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REVIEW

Oxidative Stress and Aging: Changes in Important Cell Signaling Pathways

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ABSTRACT

Important cellular signaling pathways control the basal metabolism in mammalian cells, mainly in combating oxidative stress. Several studies have correlated the increase in ROS as one of the causes of aging. However, some authors also point out that cell aging causes an increase in ROS, mainly due to the inhibition of important antioxidant pathways. Important pathways of protein kinases and transcription factors are important to combat the accumulation of ROS, promoting an increase in mitochondrial biogenesis, synthesis of antioxidant enzymes and decreasing cellular senescence. In this review, the fundamental roles of the SIRTs, AMPK, MAPK, FOXO and Nrf2 pathways are highlighted.

Key words: Aging; cell senescence; Oxidative stress; Signaling pathways

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INTRODUCTION

Aging is broadly defined as a multifactorial process of cell and organ function related to a progressive and time-dependent decline in organisms, leading to greater vulnerability to chronic disease and death. Nine candidates for aging markers are described, being identified and classified in three categories: primary markers (genomic instability, wear of telomeres, epigenetic changes and loss of proteostasis), antagonistic markers (mitochondrial dysfunction, unregulated sensor and cellular senescence) and the integrative markers (stem cell exhaustion and altered intercellular communication). Each marker must manifest itself in normal aging, it experimental aggravation must accelerate aging and it experimental improvement must delay the normal aging process and thus increase longevity[1].

Primary markers are the main cause of molecular damage inherent in aging. This is the case with senescence, which protects the body from cancer but in excess can promote aging. Similarly, *Reactive Oxygen Species* (ROS) mediate cell signaling and survival, but at chronic high levels they can produce cell damage. The Free Radicals Theory or Oxidative Stress Theory of aging was proposed by Denham Harman in 1956. According to her, organisms age because they accumulate oxidative damage. This damage comes from ROS, which are partially reduced metabolites of molecular oxygen generated as products of metabolic reactions or by products of various cellular processes, such as respiration. Based on this concept, the physiological formation of ROS during cellular metabolism produces oxidative damage to the cell itself, and this, over time, results in a biochemical and physiological decline[1,2].

However, there are cellular defense mechanisms against the

accumulation of free radicals: the antioxidants. Even though antioxidant defenses are different from species to species, their presence is universal. These defenses include enzymatic antioxidants, such as catalase (CAT), Glutathione Peroxidase (GSHPx), Superoxide Dismutase (SOD), peroxiredoxins and estrins; as well as non-enzymatic antioxidants such as vitamin C and E, glutathione (GSH), lipoic acid, carotenoids, polyphenols[3].

Aging is in fact regulated by specific signaling pathways. Simple changes in the environment, such as increased of free radicals can impair cell homeostasis. Several studies suggest that several of these pathways control longevity in response to changes in the cellular environment. The oxidative stress chronic cycle of aging defines the epigenetic processes in development of the biochemical characteristics of senescence, aging and aging-associated diseases. A major pathophysiological characteristic of aging involves the elevated and sustained endogenous level of expression of the stress response that involves some pathways. In this review, we address the signaling pathway of sirtuins (SIRT); AMP-activated protein kinase (AMPK); Mitogen-activated protein kinases (MAPK); Forkhead Box Protein (FOXO) and Nrf2 pathway. These physiological signaling processes are key factors that promote the development of characteristics of stress-induced-aging and declining tissue functions of aging. These characteristics also contribute to the progression of age-associated diseases of oxidative stress[4,5].

SIRT

Sirtuins (SIRTs) act predominantly as NAD^+-dependent deacetylases for a wide range of target proteins, which are crucial for various biological processes. Among the various subtypes, SIRT1 has a central role in the control of cellular metabolism. SIRT1 mainly exists in the nucleus and interacts with protein substrates in a variety of signaling pathways, plays a central regulatory role in cell proliferation, metabolism, differentiation, apoptosis, and senescence. Increased oxidative stress, inflammatory stimulation and inhibition of energy metabolism cause serious harm to the body. Studies shown that SIRT1 can participate in toxic damage caused by toxic substances by interacting with protein substrates, such FOXO family, nuclear factor kappa B (NF-κB), peroxisome proliferator-activated receptor gamma assisted activating factor-1 (PGC-1) and tumor suppressor p53 in some signaling pathways[6,7].

In addition to the roles in cellular senescence, it is well established that Sirtuin regulates the organismal lifespan in several animal models. Increased expression levels of Sirtuin, especially yeast SIRT2 and its homologues, extends the lifespan of budding yeast S. *cereviseasae*, worms C. *elegans*, fruit flies D. *melanogaster*, and mice. Similarly, mice overexpressing SIRT1 subtype specifically in the hypothalamus had increased median lifespan by 16% in females and 9% in males. The effects included changes in mitochondrial function and biogenesis, suppression of inflammation, and regulation of genomic stability[6]. The molecular targets of this longevity effect of Sirtuins have been actively investigated. SIRTs are found to especially interact with all the major conserved longevity pathways, such as AMPK, insulin/IGF-1 signaling (IIS), Target Of Rapamycin (TOR), and FOXO. Of these, FOXO transcription factor is the most fascinating target of Sirtuin[8].

Since SIRTs is commonly believed to mediates ROS increase, the activators of SIRTs are considered to mimic these beneficial effects and are hence attractive therapeutics for age-related diseases. High-throughput screening has identified over 14.000 Sirtuin-activating compounds. This study further revealed the most potent activator of SIRT1 to be resveratrol (3,5,4'- trihydroxystilbene), a polyphenol found in red wine with potent antioxidant activity which extended the replicative lifespan of budding yeast by 70% at 10 μM[9].

AMPK

AMP-activated kinase (AMPK) is a highly conserved sensor of increased levels of AMP and ADP originating from ATP depletion. In turn, activated, phosphorylated AMPK can be inactivated by protein phosphatases. Many physiological and pathological conditions appear to stimulate AMPK signaling, for example: exercises, several diseases and some hormones as adiponectin, ghrelin and leptin, can either activate or inhibit AMPK signaling in a tissue-specific manner[10].

The "Theory of aging" emphasizes that energy metabolism maintains homeostasis in the organism whereas excessive consumption of energy enhances the aging process. A plethora of studies have confirmed in a variety of species that controlled caloric restriction (CR) can delay the aging process and moreover, several regulatory signaling pathways have been identified. It seems that this type of lifespan extension is mostly linked to the signaling pathways controlled by AMPK[11].

Several research approaches have revealed that the responsiveness of AMPK activation declines during the aging process. Studies demonstrated that AICAR treatment and physical exercise clearly increased AMPK2 activity in the muscles of young rats whereas in old rats these insults induced no response in AMPK2 activity[12]. Moreover, the decrease in energy metabolite levels in skeletal muscles evoked by a β-guanidinopropionic acid (β-GPA) diet clearly elevated AMPK2 activity in the muscles of young rats but the increase was blunted in old animals. β-GPA treatment also increased mitochondrial biogenesis, a downstream effect of AMPK activation, in young rats but notin old animals where a greater basal oxidative stress is observed. The decline in the sensitivity of AMPK activation with aging can provoke many age-associated diseases, for example a cardiovascular diseases and metabolic syndrome. There reported that aging impaired AMPK activation and suppressed insulin-stimulated glucose uptake into rat skeletal muscles which could enhance the development of metabolic syndrome[13].

MAPK

Mitogen-activated protein kinases (MAPK) are serine-threonine kinases that mediate intracellular signaling associated with a variety of cellular activities including cell proliferation, differentiation, survival, death, and transformation. The mammalian MAPK Family consists of extracellular signal-regulated kinase (ERK), p38, and c-Jun NH2-terminal kinase. Each MAPK signaling axis comprises at least three components: a MAPK kinase kinase (MAP3K), a MAPK kinase (MAP2K), and a MAPK. MAP3Ks phosphorylate and activate MAP2Ks, which in turn phosphorylate and activate MAPKs. Activated MAPKs phosphorylate various substrate proteins including transcription factors such as Elk-1, c-Jun, ATF2, and p53. MAPK pathways are activated either as a result of a series of binary interactions between the kinase components or through the formation of a signaling complex[14].

Studies have described a mechanism that links mitochondrial-generated ROS to the activation of stress induced aging phenotypes that regulates the p38 MAPK pathway activity and its downstream targets of senescence and aging, for example, p16, p19, TNFα, JNK, apoptosis and cardiovascular diseases. These studies suggest that development of certain diseases of oxidative stress are linked to the

p38 MAPK pathway and senescence was activated by p38MAPK in rat and human endothelial cells. The results showed that ~90% of age-associated ROS originates from mitochondrial dysfunction and that the p38 MAPK and JNK pathways are activated by mitochondrial generated ROS strongly supports the hypothesis that these signaling pathways promote characteristics of senescence, aging and diseases of oxidative stress[5].

Increased and sustained levels of p38 MAPK activitie is major physiological characteristics of aging. The elevated age-associated endogenous activity of many of the stress response genes targeted by p38 MAPK may thus be a consequence of the sustained elevated activities of these pathways. Therefore, chronic elevated levels of endogenous ROS are physiological characteristics that contribute to the promotion of senescence and aging and to the vulnerability of aged tissues to diseases of oxidative stress[15,16].

FOXO

The FOXO protein family is widely involved in cell signal transduction, growth and development, apoptosis, and antioxidant stress, among which FOXO1 and FOXO3 are the most common. This family of proteins can activate or inhibit a variety of target genes, such as p27kip1 and cyclin D (CCND) CYR61, which regulate the cell cycle, the *bim* and *fasL* genes that mediate apoptosis, TNF and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and the RAD51 gene involved in DNA damage repair[17,18].

Antioxidant role of FOXO is its most crucial function. Since ROS produce conserved deteriorating effect on cells and induce aging, FOXOs could be used to influence aging by ameliorating the antioxidant potential of cells. ROS act as second messengers in various signaling pathways. The oxidative stress regulates FOXO factors, either through detection of cellular redox potential or modifying the upstream FOXO regulatory pathways. Normally, cellular detoxification keeps ROS level in normal range. Hence, the inactivation of FOXOs result in the ROS built-up in the cells; it leads to various cellular abnormalities such as the compromised proliferation and cellular senescence[19,20].

The complex interaction between FOXO and SIRT1 protects against oxidative stress. On the one hand, SIRT1 upregulates the deacetylation of FOXO, enhances FOXO-induced cell cycle arrest, activates and promotes the FOXO/MnSOD pathway, increases the expression of SOD and CAT to resist oxidative stress, and promotes the repair of DNA damage during replication. After deacetylation, FOXO can be degraded by ubiquitination, reducing the level of FOXO and inhibiting the ability of FOXO to induce cell death, thereby ultimately protecting cells from oxidative stress damage. After activation that pathway, the level of FOXO deacetylation not only regulates the oxidative stress of the body, but also involves the control of cell apoptosis and the cell cycle, which is a complex and interactive process[21,22].

Among the various subtypes, FOXO3 has been shown to induce apoptosis either upregulating the genes needed for cell death or downregulating the anti-apoptotic factors. In addition, FOXO3 has been found to regulate the Notch signaling pathway during the regeneration of muscle stem cells. Moreover, antioxidants are thought to be upregulated by FOXO3 to protect human health from oxidative stress. In addition, FOXO4 is involved in the regulation of various pathways associated to apoptosis, longevity, cell cycle, oxidative stress, and insulin signaling. FOXO4 is associated with longevity through the insulin and insulin-like growth factor signaling pathway[23].

Numerous strategies for future research are predicted. For example, the triggering of FOXO-mediated processes in the tissues with metabolically different features can be valuable to explore the mechanism of FOXO-mediated longevity. In addition, the human FOXO sequence variations and their effect on the resulting proteins should be studied, the possible findings can also reveal the underlying mechanisms of FOXO-induced healthy aging. The delay in age-related pathologies including cancer and neurodegenerative diseases and living long life depends on the control of morbidity[24].

NRF2

Nuclear factor E2-related factor 2 (Nrf2) is widely regarded as a transcription factor activated by oxidative stress that induces the coding of a series of antioxidant protective proteins and promotes the regulation of redox conditions in cells. In addition, Nrf2 is also an important negative regulator of inflammatory cytokine activation and interleukin-1-mediated vascular inflammation, and therefore participates in the process of inflammation[25].

In oxidative stress, Nrf2 translocates to the nucleus and binds to a specific DNA sequence called the antioxidant response element (ARE), found in the promoter region of several chemoprotective genes and antioxidant enzymes that are involved in the response to oxidative stress[26,27]. The activation of Nrf2 is mediated by several pathways involving ativation of protein kinases. Although phosphorylation of Nrf2 has already been demonstrated, none of them have been conclusively linked to its stabilization. Because the pathways involving protein kinases control numerous signaling processes in the cell, additional studies are needed to explore whether such mechanisms are closely involved in regulating the stability of the Nrf2 protein in response to oxidative stress. Therefore, loss of Nrf2 allows oxidative stress to go unmitigated and drive the aging phenotype[28].

Studies demonstrated that cells that expressed Nrf2 had greater protection against cell death in an environment of oxidative stress induced by H_2O_2, in addition to being able to inhibit the expression of adhesion molecules and cytokines, suggesting potential anti-inflammatory properties. In addition, data from the literature assume that Nrf2 appears to be involved in controlling mitochondrial integrity during inflammation and oxidative stress[29]. It was demonstrated that Nrf2 activation was able to protect mitochondria from the opening of transition pores from mitochondrial permeability in response to treatment with tert-butyl hydroperoxide. Apparently, this resistance is accompanied by an increase in the production of antioxidant enzymes, such as GSHPx. During oxidative stress, Nrf2 can also contribute to the regulation of mitophagy, a process by which damaged mitochondria are removed via regulation of autophagosomal degradation[30].

A link between Nrf2 and senescence in fibroblasts has been shown, as Nrf2 was downregulated in older compared to younger cells. Thus, older fibroblasts were more sensitive to the effects of general oxidative stress. Studies revealed that young fibroblasts treated with an Nrf2 inducer did not become senescent compared to untreated controls due to activation of the proteasome. In addition, treatment of already senescent cells with an Nrf2 inducer reversed the senescent phenotype and restored proliferation. Overall, Nrf2 prevents cellular senescence; therefore, when Nrf2 is reduced, senescence and the aging phenotype are increased[31].

CONCLUSION

In this review, we observed some functions of the cell signalling

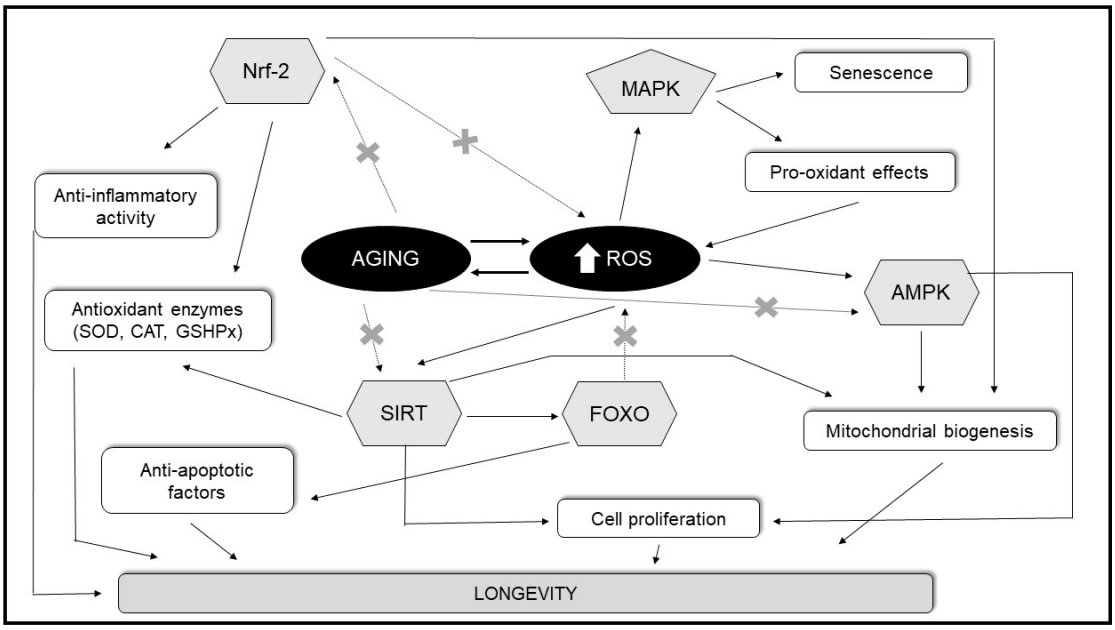

Figure 1 Mechanism of the SIRT, AMPk, MAPK, FOXO and Nrf2 signaling pathways in the control of oxidative stress and cell aging.

pathways SIRT, AMPK, MAPK, FOXO and Nrf2, mainly in combating oxidative stress generated in aging. These pathways play an important role in controlling the metabolic rate of cells, including increased mitochondrial biogenesis, cell proliferation and synthesis of anti-inflammatory cytokines and antioxidant enzymes. However, some of these pathways are silenced with aging (SIRT, AMPK and Nrf2) and others activate the pro-oxidative effects (p38MAPK) in order to attenuate cell senescence (Figure 1).

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