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Mini Review

Sirtuins in the Modulation of Oxidative Stress – A Mini View

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Abstract

Sirtuins a class III histone deacetylases are actively involved in controlling aging, aging related diseases, inflammation, metabolism and oxidative stress. They participate by switching on/off the genes, proteins and transcription factors that contribute to molecular physiology of the cell. Sirtuins role in managing metabolic stress mainly hypoxic and oxidative is remarkably evolving and have been explained in depth in earlier literatures. Since oxidative stress is a major contributor for inflammation, metabolic and aging associated diseases, in this mini review, we explained the role of sirtuin in balancing the oxidative stress by deacetylating transcription factors that take part in oxidant and anti-oxidant mechanism.

Keywords: *Sirtuins; Oxidative Stress*

Introduction

Oxidative stress/damage is mainly due to the continuous production of free radicals (ROS-reactive oxygen species) that imbalances with the production of free radicals and antioxidant system. It negatively associates with cell viability, energy metabolism, aging, metabolic and degenerative diseases. It acts as a cellular defense mechanism against pathogen attacks. Under the calorie restriction, the occurrence of reduced oxidative damage to cells/less production of free radicals explains the association of sirtuins and oxidative stress [1,2].

Sirtuins (silent information regulators) are a class of conserved proteins from flies to humans. They belong to class III histone deacetylases and use NAD+ (nicotinamide adenine dinucleotide) as a substrate that involves in electron transport chain and energy production [3]. Seven human sirtuins (sirt1-7) were reported to date. Initially they identified to prolong life span of *Saccharomyces cerevisiae (S. cerevisiae)* when depleted with glucose [4]. However, overexpression of sirtuins rescued the hydrogen peroxide treated *S. cerevisiae* from oxidative stress. Similarly, over expression of sirtuin extend the lifespan in *C. elegans* [5]. Sirtuins are involved in several cellular functions including chromosomal stability, DNA repair, cell cycle, apoptosis, metabolism and aging by deacetylating a variety of transcription factors (NF-kB, p53, FOXO, PGC-1α) histone and non-histone proteins [6].

Enzymatic activity of sirtuin

Sirtuins uses NAD+ as a substrate and produces nicotinamide (NAM) which acts as a feedback inhibitor of sirtuin. This nicotinamide converted into nicotinamide mononucleotide (NMT) using a Nicotinamide phosphoribosyl transferase (Nampt) enzyme using NAD salvage pathway. NAD+ regenerated again from nicotinamide mononucleotide (NMN) using a nicotinamide mononucleotide adenyl transferase [(Nmnat); 7,8]. NAD biosynthesis regulates the activity of sirtuins and their expression based on nutrient stress. NAD+ acts as a substrate in several reactions where an enzyme poly ADP ribose polymerase (PARP) consumes NAD+ for its activation. However, PARP activation was not only dependent on NAD levels, they also bind to DNA breaks through their DNA binding domains and get regulated [8,9]. But it has a major impact on NAD biosynthesis. It affects the intracellular NAD level, and forcing the cells to constantly synthesize NAD to

maintain cell viability. Due to the constant consumption of NAD, when the cells treated with genotoxic agents maintain the continuous activation of PARP, that reduces the levels of NAD+ in cells to 10 - 20% within 5 - 15 min of stress [8,10]. Due to its high rate of consumption they always compete with sirtuin in using NAD+. Hydrogen peroxide treated cell culture studies showed increased PARP activity which decreased the intracellular NAD+ level and reduced the sirt1. However, the addition of endogenous NAD+ to the culture medium was able to recover the cells from stress in the presence of SIRT1 [11].

Transcriptional activity of sirtuin in oxidative stress

Sirtuins regulates oxidative stress mainly through forkhead transcription factors (FOXO). FOXO controls a variety of cellular processes including reactive oxygen species production, DNA repair and apoptosis [12]. Sirtuin activates FOXO to produce anti-oxidants SOD2 (superoxide dismutase) and catalase. SODs catalyze the conversion of superoxide into oxygen and hydrogen peroxide, which is then converted to oxygen and water by catalase. This helps to promote cellular resistance against oxidative damage [13]. In astrocyte neuronal cell culture, glucose deprivation increased sirt1 and decreased ROS levels by increasing the levels of SOD2 and catalase. Mechanistically, sirt1 activation deacetylates FOXO4 that binds to the promoter region of SOD2 and catalase that increases the expression of these enzymes and suppresses ROS production [14].

Sirt1 deacetylates FOXO1 and FOXO3 and increases the cellular resistance to oxidative stress in HEK 293 cells [13]. FOXO1 is neuroprotective against ischemic neuronal injury and it promotes the apoptosis of cerebellar granule neurons upon the withdrawal of growth factors [15]. In brain, an over expression of FOXO3 protects motor neurons from apoptosis induced by mutant SOD1 or polyQ-expanded androgen receptor [16]. Sirt2 deacetylates FOXO3 and increases its transcription after calorie restriction in mice and in hydrogen peroxide treated fat and kidney cells, thus reducing cellular levels of ROS [17]. In a mouse model of myocardial infarction, sirt1-mediated upregulation of FOXO inhibits cellular damage by activating pro-survival factors such as thioredoxin-1 and Bcl-xL. They also reduced the activity of proapoptotic molecules such as Bax and cleaved caspase 3 [18]. Peroxisome proliferator activated receptor gamma coactivator 1α (PGC-1α) interacts with FOXO to synthesize many of its targets including antioxidant enzymes [19]. NADPH oxidase another enzyme mainly involved in the production of ROS and Sirt1 inhibit the upstream signal of NADPH oxidase to control ROS production. Alternatively, it activates PGC-1α which downregulates NADPH oxidase in endothelial cells [20]. Over expression of sirt1 inhibits apoptosis induced by oxidative stress/DNA damage [21].

A transcription factor that plays a key role in inflammatory responses deacetylated by sirt1 is NF-kB. It plays a major role in innate immunity and it stimulates glycolytic energy flux during acute inflammation. NF-κB transcribes pro-inflammatory mediators and its activation exacerbates oxidative damage after a variety of cellular insults [22,23]. NF-κB reduces SIRT1 activity via reactive oxygen species. Reduction in sirt1 activity disrupts energy metabolism and induce NF-κB-mediated inflammatory responses. Sirt1 deacetylates the p65 subunit of NF-κB at Lys310 and reduces its transcriptional activity, protecting cells from apoptosis [24]. Similarly, RelA/p65 expression was increased in hypoxic (cellular stress) choroidal vascular endothelial cells but the inhibition of sirt1 reduces RelA/p65 levels [25]. In vascular smooth muscles cells, experimental overexpression of RelA/p65 protein upregulated the expression of SIRT1 at mRNA and protein levels whereas reducing RelA/p65 expression decreased the TNF-α-induced SIRT1 expression. They also found that the RelA/p65 protein could bind to NF-κB motifs on the SIRT1 promoter. This indicates that NF-κB could stimulate sirt1 expression [26,27]. NF-κB activates induced and endothelial nitric oxide synthases (iNOS and eNOS) that produce NO (nitric oxide) free radicals which in turn cause SIRT1 nitrosylation that further inhibits its activity [28].

Another transcription factor that had mutual regulation with sirt1 is E2F1. E2F transcription factor 1(E2F1) is multifunctional plays a major role in energy homeostasis. It controls the cell cycle, inflammation and apoptosis [29]. Oxidative stress induces its gene expression and it interacts with RelA/p65 subunit of NF-κB complex and augments inflammatory responses. Sirt1 binds to E2F1 and inhibit E2F1 activities. In retina, absence of E2F downregulates p53 deacetylase functions of sirt1 and increases retinal apoptosis [30]. Similarly, sirt1 knock down increases E2F1 expression and increases apoptosis [31].

A major producer of reactive oxygen species is cigarette smoke which combines with hydrogen peroxide treatment cause sirt1 carbonylation and shifting the sirt1 from nucleus to cytoplasm. This leads to degradation of sirt1 compared to H_2O_2 stress alone where it does not cause sirt1 degradation [32]. The shuttling of sirt1 can be reduced by the pretreatment of cells with an antioxidant N-acetyl-L-cysteine (NAC), suggesting that nucleocytoplasmic shift is mediated through a redox-sensitive mechanism. H_2O_2 treatment down regulates the sirt1 and sirt6 but elevates the levels of miR-34a in immortalized human bronchial epithelial cells via PI3K pathway. miR-34a targets the 3′ UTR of sirt1 and inhibits the expression of sirt1 [33]. However, inhibition of PI3Kα increased sirt1 and sirt6 levels in H_2O_2 treated cells compared to control [34].

Resveratrol, a known activator of sirt1 has been shown to have a protective effect against phototoxic degeneration of the mouse retina *in vivo* [35]. They induce apoptosis in several cancer cell lines by increasing Bax expression and activates caspase3 and caspase9 [36,37]. It inhibits hypoxic cell proliferation by decreasing sirt1 and increasing caspase3 activity [37]. Sirt1 protects retinal ganglion cells from hypoxic stress through SAPK/JNK pathway. Inhibition of JNK (SP600125) showed increased sirt1 levels which explain the interaction of JNK and sirt1 with apoptosis. Renal apoptosis was noted in sirt1 knockdown mice and apoptosis was attenuated in presence of sirt1 activator. In depth, sirt1 knockdown cause decreased oxidative stress-induced expression of cyclo-oxygenase 2 (COX2), while sirt1 activator increased COX2 expression [6].

In summary, sirtuin has protective role in controlling the oxidative stress through the activation of various transcription factors and enzymes. Their role has been studied in detail. In this review, we just scraped off the 'surface of the sirtuin that plays a role in controlling oxidative stress.

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