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Editorial

Nrf2/ARE Signaling as a Therapeutic Target of Osteoarthritis

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Osteoarthritis (OA) is the most common form of joint disease worldwide and accounts for approximately 50% of the entire musculoskeletal disease burden which affects more than 30 million adults in USA. The prevalence of OA is projected to increase due to aging of the population, with a corresponding increase in the associated socioeconomic impact. OA is characterized by degeneration of articular cartilage, chronic low grade inflammation accompanied with synovitis, and changes subchondral bone. It is multi- factorial disease which includes mechanical forces, genetic factors, effects of aging on cartilage matrix composition and structure. The pathogenesis of OA involves decreased cell proliferation and synthesis of matrix proteins, proteinases, growth factors, cytokines, and other inflammatory mediators released by chondrocytes [1]. Currently, there is no disease-modifying drug for OA, only symptomatic treatments are available that address chronic pain and has no proven structure-modifying effects. Since molecular pathogeneses of OA exhibited common underlying factors, such as excessive levels of reactive oxygen species (ROS), with involvement of mitochondrial impairment, low grade inflammation and disturbances in autophagy pathway [2,3]. Oxidative stress is involved in the production of inflammatory mediators which contributes to joint degeneration through reduction in extracellular matrix synthesis, the induction of apoptosis and activation of MMP-13, MMP-3 and MMP-9 [3-5]. This raises the exciting possibility for developing a universal treatment, targeting these common pathological drivers of OA.

The transcription factor Nrf2 (NF-E2-related factor2) plays a major role in cellular defenses against oxidative, electrophilic and environmental stress [6]. Recently it has been shown that Nrf2 signaling plays a role in inflammation and in the maintenance of mitochondrial function suggesting potential benefits of therapeutic targeting of Nrf2 to counteract pathogenic events of OA [4,7]. Under pathological conditions, oxidative stress activates Nrf2/ARE (antioxidant response element) signaling pathway which induces transcriptional upregulation of a plethora of cyto-protective genes such as HMOX1, NQO1, GCLC, SOD2 etc. which allow adaptation and survival of cells. Therefore, control of oxidative stress and chronic inflammation by Nrf2 would result in protective effects against joint degradations in OA. Since oxidative stress and inflammation constitute pathological hallmarks of OA, a therapeutic role of Nrf2 signaling has emerged as promising strategy for OA. There are a number of recent publications which demonstrate the efficacy of Nrf2 activators in OA *in vitro* and *in vivo*.

A recent report from our laboratory demonstrate that natural flavonoid Wogonin exerts anti-inflammatory and chondro- protective effects in human OA chondrocytes and OA cartilage explants [4,5,8,9]. Wogonin modulates the ROS mediated activation of Nrf2/ARE signaling axis by disrupting Keap 1/Nrf2 interaction through blocking Kelch domain, the binding site of Nrf2 in Keap 1 protein [4]. Additionally, our recent data further dissect the molecular effectors of Nrf2 for its chondroprotective effects. Nrf2/ARE signaling inhibited the activation of both extrinsic and intrinsic apoptotic pathway of OA [10]. Nrf2 activation induced cytoprotective MAPK, the ERK1/2 and its downstream targets-ELK1, P70S6K and P90RSK and suppressed the molecular events of apoptosis by inducing anti-apoptotic genes such as Bcl-2, Bcl-xl and Mcl-1 and suppressing the pro-apoptotic genes including Bax and Bad [10]. Figure 1 summarized our experimental findings which demonstrate the molecular effectors of Nrf2/ARE signaling for chondro-protective effect in human osteoarthritic chondrocytes. The schematic representation (Figure 1) showed that Nrf2 activation represses oxidative stress, inflammation, protease activation and apoptosis in human OA chondrocytes.

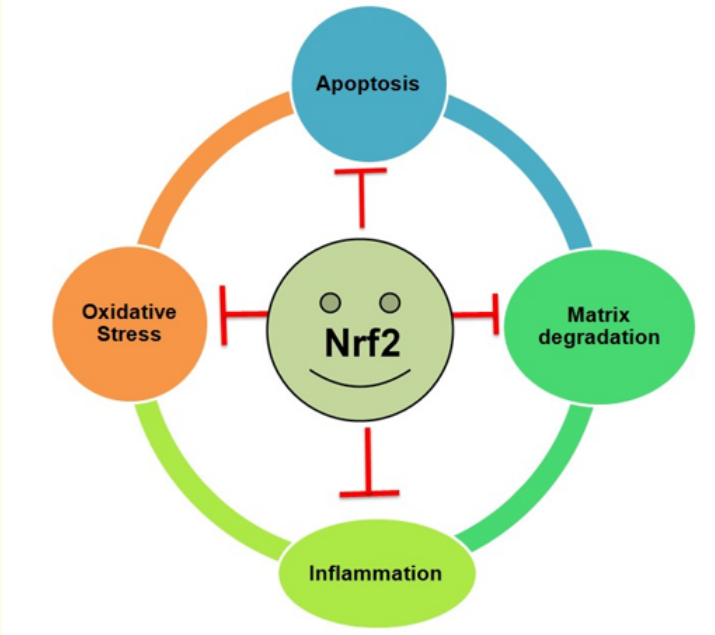

Figure 1: *Figure shows the molecular effectors of Nrf2 signaling for chondro-protective effects through suppression of pathogenic events involved in OA including oxidative stress, apoptosis, inflammation and matrix degeneration.*

In summary, targeting Nrf2 signaling may provide an exciting therapeutic option to ameliorate disease pathology of OA. Because pharmacological Nrf2 activation targets broad mechanisms of OA pathology, degenerative joint disease would be eligible for this therapy. Therefore, it is expected that Nrf2 activating drugs from natural products/nutraceutical would be helpful in diminishing the joint degeneration in OA. Thus, strategies aimed at stimulating antioxidant gene expression through Nrf2 activation in aging cartilage may hold promise for OA therapy.

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