OPEN ACCESS Freely available online

Lupus: Open Access

Mini-Review

Different Effects of Lupus IgG on Joint

Guo-Min Deng

Department of Rheumatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China

ABSTRACT

Bone destruction is a remarkable feature of inflammatory arthritis. It remains unknown why arthritis associated with systemic lupus erythematosus (SLE) does not result in erosion and destruction. Our recent published paper reports that lupus IgG has different effects on joint tissue, joint deposited lupus IgG induces synovitis but inhibits osteoclastogenesis. Lupus IgG induces synovitis through binding to FcγRI on monocytes/macrophages and inhibits RANKL-induced osteoclastogenesis through competing for FcγRI binding with RANKL. This study enhances the understanding of the pathophysiology of SLE-associated arthritis and provides a protective therapeutic target to against bone destruction in inflammatory arthritis.

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

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the presence of high levels of autoantibodies and multi-organ tissue damage [1,2]. Most of SLE patients suffer from joint problem [3,4].

Bone erosion is an important feature in autoimmune/inflammatory arthritis, such as in rheumatoid arthritis (RA). However, they are usually absent in SLE patients and are observed in less than 5% of cases [5]. This is particularly striking because synovial biopsies from SLE patients display similar synovial inflammation to those in RA [6,7]. Although tumor necrosis factor alpha (TNF-α) and interleukin (IL-)6 play a critical role in RA, only serum IL-6 levels correlate with arthritis in SLE patients [8]. Furthermore, high levels of autoantibodies in the serum and immunoglobulin G (IgG) and immune complex deposition in tissues are characteristic for SLE and less typical for RA [1,2]. Tissue deposited lupus IgG has been shown to exert a key role in initiating inflammation in organ tissue including kidney, brain, skin and liver [9-11]. However, it remains unclear whether and how autoantibody IgG contribute to the development of arthritis with the absent of bone erosions in SLE.

In our recent published paper titled "Lupus IgG deposition causes arthritis but inhibits bone destruction through competitive occupation of FcγRI and reduced RANKL signaling" [12], we found that intraarticular injection of lupus IgG induces arthritis in dose dependent manner, but does not results in bone destruction, tissue deposition of lupus IgG, monocytes and TNF are required for the development of this arthritis [12]. Lupus IgG inhibits RANKL-induced monocyte differentiation into osteoclast that contribute to bone erosion.

In lupus MRL/lpr mice, there is IgG deposition and inflammatory cell infiltration in the synovial tissue, but absence of bone erosions in joints [12]. IgG deposition in joints of normal mice was performed by intraarticular injection of serum from SLE patients and lupus mice. Arthritis without bone erosions was developed in normal mice with injection of serum from SLE patients and lupus mice but not from healthy controls [12]. 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 [12]. In model of arthritis induced by lupus IgG, the severity of arthritis was significantly reduced in monocyte depleted mice but not affected in lymphocyte deficient mice and neutrophil depleted mice [12]. The severity of arthritis

Correspondence to: Guo-Min Deng, Department of Rheumatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China, Tel: 3128807305; E-mail: gmdeng@hust.edu.cn

Received: November 30, 2020; **Accepted:** December 07, 2020; **Published:** December 20, 2020

Citation: Deng G-M (2020) Different Effects of Lupus IgG on Joint. Lupus: Open Access. 6:159.

was significantly decreased in TNFα deficient mice compared to wild mice [12]. These results indicate that lupus IgG deposited in the joint can instigate arthritis through monocytes/macrophages and TNFα.

Because monocytes can differentiate into osteoclasts in the presence of RANKL, the effect of lupus IgG on RANKL-induced osteoclastogenesis was investigated [13]. The results demonstrate that IgG from SLE patients and lupus mice directly suppressed RANKL-induced osteoclastogenesis [12]. The Fcγ receptor (FcγR) is not only receptor for IgG, but also a costimulatory molecule for RANKL-induced osteoclastogenesis and FcγR includes FcγRI, FcγRII and FcγRIII [14,15]. We found that FcγRIIB and FcγRIII do not play a central role in the inhibitory effect of lupus IgG on RANKL-induced osteoclastogenesis because effect of lupus IgG on osteoclastogeneis was significantly affected in monocytes with FcγRIIB or FcγRIII deficiency. Flow cytometry was used to quantify surface expression of FcγRI and FcγRII and FcγRIII on monocytes in absence or presence of lupus IgG or RANKL. Results indicate that lupus IgG can significantly decrease expression of FcγRI but not FcγRII and FcγRIII on monocytes. Data demonstrate that RANKL significantly reduces expression of FcγRI but not FcγRII and FcγRIII on monocytes [12]. These data indicate that lupus IgG inhibits RANKL-induced osteoclastogenesis through FcγRI.

There are stronger inhibitory effects on osteoclastogenesis in high doses of lupus IgG than lower doses of lupus IgG [12]. Inhibitory effects of lupus IgG on osteoclastogenesis was gradually blocked by increasing doses of RANKL suggesting competition between molecules. 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 [12]. 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 [12]. 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 shows that lupus IgG can induce synovitis but inhibit RANKL-induced osteoclastogenesis, suggesting that joint deposited lupus IgG can have different effects on joint tissues. There are several lines of evidence strongly to support that lupus IgG-induced inflammation can block RANKL-induced osteoclastogenesis through competing for binding to FcγRI. Lupus IgG was reported to promote monocytes differentiation into dendritic cells that are important for initiating inflammation [10]. FcγRI is required for IgG and RANKL induced signal transduction, and both lupus IgG and RANKL can significantly reduce FcγRI surface expression on monocytes in vitro. Thus the observation that lupus IgG and RANKL compete for FcγRI is a very critical. Lupus IgG binding to FcγRI may lead to functional deficiency of FcγRI required for RANKL-induced osteoclastogenesis. On the other hand, RANKL-induced osteoclastogenesis may result in functional deficiency of FcγRI required for IgG signaling transduction. Data presented in this study demonstrates that lupus IgG has stronger inhibitory effect on osteoclastogenesis at 24h prior to RANKL stimulation, and lupus IgG loses inhibitory effect on osteoclastogenesis at 24h after RANKL stimulation. Thus, the presence of IgG in SLE patients may have long-standing inhibitory effects on RANKL recruitment to FcγRI and osteoclastogenesis. 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 observation that activating FcγR, but not inhibitory FcγR, are decreased on osteoclasts as compared to monocytes/macrophages [16].

Lupus IgG deposition in joints can induce synovial inflammation while inhibiting erosion. 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 path mechanism of non-destructive arthritis in SLE. It provides new therapeutic approaches to autoimmune/inflammatory arthritis through FcγRI inhibition.

ACKNOWLEDGMENTS

This study was supported by Research Initiating Fund (GM Deng, 02.03.2018-41) of Union hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology.

REFERENCES

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(1):2110-2121.
2. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929-939.
3. Sakamoto AP, Silva CA, Ferriani MP, Pereira RM, Bonfa E, et al. Characterization of chronic arthritis in a multicenter study of 852 childhood-onset systemic lupus erythematosus patients. Rheumatol Int. 2016;36(12):1641-1648.
4. Gormezano NW, Silva CA, Aikawa NE, Barros DL, da Silva MA,Salume MHT, et al. Chronic arthritis in systemic lupus erythematosus: distinct features in 336 paediatric and 1830 adult patients. Clin Rheumatol. 2016;35(1):227-231.
5. Martinez JB, Valero JS, Bautista AJ, Restrepo JF, Matteson EL,Rondon F, et al. Erosive arthropathy: clinical variance in lupus erythematosus and association with anti-CCP case series and review of the literature. Clin Exp Rheumatol. 2007; 25(1): 47-53.
6. Rodnan GP, Yunis EJ, Totten RS. Experience with punch biopsy of synovium in the study of joint disease. Ann Intern Med. 1960;53(2): 319-331.
7. Seibold JR, Wechsler LR, Cammarata RJ. LE cells in intermittent hydrarthrosis. Arthritis Rheum. 1980;23(8):958-959.
8. Ball EM, Gibson DS, Bell AL, Rooney MR. Plasma IL-6 levels correlate with clinical and ultrasound measures of arthritis in patients with systemic lupus erythematosus. Lupus. 2014;23(8): 46-56.
9. Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nat Med. 2012;18(6): 871-882.
10. Deng GM, Liu L, Kyttaris VC, Tsokos GC. Lupus serum IgG induces skin inflammation through the TNFR1 signaling pathway. J Immuol. 2010;184(12):7154-7161.

11. Fang X, Zaman MH, Guo X, Ding H, Xie C,Zhang X, et al. Role of Hepatic Deposited Immunoglobulin G in the Pathogenesis of Liver Damage in Systemic Lupus Erythematosus. Front Immunol. 2018;9(1):1455-1457
12. Qiao W, Ding H, Zuo Y, Jiang L, Zhou J,Rong D, et al. Lupus IgG deposition causes arthritis but inhibits bone destruction through competitive occupation of FcRI and reduced RANKL signalling. Clin Transl Immunology. 2020;9(9):e1174.
13. Deng GM, Zheng L, Chan FK, Lenardo M. Amelioration of inflammatory arthritis by targeting the pre-ligand assembly domain of tumor necrosis factor receptors. Nat Med. 2005;11(10): 1066-1072.
14. Takai T. Roles of Fc receptors in autoimmunity. Nat Rev Immunol. 2002;2(8):580-592.
15. Koga T, Inui M, Inoue K, Kim S, Suematsu A,Kodam T, et al. Costimulatory signals mediated by the ITAM motif cooperate with RANKL for bone homeostasis. Nature. 2004; 428(6984):758-763.
16. Grevers LC, de Vries TJ, Everts V, Verbeek JS, van den Berg WB,Lent PLEV, et al. Immune complex-induced inhibition of osteoclastogenesis is mediated via activating but not inhibitory Fcgamma receptors on myeloid precursor cells. Ann Rheum Dis. 2013;72(2):278-285.