.*, the dauer larva stage, in unfavorable environmental conditions [22, 23]. The formation of the dauer stage involves the induction of alternate metabolism regulated by endocrine changes [4]. Over 30 dauer pathway genes have been cloned and named as *daf* genes [24, 25]. The most extensively studied and important of dauer pathways is the DAF-2 pathway, which includes DAF-2 (homolog to mammalian insulin/IGF-1 receptor), AGE-1 (PI-3K), DAF-18 (PTEN) and DAF-16 (FoxOs). Mutations in the genes of the DAF-2 pathway considerably extend the lifespan and can induce a dauer stage in the larva [23, 25, 26]. The DAF-2 pathway is an analog to mammalian insulin/IGF pathway and DAF-16 (the homolog to mammalian FoxOs) seems to be a key factor in the longevity regulation in *C. elegans*. DAF-16 is a transcription factor that has numerous target genes, many of which regulate stress resistance and longevity [27–29]. Assurance of energy availability may be the main function of DAF-16 in *C. elegans* supporting the disposable soma theory of aging [30]. The mammalian FoxO gene family contains four members: FoxO1 (earlier FKHR), FoxO3 (FKHRL1), FoxO4 (AFX) and FoxO6 [31, 32]. The function of FoxOs is regulated by phosphorylation, acetylation and ubiquitination [31–33] with phosphorylation being the most critical since it regulates the nucleo-cytoplasmic shuttling of most FoxO factors, except that of FoxO6 which is a nuclear factor. The