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## Research Article

# Oxidative Stress & FoxO Transcription Factors on Cardiovascular Aging - @

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Aging is a phenomena in which the functions, applicability and resistance of an organism reduces over time. With the globally aging at an accelerating pace, delaying the negative aspects of aging is vital for advancing the human life span and quality of life. The aging of multiple organs can lead to a lot of disease and no exception for cardiovascular system. Actually, one of the primary risk factors for cardiovascular diseases is aging because of altered cardiovascular metabolism resulting in metabolic disorders and inflammation. In this review, we discuss about the relationship of oxidative stress with aging and FoxO proteins, which is essential factor for anti-aging of cardiovascular systems.

## OXIDATIVE STRESS AND AGING

The free radical/oxidative stress theory of aging first proposed by Harman (1953) suggested that the accumulation of irreversible molecular damage caused by reactive oxygen species (ROS) is one of the most significant factors in aging [1]. It is believed that irreversibly oxidised biomolecules do not function properly and that the accumulation of oxidised biomolecules accelerates aging. This theory has been supported by a number of studies in various model organisms demonstrating a correlation between aging and redox state or demonstrating an increase in longevity associated with exogenous treatment with various antioxidants [2-4]. Therefore, understanding the aging-related alterations induced by changes in redox state will provide a clue to anti-aging strategies that may be applied in complex organisms.

## OXIDATIVE STRESS AND FOXO TRANSCRIPTION FACTORS

It has been reported that moderate oxidative stresses promote the nuclear localization of FoxO, resulting in the expression of target genes [5]. This process results in both lifespan extension and metabolic changes in aging model organism nematode, *C. elegans* [6]. The relatively recent development of this more nuanced view presents a challenge to the biomedical research community in terms of the possible assessment of the significance of ROS and scavenging of ROS in biological systems [5]. As many researches have shown [7-8], FoxO plays a pivotal role in redox signaling, but it is unclear whether and how redox signaling to and from FoxO contributes to its effects on longevity. One emerging theme is that the consequences of FoxO activation depend on the cellular environment and can produce a switch in the FoxO-mediated gene expression profile. FoxO protein expression, subcellular localization, and transcriptional activity are regulated predominantly by two modes of signaling, namely, antioxidant-induced PDK-1/SGK-1 signaling and oxidative stress-induced JNK-1/MST-1 signaling. FoxO localization is regulated differently by the PDK-1/SGK-1 and JNK-1/MST-1 signaling pathways [5, 9]. In addition to this mechanism, a number of other post-translational modifications control the activity of FoxO. Most likely, the physiological response triggered by FoxO is determined by cellular context as well as the cofactors involved, although the mode of action through which cell context modifies FoxO is yet to be fully determined. ROS are known to regulate FoxO transcriptional activity through posttranscriptional modifications including phosphorylation, which changes the ability of FoxO to transactivate target-gene transcription. The effects of ROS on FoxO activity depend on cellular context, duration, and possibly the intensity of ROS

accumulation.

## AN EFFECTIVE REDOX STRATEGY FOR ANTI-AGING BY REGULATE CELLULAR REDOX STATE

FoxO activation can induce cell cycle arrest through the direct induction of multiple changes in factors associated with the cell cycle transition [10]. The cell cycle arrest induced by FoxO can influence the eventual outcome in terms of cell fate and may also promote DNA damage repair and stress resistance. In our previous results [5], antioxidants appear to act as inducers of DNA repair. The transcription levels of the cell cycle arrest- and DNA repair-related genes were increased, but the transcription levels were decreased in antioxidant-treated cells. Under low/moderate oxidative stress conditions, GADD45 has been shown to be a downstream target of FoxO that mediates DNA repair mechanisms and regulates growth arrest at the G2-M checkpoint. Although oxidant treatment did not affect these cell cycle arrest and DNA repair genes at our experimental concentrations, higher concentrations of oxidants increased the expression of these genes significantly. However, the oxidant concentrations required to increase these genes are much higher than the optimal concentration for FoxO nuclear translocation. FoxO proteins also play a significant role in regulating whole-body energy metabolism [11]. FoxO activation results in the repression of a large number of nuclear-encoded genes with mitochondrial functions, a process mediated by the FoxO-dependent inhibition of c-Myc. The expression of the metabolism-related genes decreased under the antioxidant condition. In addition, the expression of the mitochondrial gene decreased under antioxidant conditions. Antioxidant-mediated FoxO activation may regulate mitochondrial activity through the inhibition of c-Myc function. Moreover, the expression levels of these genes were increased at oxidant concentrations higher than our experimental concentration but decreased under severe oxidative stress.

Our previous data suggest that antioxidants work as protectors, maintaining cell integrity by DNA repair [5]. Antioxidants may also exert calorie restriction-like effects by inhibiting the insulin pathway, one of the major signaling pathways in calorie restriction-induced longevity, possibly through c-Myc inhibition. Therefore, antioxidants appear to act primarily by helping active cells maintain cell integrity and attenuate any unnecessary hyperactivity. In contrast, oxidant treatment can activate detoxification enzymes that are typically reduced in aged cells, which could promote aged cell recovery and revitalisation by inducing detoxification and energy hormesis. These different mechanisms of action suggest that there may be a way to maximise the positive effects of antioxidants and oxidants to achieve lifespan extension. However, in higher animals, such as mice or humans, there may be much more variation in the optimal concentration of FoxO nuclear translocation due to individual genetic backgrounds, the physiological conditions of specific organs and tissues, and specific cell types. The key might be in the fine tuning of FoxO activity in response to certain ROS levels and cellular environments, leading to the most appropriate cell fate decision (detoxify, arrest and repair or initiate apoptosis or senescence) for whole-organism longevity like as propose for proteostasis or mitohormesis. A personalised approach may yield good results in humans if applied after thorough genetic, physiological, and biochemical analyses of a patient's organs, tissues, and cells accompanied by the development of a local delivery system that can deliver an antioxidant or an oxidant where they are needed.

## THE CRITICAL ROLE OF FOXO IN CARDIOVASCULAR FUNCTION

FoxO stimulates cell growth and proliferation and also decreases VEGF secretion and mediates eNOS phosphorylation, vasorelaxation and angiogenesis by Akt kinase [12]. The action of Akt on its downstream target FoxO determines a function in cardiovascular physiology [13]. The alteration of FoxO signaling plays an important role in many cardiovascular pathological processes such as atherosclerosis, cardiac hypertrophy, and vascular remodeling. FoxO induces pro-apoptotic Bcl-2 family of proteins or stimulates expression of death receptor ligands such as Fas ligand and tumor necrosis factor-related apoptosis-inducing ligand, TRAIL. It can also enhance the levels of cyclin dependent kinase inhibitors. Phosphorylation of FoxO by Akt inhibits the transcriptional functions of FoxO and leads to decrease Bcl-2 and increased cell survival [14]. Furthermore, endothelial cell-directed deletion of FoxO1 in adult mice induced overzealous proliferation along with reduced apoptosis [15]. However, in endothelial cells, FoxO1 inhibits transcription of endothelial nitric oxide synthase (eNOS) and accelerates inducible NOS expression in response to oxidative stress, leading to generation of peroxynitrite and endothelial dysfunction [16] which contributes to atherogenesis. In addition, ablation of the three genes encoding isoforms of FoxO in endothelial cells blocks atherosclerosis in low-density lipoprotein receptor knockout mice [17]. Fine-tuning of FoxO is essential to controlling cellular functions in cardiovascular function.

### Atherosclerosis

In atherosclerosis, lability and abolish of the plaque leads to myocardial infarction, which could be caused by apoptosis of vascular smooth muscle cells [18]. FoxO seems to have an action in smooth muscle cell apoptosis through insulin/insulin-like growth factor 1 (IGF1) receptor signaling. Reduced IGF1R signaling and inhibition of phosphorylation of Akt, FoxO3a and GSK3 induce apoptosis of vascular smooth muscle cells [19]. Inhibition of Akt in vascular smooth muscle cells can result in significant increase in phosphorylation of JNK and c-jun, pro-apoptotic proteins, opposite manner in immune cells [20]. In addition, FoxO1 regulates asymmetric dimethyl-arginine through downregulation of dimethyl-aminohydrolase 1 in endothelial cells and subjects with atherosclerosis [21]. These studies strongly suggest that FoxO is a pivotal element in the regulation of endothelial activation.

### Vascular remodeling

Vascular remodeling process is composed of changes of cell growth, death, migration and generation or degradation of extracellular matrix [22]. FoxO proteins act a pivotal role in pathogenesis of vascular remodeling. Akt substrate GSK3 $\beta$  has an essential role in smooth muscle proliferation [23]. Recent study also reveals that growth arrest-specific protein 6 delays senescence in vascular smooth muscle cells through the FoxO signaling pathway [24]. In restenosis and atherosclerosis, increased proliferation of vascular smooth muscle cells contribute to medial thickening. FoxO also affects the activity of adventitia in the vasculature. In case of arterial injury, FoxO activity is remarkably lower in the adventitia and attributes the increased proliferation of adventitial fibroblasts [25].

### Cardiac hypertrophy

Cardiac hypertrophy can be defined at a cellular level as elevated

cardiomyocyte cell volume [26]. In normal growth, physical condition and growth induced by pathologic stimulation are the major types of cardiac hypertrophy [27]. Maladaptive hypertrophy could be caused as a response to excessive hemodynamic workload or by genetic mutations. Over-expression of Akt induces cardiac hypertrophy, which may lead to heart failure. Preventing cardiac hypertrophy by inhibiting mTOR failed to prevent the decline in mitochondrial function, but glucose utilization was maintained [28]. Reducing FoxO-mediated transcriptional activation of mitochondrion-targeted nuclear genes results in repressed expression of mitochondrial regulation. In myocytes, Akt activation abolished mitochondrial bioenergetics, which could be partially reversed by maintaining nuclear FoxO [29]. Constitutively activated Akt could raise the angiogenesis in heart and contribute to adaptive cardiac hypertrophy. Later stage of this can lead to heart failure [30]. There is a dilemma cause exercise is known to increase the cardiovascular health by raised Akt activity [31]. There must be a fine balance among with the optimal and maladaptive FoxO activation levels and duration which is yet to be investigated.

## SUMMARY AND PERSPECTIVES

Aging is a phenomenon in which the functions, adaptability and resistance of an organism decrease over time, which are triggered by mainly accumulated oxidative stress. The aging of multiple organs can ultimately lead to diseases and the cardiovascular system is no exception. In fact, aging is primary risk factors for cardiovascular diseases by altered cardiovascular metabolism, metabolic disorders of the extracellular matrix, abnormal apoptosis, and inflammation. Therefore, delaying many of the negative aspect of cardiovascular aging is vitally important for improving the human healthy life span and quality of life. Most of the studies on FOXO on cancer research, there are some similarities between pathological conditions in cardiovascular diseases and the hallmarks of cancer. Although, more studies should be done to understand actions of ROS and FOXO in cardiovascular diseases, there is a mandatory need to develop potent tissue specific inhibitors or activators of the FOXO pathway for cardiovascular research and therapeutic interests.

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## AUTHOR CONTRIBUTIONS

The author(s) have made the following declarations regarding their contributions. JK and SC wrote and discussed the paper.

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