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EDITORIAL

Green tea: a new option for the prevention or control of osteoarthritis

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See related research by Akhtar and Haqqi, http://arthritis-research.com/content/13/3/R93

Abstract

IL-1β is a major cytokine driving the inflammatory processes leading to the pathophysiology of osteoarthritis and other inflammatory diseases. Blockade of IL-1β activity using substances such as the naturally occurring IL-1 receptor antagonist or anti-IL-1β monoclonal antibody are currently being used or tested as therapy. However, such treatments are ineffective in osteoarthritis. In a recent study, epigallocatechin-3-gallate, a green tea polyphenol, was found to be effective in reducing IL-1β-induced inflammatory cytokines, TNFα, IL-6, granulocyte–macrophage colony-stimulating factor and several chemokines from human chondrocytes. The use of green tea polyphenols may be beneficial as a therapeutic addition to biologics that control IL-1β activity by increasing effectiveness and/or reducing dosage.

Inflammation plays a key role in osteoarthritis (OA). The overexpression of cyclooxygenase-2 and proinflammatory cytokines has been reported to contribute to the development of OA. Since chronic inflammation is the leading cause of connective tissue remodeling and destruction in OA, an approach that decreases inflammation may facilitate the development of an effective strategy for its treatment and/or prevention. The use of some drugs has demonstrated potential in treatment of OA but long-term safety, resistance and toxicity concerns have hindered their long-term acceptance as viable clinical chemopreventive agents. The exploration of new agents, particularly dietary, with low toxicity that can target inflammatory responses should form the basis for chemopreventive strategies that will reduce the destruction of cartilage matrix.

Green tea polyphenols (GTPs) – a mixture of major polyphenolic constituents found in green tea, including (–)-epicatechin, (–)-epigallocatechin, (–)-epicatechin gallate and (–)-epigallocatechin-3 gallate (EGCG) – offer promising new options for the development of more effective strategies for the prevention of inflammation-associated diseases, including OA. The recent study by Akhtar and Haqqi in *Arthritis Research and Therapy* indicates that EGCG, the major and most active component of GTPs, protects human chondrocytes from IL-1β-induced inflammatory responses, and suggests the potential of EGCG in OA treatment/prevention [1].

Multiple studies were conducted in the research laboratory of Dr Haqqi on the effect of GTPs in arthritis using *in vitro* and *in vivo* animal models [2-4]. These studies suggest that GTPs given in drinking water of mice prevented collagen-induced arthritis in the mice, and that this effect of GTPs was associated with the marked reduction of collagen-induced inflammatory mediators such as cyclooxygenase-2 and TNFα in arthritic joints of GTP-fed mice [2]. *In vitro* studies showed that treatment of human chondrocytes derived from OA cartilage with EGCG inhibits IL-1β-induced activity and expression of cyclooxygenase-2 and inducible nitric oxide synthase, and inhibits the production of nitric oxide and prostaglandin E_2 in chondrocytes. The inhibition of IL-1β-induced proinflammatory mediators by EGCG in human chondrocytes was associated with its inhibitory effects on the activation and nuclear translocation of NF-κB. These data thus provide a mechanistic link in prevention of arthritis responses as well as potential therapeutic value for EGCG/GTPs inhibiting cartilage resorption in arthritic joints [2-4].

The IL-1 family consists of 11 members including IL-1β, and the IL-1 receptor family consists of nine separate genes [5]. IL-1β, TNFα and IL-6 are among the key cytokines involved in the pathophysiology of OA. A recent meta-analysis study showed a small but significant association between carriers of the C-T-A haplotype of the *Ilirn* gene (IL-1 receptor antagonist) and decreased

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severity of OA [6]. IL-1 receptor agonist exerts anti-IL-1β inflammatory activity by binding to the IL-1 receptor, the receptor for both IL-1α and IL-1β [5]. Therapeutic use of an IL-1 receptor agonist, anakinra, to antagonize IL-1 (IL-1α and IL-1β) activity is a US Food and Drug Administration approved therapy for the treatment of rheumatoid arthritis but not for OA due to its limited and short-term effectiveness. Maintaining a balance in levels of IL-1β might be important as a treatment approach for OA, and agents such as GTPs could fill the gap. In fact, complete deletion of the *Il1b* gene leads to disease exacerbation in a mouse model of OA, suggesting both a catabolic and an anabolic role for IL-1β [7].

Akhtar and Haqqi also showed that GTPs reduce IL-1β-induced granulocyte–macrophage colony-stimulating factor production by chondrocytes [1]. This might be of significance in light of the recent exciting finding that IL-1-induced granulocyte–macrophage colony-stimulating factor is important for the pathogenicity of Th17, a major effector cell driving inflammation and autoimmunity [8]. In the photocarcinogenesis model, UV radiation-induced inflammation has been implicated in nonmelanoma and melanoma skin cancers. Topical treatment of the mouse skin with EGCG or oral administration of GTPs in drinking water of mice significantly inhibited UVB radiation-induced inflammatory responses, and this effect of GTPs led to prevention of UV radiation-induced inflammation-associated skin diseases including skin cancers [9,10].

The physician and the patients want to understand the real targets and mechanism of action of GTPs that lead to the prevention of arthritis/OA. More *in vivo* studies are definitely required to understand the targets of GTPs in general, and of EGCG in particular, in arthritic/OA animal models. The use of GTPs may be better than EGCG as GTPs may have synergistic effects, are more stable and are easily affordable. It may also be useful to test the effect of EGCG or GTPs in combination with other phytochemicals that have anti-inflammatory activities. Additionally, GTPs should be examined in combination with already known drugs for rheumatoid arthritis/OA. This combination may enhance the chemoprotective effect of these drugs, lowering the dose of already available drugs that would reduce the toxicity of these drugs if used for treatment long term. The road to that point will be long but the study by Akhtar and Haqqi is a promising start in the right direction.

Abbreviations

EGCG, (–)-epigallocatechin-3-gallate; GTP, green tea polyphenol; IL, interleukin; NF, nuclear factor; OA, osteoarthritis; Th, T-helper type cell; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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