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RESEARCH HIGHLIGHT

Lupus pathogenesis: role of IgE autoantibodies

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IgE is commonly known for its role in the Th2 responses, protection against helminth parasites and pathogenesis of allergy. A recent report shows that IgE autoantibodies to dsDNA plays a major role in the pathogenesis of lupus nephritis by exacerbating the interferon-α responses in plasmacytoid dendritic cells.

Systemic lupus erythematosus (SLE), one of the common multi-system autoimmune diseases, is characterized by an aberrant activation of effector T lymphocytes and development of autoantibodies to nuclear antigens, particularly double-stranded DNA (dsDNA). Deposition of immune complexes (ICs) formed by autoantibodies and nuclear antigens, and infiltration of inflammatory cells to the kidneys cause lupus nephritis and is the most serious manifestation of SLE [1]. One of the well-characterized cellular and molecular mechanisms that underlie pathogenesis of SLE is that the activation of plasmacytoid dendritic cells (pDCs) by dsDNA-IgG ICs that are sensed by TLR9, leads to interferon-α (IFN-α) responses [2]. IFN-α and pDCs then support B cells to undergo activation, proliferation and plasma cell differentiation to produce autoantibodies.

IgE, one of the antibody (immunoglobulin) isotypes, is classically known for its role in Th2 responses and in the pathogenesis of allergy. Growing evidences suggest that the pathogenic role of IgE antibodies is not restricted only to allergy but they might have a role in other inflammatory and autoimmune conditions as well [3, 4]. The presence of IgE autoantibodies to dsDNA has been reported previously in several lupus patients [5-7]. Recent report in mice has shown that dsDNA-specific IgE (dsDNA-IgE) plays a significant role in the progression of lupus-like disease. In fact, IgE deficiency in *FcγRIIB*$^{-/-}$ mice delayed the development and severity of lupus-like disease, and was associated with significantly reduced activation of basophils and homing of inflammatory cells to spleen [6]. It was proposed that activation of basophils and their migration to spleen mediate the differentiation of B cells and production of autoantibodies in lupus. Activation of basophils and dsDNA-IgE antibody levels were also correlated with the disease activity in SLE patients [6]. However, the precise cellular and molecular mechanisms by which autoreactive IgE mediates the pathogenesis of lupus remain an enigma.

As IFN-α is a major player of lupus pathogenesis, Henault *et al*. [8] recently explored whether dsDNA-IgE antibodies have any role in the regulation of pDC IFN-α response. They report that > 50% lupus patients exhibit dsDNA-IgE, with elevated concentrations in active lupus. Surprisingly, IgE blocking antibodies significantly reduced the IFN-α secretion by peripheral blood mononuclear cells when incubated with serum from dsDNA-IgE^{+} patients, suggesting that IgE autoantibodies propel IFN-α responses from pDCs. Indeed, by using an engineered IgE monoclonal antibody with specificity for dsDNA, they confirmed the ability of dsDNA-IgE ICs to induce large quantities of IFN-α from pDCs, thus uncovering the previously unknown molecular mechanism that contributes to lupus pathogenesis.

How does dsDNA-IgE mediate activation of pDCs and exacerbate autoimmune response? Like other immunoglobulins, IgE exerts effector functions via Fc receptors (FcR) and hence FcεR-mediated uptake of dsDNA-IgE ICs represents a potential pathway of pDC activation. Indeed, pDCs express high-affinity FcεRI that routed dsDNA-IgE ICs to phago-lysosome to enable TLR9 sensing and nuclear translocation of IRF7, and to trigger inflammatory cytokine responses including IFN-α, IL-6, IL-8 and TNF (Figure 1) [8]. Furthermore, these activated pDCs supported B cell proliferation in the co-culture, and promoted plasma cell differentiation and immunoglobulin production, the process mediated by pDC-derived IFN-α and IL-6 [9]. Demonstration of IgE deposition in the glomeruli and extraglomerular areas as well as close proximity of pDCs and B cells in the kidney biopsies of lupus nephritis patients led to a conclusion that the aforementioned *in vitro* phenomenon might be true in the patients as well.

IgG autoantibodies to nuclear antigens is the classical feature of SLE and it is not surprising that lupus patients positive for dsDNA-IgE also contained dsDNA-IgG. As dsDNA is available both for IgG and IgE autoantibodies in the circulation to form ICs, these immunoglobulins can signal the activation either individually or in synergy. To test this hypothesis, Henault *et al*. [8] used the previously described dsDNA-IgG and an engineered IgE with variable regions of dsDNA-IgG. They found that dsDNA-IgE ICs were superior to dsDNA-IgG ICs in their ability to induce maturation of pDCs. Although both ICs induced similar quantities of

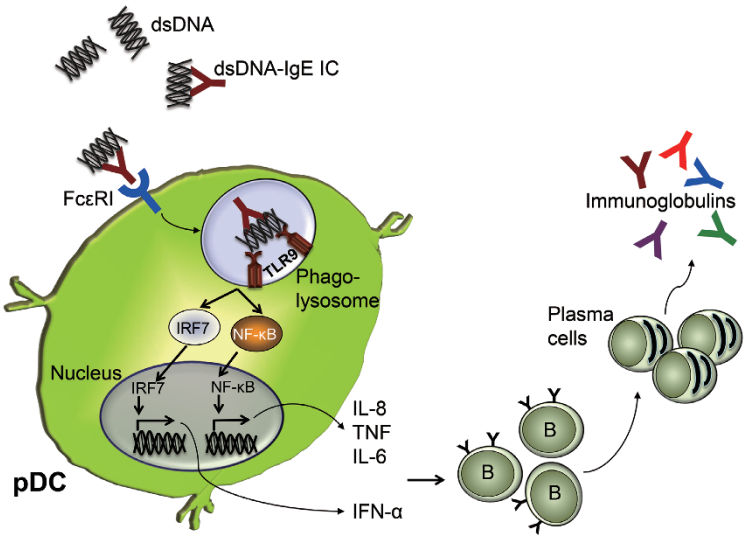

Figure 1 Pathogenic role of IgE autoantibodies to dsDNA in systemic lupus erythematosus. IgE autoantibodies to dsDNA form immune complexes (dsDNA-IgE IC) and bind to FcεRI on plasmacytoid dendritic cells (pDCs). Subsequent delivery of dsDNA-IgE ICs to phago-lysosome leads to TLR9 sensing, nuclear translocation of IRF7 and NF-κB, activation of pDCs, and IFN-α, IL-6, IL-8 and TNF cytokine production. The activated pDCs promote B cell proliferation, plasma cell differentiation and immunoglobulin production via IFN-α and IL-6.

IFN-α, its peak production was quicker with dsDNA-IgE ICs. Interestingly, synergistic activity was observed when both isotypes were combined at equal ratios in the dsDNA-ICs. Such a synergy was also confirmed in the ability of pDCs to mediate T cell proliferation, a key function of antigen presenting cells. Mechanistically, the synergy was due to enhanced phagocytosis of dsDNA by pDCs. The synergy was preserved even when IgE was used 10 or 100 times lower than IgG, corresponding to the levels found in SLE patients. As IgE binds to high-affinity FcεRI on pDCs with an affinity constant at least 1 000 times higher than the binding of IgG to low-affinity FcγRIIa on pDCs [10], dsDNA-IgE ICs would reduce the threshold of activation for pDCs. Thus, dsDNA-IgE-mediated pDC activation exacerbates the inflammatory cytokine, and T and B cell responses in lupus patients.

The key question that requires further investigation is why allergic manifestations are not observed in lupus nephritis patients although they have dsDNA-IgE. It is known that cross-linking of surface-bound IgE or IgE-ICs activate basophils and mast cells leading to their degranulation and release of histamine, proteoglycans, lipid mediators and Th2 cytokines. From the point of basophils, FcγRIIB might explain the absence of allergic manifestations in lupus patients. Among all the human immune cells, the intensity of expression of FcγRIIB is highest on the basophils [11]. Of note, FcγRIIB dominates activating FcγRIIA and also inhibits IgE-FcεRI-mediated basophil responses [11]. As dsDNA-IgE antibodies in the circulation are 10- to 100-fold lesser than dsDNA-IgG in the lupus patients, it is likely that dsDNA-IgG ICs might inhibit dsDNA-IgE ICs-mediated activation of basophils by signaling through FcγRIIB. However, mast cells that are tissue resident lack FcγRIIB and hence alternative mechanism(s) might be in operation. Of note, IFN-α/β has been reported to inhibit IgE-mediated histamine release from rat mast cells [12]. Thus, possible suppression of mast cell-derived histamine by pDC-derived IFN-α might provide another explanation for the lack of allergic manifestations in lupus patients.

To conclude, this report is a major breakthrough in understanding the complex pathogenesis of lupus nephritis. IgE or FcεRI can represent novel targets for the therapy of lupus nephritis.

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