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Editorial

Essence of Antioxidants in Aging Science: NRF2, a True Fact

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Aging Science

Literally, 'Aging' is the term meaning the gradual declination of our life span to death. More simply, it is the term depicting the gradual changes from younger age to older age. Aging and aging associated disorders (such as diabetes, cancer, autoimmune diseases, neuronal disorders etc) are the burning question to scientists in the medical as well as life sciences. Age is the greatest risk factor for nearly every major cause of mortality in developed nations. Despite this, most biomedical research focuses on individual disease processes without much consideration for the relationships between aging and disease. The dream of cheating death has evolved into a scientific desire to extend healthy life span. Scientists and doctors are looking for ways to maximize the number of years that we live free of chronic diseases, cancer, and cognitive decline. But before we can remedy, we have to understand the cellular and molecular mechanisms that drive aging and senescence.

Some clues reside in our telomeres; the tips of our chromosomes that become shorten with age. Others lie in our stem cells, which can only go on for so long repairing our tissues. Our mitochondria, too, the so-called powerhouses of the cell, may hold some answers to prolonging youthfulness. Other research points to the decreased or aberrant antioxidant capacity. Current aging science initiatives aim to explain biological mechanisms of aging, have provided insights into molecular processes that underlie biological aging and perhaps more importantly, potential interventions to delay aging and promote healthy longevity. Here it has been aimed to describe some of the advanced approaches along with efforts to move aging science from

the bench to the clinic. This editorial emphasizes on the cellular antioxidant system, preferably KEAP1-NRF2 system, which play very important role in cytoprotection from oxidative stress.

KEAP1-NRF2 System in Aging Science

The KEAP1-NRF2 system forms the major node of cellular and organismal defense against oxidative and electrophilic stresses of exogenous and endogenous origins. KEAP1 acts as a sensor of redox insults, whereas NRF2 (nuclear factor erythroid 2-related factor 2) is a key transcriptional activator that mediates the inducible expression of antioxidant genes. Under normal conditions, NRF2 is ubiquitinated by KEAP1 (Kelch-like ECH-associated protein 1) and subsequently degraded by proteasomes. KEAP1 is inactivated when cells are exposed to electrophiles and/or reactive oxygen species, resulting in NRF2 stabilization and induction of its target genes that are involved in the detoxification or elimination of various toxic insults [1]. Recent studies have unveiled the functional contributions of the KEAP1-NRF2 system and defined its broader involvement in biological processes, including cell proliferation and differentiation as well as cytoprotection [2,3].

In response to electrophiles, NRF2 has been identified as a key regulator of phase II detoxication enzymes and the first phenotypes has been found in murine model (*Nrf2*-null mice) that reflected susceptibility to xenobiotic stresses. NRF2 plays cytoprotective role in case of liver damage [4]. Drug-induced (Pharmacologic) activation of NRF2 signaling effectively abated cigarette-induced emphysema, among bunch of toxicological studies. From DNA damaging insults, NRF2 gives safeguard to cells, such as reactive oxygen species (ROS) and electrophilic toxicants, thereby inhibiting cancer initiation [5,6].

It is very well known that NRF2 activates oxidative-stress inducible genes for cytoprotection. An example of oxidative tissue damage is ischemia reperfusion injury, such as in brain, heart and kidney. Both exogenous and endogenous NRF2 inducers deaden oxidative tissue damage after ischemia-reperfusion [7]. Noise-induced hearing loss, which is also considered as an ischemia-reperfusion injury, is effectively prevented by the pretreatment with NRF2 inducers like CDDO-Im [8]. Oxygen stress-induced tissue damage particularly in the lung, is effectively prevented by NRF2 activation [9]. NRF2 inducers also protect skin from the UV and X-rays-induced dermatitis [10] (Figure-1).

Aging associated disorders or metabolic disorders, such as obesity, diabetes and its complications, are closely related to dysregulation of oxidative stress and effectively treated with NRF2 inducers. NRF2 activation in each organ appears to orchestrate the anti-diabetic effects through suppressing the oxidative damage of pancreatic islets and also by restoring the insulin secretion under diabetic conditions. Glycogen metabolism in skeletal muscles has been regulated by NRF2 activation [11,12].

Atypical important category of diseases whose pathogeneses are intently related to oxidative stress is neurodegenerative diseases, such as Alzheimer's disease, Huntington's diseases etc. NRF2 activation has been shown effective for mitigating the abnormal neuronal signs in murine models of these diseases. Beside these, NRF2 also ameliorates chronic inflammation, which is beneficial to the treatment of autoimmune disease such as rheumatoid arthritis [13] (Figure-1).

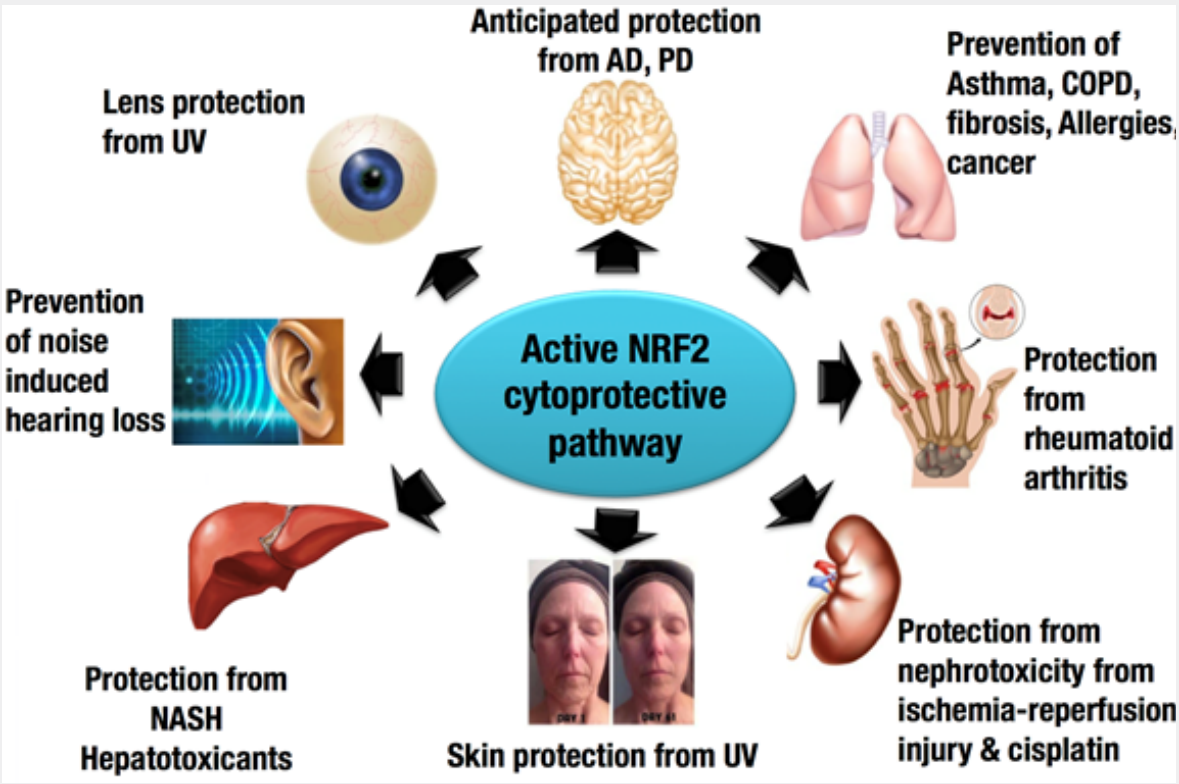

Figure 1: *Cytoprotective role of NRF2 in Aging-associated pathology*

Based on profound contributions of NRF2 to prevention and alleviation of a wide variety of pathological conditions, worldwide efforts have been made to develop potent and potentially specific NRF2 inducing chemicals or NRF2-inducing targeted drug delivery. Among them, currently, dimethyl fumarate (Trade name: Tecfidera®) has been approved by FDA and PMDA, and clinically prescribed to patients of multiple sclerosis. CDDO-Me, a member of the exceedingly potent class of oleanane triterpenoid NRF2 inducers, is in clinical trial for diabetic nephropathy in Japan [14]. Several small trials with sulforaphane in the form of broccoli extracts have shown promising effects likely to be NRF2-dependent, at least in part, in the settings of autism and air pollution [15,16].

As the progression of aging associated disorders are executed at the cellular level due to increased oxidative stress, DNA damage, increased apoptosis-senescence, so that inhibition or prevention of these cytotoxic effects could be taken the edge off by the induction of NRF2-dependent antioxidant response pathway. And in this line, optimal exercise and food habituation is the best prescription such as up taking optimal level of grapes, honey, garlic, broccoli, cabbage, peanuts, chocolates, green tea, ginger and so on.

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