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Short Communication

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Lupus IgG Induces Synovial Inflammation but Inhibits Bone Erosions in SLE Arthritis

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Abstract

Bone erosion is an important feature of inflammatory arthritis. It remains unknown why lupus arthritis lacks bone erosion and destruction. Our recent published paper presents the interesting discovery that joint deposited lupus IgG triggers synovitis but suppresses osteoclastogenesis which is responsible for bone destruction. In this paper, data show that joint deposited lupus IgG induces synovitis through FcγRI on monocytes/macrophages and blocks RANKL-induced osteoclastogenesis through competing for FcγRI binding with RANKL. This study promotes understanding the pathogenesis of lupus arthritis and provides a novel therapeutic target of FcγRI to inhibit bone destruction in inflammatory arthritis.

Keywords: Systemic lupus erythematosus, Arthritis, Bone destruction, IgG, Osteoclastogenesis, Fcgamma receptor,

Review

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by high levels of autoantibodies and multi-organ tissue damage [1]. Arthritis is common in patients with SLE [2]. Bone erosion is a remarkable feature in arthritis such as rheumatoid arthritis (RA) but they are usually absent in arthritis of SLE [3]. Thus, this is particularly striking for clinical doctors because synovial biopsies from SLE patients show similar synovial inflammation to those in RA [4]. Compared arthritis in SLE to RA, it is known that TNF-α and IL-6 play an important role in RA, only high levels of serum IL-6 levels correlate with arthritis in SLE patients [5]. Furthermore, high levels of autoantibodies in the serum and immunoglobulin G (IgG) and immune complex deposition in organ tissues are characteristic for SLE and less typical for RA [1]. Tissue deposited lupus IgG displays a key role in initiating inflammation in organ tissue including kidney, brain, skin and liver [6-8]. It remains unknown whether and how joint deposited lupus IgG contributes to arthritis without bone erosions in SLE.

The recent published paper presents data that lupus IgG deposition causes arthritis but inhibits bone destruction through competitive occupation of FcγRI and reduced RANKL signaling, intra articular injection of lupus IgG triggers arthritis, but does not results in bone destruction, tissue deposition of lupus IgG, monocytes are required for the development of this arthritis [9]. Lupus IgG blocks RANKL-induced monocyte differentiation into osteoclasts that contribute to bone erosion, FcγRI exerts a critical role in pathogenesis of lupus arthritis lacking bone erosion.

In lupus MRL/*lpr* mice, there is IgG deposition and synovial inflammation in absence of bone erosions in joints [9]. In normal mice, intra articular injection of lupus IgG can trigger synovial inflammation but no bone destruction [9].

Arthritis occurred 3 hours after injection, peaked after 3 days, lasted for at least 14 days and the severity of the arthritis was dose-dependent. IgG has been shown to play a critical role in the arthritis induced by lupus serum because synovial inflammation was significantly reduced in mice with intraarticular injection of IgG-depleted lupus serum compared to lupus serum without IgG depletion. Intraarticular of lupus IgG directly induced arthritis [9].

In mouse model of arthritis induced by intraarticular injection of lupus IgG, the severity of arthritis was significantly reduced in mice with monocyte depletion but not affected in mice with lymphocyte deficiency and mice with neutrophil depletion [9]. These results indicate that lupus IgG deposited in the joint can trigger arthritis by activating monocytes/macrophages.

Because monocytes/macrophages can differentiate into osteoclasts in the presence of RANKL, the role of lupus IgG on RANKL-induced monocytes differentiation into osteoclast was determined [10]. The result demonstrates that lupus IgG directly inhibited RANKL-induced monocytes differentiation into osteoclast [9]. Besides the Fcγ receptor (FcγR) is receptor for IgG, FcγR is also required for RANKL-induced osteoclastogenesis, and FcγR includes FcγRI, FcγRII and FcγRIII. Deficiency of FcγRIIB or FcγRIII did not affect inhibitory effect of lupus IgG on RANKL-induced monocyte differentiation into osteoclast [11, 12]. The level of FcγRI and FcγRII and FcγRIII on monocytes in absence or presence of lupus IgG or RANKL was evaluated by flow cytometry. Data from flow cytometry demonstrates that lupus IgG significantly decreased surface level of FcγRI but not FcγRII and FcγRIII on monocytes. Data demonstrate that RANKL significantly reduces surface level of FcγRI but not FcγRII and FcγRIII on monocytes [9]. These results indicate that lupus IgG inhibits RANKL-induced osteoclastogenesis through FcγRI.

Relationship among lupus IgG, RANKL and FcγRI was investigated. The stronger inhibitory effect on osteoclastogenesis was observed in high doses of lupus IgG than lower doses of lupus IgG [9]. Inhibitory effects of lupus IgG on osteoclastogenesis was gradually blocked by increasing doses of RANKL suggesting competition between lupus IgG and RANKL. The stronger inhibitory effects of lupus IgG on RANKL-induced osteoclastogenesis were shown in cells pretreated for 24h when compared to cells treated with both RANKL and IgG at the same time [9]. This data indicates that inhibitory effects of lupus IgG on osteoclastogenesis depend on the extent of IgG binding to FcγRI. The inhibitory effect of lupus IgG on osteoclastogenesis was converted at 24 hours after RANKL stimulation [9]. It suggests that inhibitory effect of lupus IgG on osteoclastogenesis is blocked by the extent of RANKL binding to FcγRI. These data suggest that lupus IgG inhibits RANKL-induced osteoclastogenesis through competition for FcγRI binding.

This study demonstrates that lupus IgG can induce synovitis but inhibit RANKL-induced osteoclastogenesis, suggesting that joint deposited lupus IgG can have different effects on joint tissues. Several lines of evidence strongly support that lupus IgG-induced synovial inflammation can block RANKL-induced osteoclastogenesis through competing for occupation of FcγRI. Lupus IgG can promote monocytes differentiation into dendritic cells that are important for initiating inflammation through cytokines [7]. First, both lupus IgG and RANKL can significantly reduce FcγRI surface expression on monocytes *in vitro*, FcγRI is required for both lupus IgG and RANKL mediated signal transduction. Thus, relationship between lupus IgG and RANKL is competition for FcγRI. Second, lupus IgG binding to FcγRI may lead to functional deficiency of FcγRI required for RANKL-induced osteoclastogenesis. RANKL-induced osteoclastogenesis mayd also result in functional deficiency of FcγRI required for IgG signaling transduction. Third, data presented in this study demonstrates that lupus IgG has stronger inhibitory effect on osteoclastogenesis prior to RANKL stimulation, and lupus IgG loses inhibitory effect on osteoclastogenesis after RANKL stimulation. Conversely, deficiency of FcγRIII and FcγRIIB did not significantly block inhibitory effect of lupus IgG on osteoclastogenesis suggesting that effects are specific to FcγRI. This is in line with the report that activating FcγR, but not inhibitory FcγR, are decreased on osteoclasts as compared to monocytes/macrophages [13].

Recruitment of lupus IgG to FcγRI may result in functional deficiency of FcγRI on the cellular membrane, which is required for RANKL-induced osteoclastogenesis. This study enhances the understanding of pathomechanism of non-destructive arthritis in SLE. The competitive occupation of FcγRI by IgG may develop new therapeutic approaches to prevent bone destruction in autoimmune/inflammatory arthritis.

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