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Does Progranulin Account for the Opposite Effects of Etanercept and Infliximab/Adalimumab in Osteoarthritis?†

Jian-lu Wei[a], **John Buza III**[a], and **Chuan-ju Liu**[a,b]

[a]Department of Orthopaedic Surgery, New York University Medical Center, New York, NY, 10003, USA

[b]Department of Cell Biology, New York University School of Medicine, New York, NY 10016, USA

Dear Editors:

We read with great interest the recent article by Guilak et al[1], which summarizes the significant advancements that have been made in our understanding of the development of post-traumatic arthritis (PTOA) after articular fracture (AF). We would like to congratulate the authors on their significant contributions to this field, including the development of a murine model of AF[2], the assessment of histologic changes and quantitative synovial fluid biomarker concentrations involved in PTOA[3,4], and the identification of pharmacologic agents that can lessen the severity of PTOA after AF[5,6].

We were most interested in the authors recent study on the use of anti-cytokine therapy to prevent PTOA, in which the authors hypothesized that the intra-articular inhibition of IL-1, TNF-α, or both would prevent the development of PTOA after AF[6]. The authors demonstrated that sustained local inhibition of IL-1 by Interleukin-1 Receptor antagonist (IL-1RA, anakinra, Kineret®) reduced the severity of arthritic changes in both the cartilage and synovium after AF. Paradoxically, however, the authors found that the local inhibition of TNF-α using soluble tumor necrosis factor receptor II (sTNFRII, etanercept, Enbrel®) resulted in detrimental effects on bone morphology, cartilage degeneration, and synovial inflammation[6].

There has been much interest in the role of TNF-α in the development of PTOA, as it is significantly up-regulated after fracture[4,7] and is associated with chondrocyte destruction and death[8]. There exists two distinct receptors for TNF-α, TNFR1 and TNFR2[9,10]. Although these receptors bind to TNF-α with almost equal affinity, they have been shown to mediate different intracellular pathways. TNFR1 recruits TRADD, TRAF-2, and FADD, and activates an inflammatory response[11]. While TNFR2 signaling is less well understood, several studies have shown that TNFR2 instead mediates an anti-inflammatory response[12,13]. Using mouse models of inflammatory arthritis, investigators have shown that

Please address correspondence to: Chuanju Liu, PhD, NYU Hospital for Joint Diseases, 301 East 17th Street, Suite 1600, New York, NY 10003, Tel: 212-598-6103, Fax: 212-598-6096, chuanju.liu@med.nyu.edu.

TNFR2 has an immunoregulatory role in reducing inflammation and preventing bone destruction[12,14]. Studies from other fields have confirmed these findings, as TNF-α induced cardiomyopathy and heart failure is mediated largely through TNFR1, whereas TNFR2 has been shown to have cardioprotective effects[15].

Studies from our laboratory also reveal the differential role of TNFR1 and TNFR2 in fracture healing and OA[16-18]. Our area of focus has been on a molecule termed progranulin (PGRN), a potent anti-inflammatory growth factor[19-23]. Interestingly, our global genetic screen for PGRN-associated proteins led to the discovery of TNFRs as PGRN-binding receptors[16]. PGRN and TNFα showed comparable binding affinity to TNFR1, in contrast, PGRN had an approximately 600-fold higher binding affinity for TFNR2 than TNFα[16]. Since PGRN and TNFα compete for binding to the same extracellular CRD2 and CRD3 domains of TNFR[24], PGRN acts as a physiological antagonist of TNFα and disturbs the binding of TNFα and TNFRs[16]. More importantly, PGRN also acts as an optimal ligand of TNFR2 and directly activates the PGRN/TNFR2 protective and anti-inflammatory pathway. We have demonstrated that TNFR2 is critical for PGRN-mediated protection in OA development and bone fracture healing[17,18,25]. Another group recently showed that Atsttrin, an engineered protein composed of three TNFR-binding fragments of PGRN, ameliorated OA development in a surgically-induced mouse model[26]. In brief, PGRN and its derived Atsttrin appear to exert their anti-inflammatory and protective activities in OA by activation of the PGRN/TNFR2 protective/anabolic pathway[12,14,27-29], and by inhibition of TNFα/TNFR1 inflammatory/catabolic signaling[17,26].

Etanercept (Enbrel) is a fusion-soluble TNFR2 extracellular protein, and therefore inhibits both TNFα and PGRN. PGRN may be even more inhibited than TNFα, as PGRN has a much higher binding affinity to TNFR2 than TNFα[16]. In this way, Etanercept may be blocking PGRN's protective and anti-inflammatory effect against the development of OA. This would explain the detrimental effects of Etanercept in OA observed by Olson et al[1,6]. Unlike Etanercept, mouse TNFα monoclonal antibody (Infliximab, Remicade) and humanized TNFα monoclonal antibody (Adalimumab, Humira) are specific for TNFα, and have been shown to be protective against the development of OA in animal models[30-32]. This is supported by clinical trials in which Infliximab and Adalimumab have been reported to alleviate symptoms of OA[33-35]. The opposing effects of TNFα-specific (i.e. Infliximab and Adalimumab) and non-specific (i.e. Etanercept) inhibitors in OA indicate the critical role of other ligand(s) of TNFR, such as PGRN, in the regulation of OA. TNFα is known to be the dominant inflammatory molecule in the pathogenesis of rheumatoid arthritis, and blocking TNFα with Etanercept is thus beneficial to the patients with rheumatoid arthritis. However, in the case of OA, the PGRN/TNFR2 protective/anabolic pathway is likely to outweigh the TNFα/TNFR1 inflammatory/catabolic pathway in regulating OA development. Therefore, blocking both PGRN and TNFα with Etanercept may lead to more severe OA.

In summary, the findings of Guilak et al on the negative effect of Etanercept in OA[1,6], reports on the positive role of Infliximab and Adalimumab in OA[30-32], and our data on PGRN-mediated protection in OA through TNFR signaling[16,17], all suggest a complex interplay between TNFα, PGRN and their receptors in the pathogenesis of OA. Future studies are warranted to clarify these molecular mechanisms, which will not only better our

understanding of TNFR signaling in the pathogenesis of OA, but may lead to innovative therapies for OA and other degenerative joint diseases via selectively targeting distinct TNFR pathways.

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