EDITORIAL

Green Tea Bioactive Polyphenol Epigallocatechin-3-*O*-Gallate in Osteoarthritis: Current Status and Future Perspectives

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Osteoarthritis (OA) is the most common and the leading cause of joints pain and disability around the world. Despite the power of modern molecular approaches and persisting investigative efforts, therapeutic options for OA treatment are still limited, while providing relief from pain, none of the treatments has been proved to inhibit disease progression; they also have varying degrees of adverse effects such as gastrointestinal toxicity, ulcers, cardiovascular effects *etc.* [1,2] In cases of late OA, only a total joint replacement can provide relief; however, many patients are not the right candidates for joint replacement, as the surgery is highly invasive and the procedure is extremely expensive. [3] In OA, cartilage cellularity is reduced due to chondrocytes death, and the remaining chondrocytes are activated by inflammatory signals to a catabolic and abnormal differentiation that leads to the breakdown of articular cartilage. [4] In chondrocytes and/or synoviocytes, activation of mitogen activated protein kinases (MAPKs): p38-MAPK, extracellular receptor kinases (ERK) and cJun N-terminal kinases (JNK) and the activation of transcription factors: nuclear factor-κB (NF-κB) and activator protein 1 (AP-1) are critical cellular events that lead to the expression/production of several inflammatory mediators such as matrix metalloproteinases (MMPs), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, *etc.* which are well known for their catabolic responses on articular cartilage degradation, [5,6] therefore suggesting that targeting inflammatory mediators and their associated cellular events could offer therapeutic options for OA therapy.

Green tea from plant *Camellia sinensis* is one of the most popular beverages consumed globally. The health benefits of consuming green tea have been well documented; [7,8] including prevention of cancer onset, cardiovascular diseases, diabetes, antioxidant, antibacterial, antiviral, neuroprotective, antiangiogenic, cholesterol-lowering effects, *etc*. Most of these beneficial effects of drinking green tea are related to its catechin, especially epigallocatechin-3-*O*-gallate (EGCG), which is a most abundant bioactive polyphenol of green tea and its potential value as an anti-arthritis agent has been demonstrated in several cellular and animal investigations. [7-9] Reports from the past decade or so have shown that EGCG has cartilage-preserving and chondroprotective activities. [10-12] EGCG inhibits the IL-1β-induced expression of iNOS and production of nitric oxide (NO) via inhibiting the activation of NF-κB inflammatory signaling events in human OA chondrocytes. [10] It is also reported that EGCG also inhibits the excessive production of prostaglandin E_2 (PGE_2) via blocking of COX-2 activity in human chondrocytes. [11] Furthermore, a wide range of biological effects of EGCG has also been reported that provide evidences of EGCG induced protective effects on OA cartilage via blocking of various pro-inflammatory events. [12] Moreover, I and some of my colleagues also have demonstrated that EGCG is non-toxic to human OA chondrocytes and inhibited the expression and production of TNF-α and MMP-13 in stimulated human chondrocytes. [13] The inhibitory effect of EGCG on the expression of TNF-α and MMP-13 may be via suppression of p38-MAPK and JNK activation. In the same study we have also shown that EGCG inhibits phosphorylating activity of IKKβ kinase and also inhibits DNA binding activity of NF-κB by suppressing the degradation of its inhibitory protein IκBα in the cytoplasm. [13] Studies from other investigators have shown that EGCG inhibits the degradation of human cartilage proteoglycan and type-2 collagen [8,14] and selectively inhibits the A disintegrin and

metalloproteinase with thrombospondin motifs (ADAMTS)1, ADAMTS4, and ADAMTS5. [15] Importantly, Leong *et al* have shown that EGCG significantly slows OA disease progression and exerts a relaxing effect in an OA animal model. [16] They demonstrated that EGCG-treated arthritic mice exhibited reduced levels of IL-1β, TNF-α, ADAMTS5, and MMP-1, -3, -8, and -13. Moreover, they also noticed reduced OA associated pain, as indicated by higher movement behavior of arthritic mice. [16] These excellent findings clearly indicating potential of EGCG as a therapeutic agent for OA progression.

MicroRNAs (miRNAs) are endogenous and non-coding single-stranded RNAs with a profound role in gene regulation at posttranscriptional levels. [17] Currently, 1881 precursors of human miRNA and 2588 mature human miRNAs are registered in the latest miRBase database (release 21, June 2014, www.miRBase.org). In OA, alterations in miRNAs expression have been reported in the pathophysiology of cartilage and in maintaining cartilage homeostasis. [17] Recently, I and some of my colleagues have demonstrated the global expression of miRNAs in stimulated human OA chondrocytes and also have shown that miRNAs are capable to regulate most of OA relevant genes. [18] In another study, we demonstrated that microRNA miR-27b is a direct regulator of MMP-13 in human OA chondrocytes. [19] More recently, we also demonstrated for the first time that microRNA hsa-miR-26a-5p regulates the expression of iNOS via activation of NF-κB signaling events. [20] In addition, other miRNAs including miR-127-5p, miR-602, miR-608, miR-320, miR-558, miR-9, miR-381, *etc.* have also been recently demonstrated to have significant roles in regulation of key inflammatory genes which are relevant to OA pathogenesis. [21-26] These findings clearly indicating potential role of miRNAs in the pathogenesis of OA. In recent years, several studies revealed that EGCG has potential to modulate miRNAs expression in cells from various patients. [27-30] Recently, I and my colleagues have addressed the question for the first time of a possible role of EGCG on miRNAs regulation in OA. [31] Our novel findings demonstrated that EGCG inhibits COX-2 mRNA/protein expression via up-regulating microRNA hsa-miR-199a-3p expression in IL-1β-stimulated human OA chondrocytes. [31] Moreover, in another study we demonstrated the potential role of EGCG on global miRNA modulation (unpublished data). Our results identified several novel OA-relevant miRNAs which have been targeted and negatively regulated by EGCG. These novel pharmacological actions of EGCG on stimulated human OA chondrocytes provide new suggestions that EGCG or compounds derived from it inhibit inflammatory events by regulating miRNAs in OA. In conclusion, for the drug designers, EGCG is a safer molecular for testing in humans, as the positive outcomes from the studies reported here, EGCG has a potential for a clinical development as an anti-arthritic agent for prevention/treatment of OA and other degenerative disorders.

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