Editorial

Intake of Pomegranate Prevents the Onset of Osteoarthritis: Molecular Evidences

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The developed world's aging population has experienced a dramatic increase in the incidence of joints dysfunction. Osteoarthritis (OA) is the most common forms of joints disorder that has a major impact on the patient's quality of life. The most important risk for OA besides female sex, obesity, and joint trauma is aging. [1] OA is characterized by joint pain, tenderness, limitation of movement, variable degrees of inflammation, *etc.* The mechanisms responsible appear to be multifactorial and are poorly understood. [1, 2] Recent therapeutic advancements in understanding of molecular and cellular mechanisms of joint disorders have highlighted the strategies that aim to inhibit the harmful effects of up-regulated inflammatory mediators and to inhibit their associated signaling events. [3, 4] Activated p38-mitogen activated protein kinase (p38-MAPK), c-Jun N-terminal kinases (JNK) and nuclear factor (NF)-κB pathways regulate pro-inflammatory genes such as cyclooxygenease (COX)-2, inducible nitric oxide synthase (iNOS), matrix metallo-proteinases (MMPs), *etc.* and are major targets of drug discovery in OA. [4-6] (Fig.1). Although OA is present in every population but the treatment is still limited to a few classes of drugs, primarily non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. While providing relief from pain, however, none of these drugs has been shown to inhibit cartilage breakdown or to inhibit disease progress; they also have varying degrees of gastrointestinal toxicity, ulcers, cardiovascular adverse effects, *etc.* [7] Therefore novel, safe and non-toxic anti-OA-therapies are needed that retard disease progression at an earlier stage and delay/prevent the need for joint replacement.

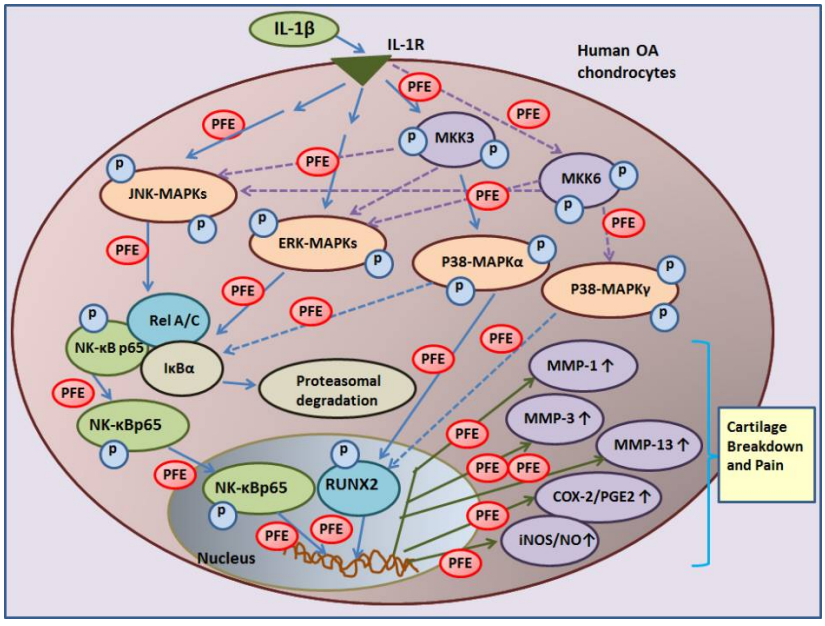

Fig. 1: Pomegranate fruit extract (PEF) induced silencing of OA relevant genes via inhibition of IL-1β-induced signaling cascade in human OA chondrocytes. Solid lines indicate activation, breaking lines indicate expected activation, p in blue circles indicates phosphorylation, and PFE targets are shown in red.

Natural products use by patients to alleviate symptoms is now rising globally. However, the quality of these products is poorly regulated and their efficacy, toxicity and mechanisms of action are largely unknown. [8] Pomegranate fruit (*Punica granatum* L.) is used in traditional medicines for the treatment of patients with high blood pressure, high glucose, high cholesterol, oxidative stress, and inflammatory activities. Studies have shown that the pomegranate fruit rich in bioactive compounds

such as polyphenols, anthocyanin, flavonoids, *etc*. [9] The use of pomegranate juice is increasing in popularity because of its high antioxidant content and is known to help in the prevention of cardiovascular disorders. [9,10] For the last decade, Haqqi and colleagues working on pomegranate fruit whose therapeutic potentials, and mode of action on cartilage degenerative mechanisms to understand the pivotal molecular targets involved in inflammation and the joint destruction process for OA management. [11-14] They have shown that a standardized pomegranate fruit extract (PFE) is highly effective in exerting human cartilage sparing effects and is non-toxic to human cartilage cells. Pretreatment of human OA chondrocytes with PFE inhibited IL-1β-induced expression of MMP 1, 3, and 13, which are classical markers of inflammation and cartilage degradation in arthritic joints. [11] In another study Haqqi and colleagues [12] demonstrated that oral administration of commercially prepared PFE (POMx) in inflammatory arthritis mouse model protects joints from inflammatory arthritis. They have shown that consumption of POMx potentially delayed the onset and reduced the incidence of inflammatory arthritis in mice. They also showed that in mouse macrophages, POMx abrogated multiple signal transduction pathways and downstream mediators implicated in the pathogenesis of arthritis. [12] Haqqi and colleagues also demonstrated that bioavailable constituents and/or metabolites of PFE exert an anti-inflammatory effect by inhibiting the activity of eicosanoid generating enzyme COX-2 and the production of nitric oxide, [13] which are key mediators for inflammation in OA. This further suggests that consumption of pomegranate may be of value in inhibiting inflammatory stimuli-induced cartilage breakdown and production of inflammatory mediators in arthritis. The cartilage protective effects by PFE were reconfirmed by another study in the monoiodoactate-induced OA animal model. [15]

I and some of my colleagues [16] demonstrated for the first time that human chondrocytes expressed the p38-MAPK isoforms p38α, -γ and -δ, but not p38β-MAPK. Moreover, IL-1β enhances the phosphorylation of the p38α- and p38γ- MAPK isoforms but not of p38δ-MAPK. We also showed by gene silencing that p38-MAPK activation was mediated by upstream MAPK kinase 3 (MKK3). [16] Importantly, in the same study we also demonstrated that PFE selectively inhibited the IL-1β-induced activation of MKK3, p38α-MAPK isoform and DNA binding activity of runt-related transcription factor 2 (Runx2). [16] Runx2-deficient mice with OA showed reduced cartilage destruction and MMP-13 expression. [8, 17] Moreover, Runx2 regulates induction of genes of major cartilage degrading enzymes MMP-13 and ADAMTS-5 (A disintegrin and metalloproteinase with thrombospondin motifs 5), [18] whose inhibition by PFE could potentially reduce cartilage degradation. In another study, we demonstrated that PFE significantly inhibited the excessive production of IL-6 and IL-8 via suppression of the JNK-, extracellular signal-regulated kinases (ERK)- MAPKs and NF-κB-signaling events. [19] All possible PFE target on IL-1β-induced signaling cascade in human OA chondrocytes has been summarized in Figure 1. Thus, beneficial effects of PFE may be through these important therapeutic targets. Studies have also shown that oil extracted from pomegranate seeds is rich in punicic acid and has anti-arthritic activity. [9, 20] Experiments on arthritic animals conclude that consumption of pomegranate seed oil in diet increases the bone mineral density and inhibits the pro-inflammatory activities. [20] Unlike NSAIDs or corticosteroids drugs that are currently in use for OA treatment, are having severe side effects, pomegranate in all forms has no side effects and are considered to be safe and non-toxic. Thus pomegranate or pomegranate-derived compounds can be emerged as novel therapeutic use for the treatment of OA and other degenerative/inflammatory diseases. In view of identified pharmacological targets and therapeutic potentials of pomegranate, clinical trials are in progress to explore its therapeutic potential for OA treatment, thus it may be anticipated that many of the open issues about the biological effect of pomegranate will be answered in the near future.

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