



The role of IgE in systemic lupus erythematosus

Dear Editor,

Although the presence of immunoglobulin E (IgE) autoantibodies in patients with systemic lupus erythematosus (SLE) has been known for more than 40 years [1,2], their association with SLE has been investigated in greater depth in recent years [1–3].

The IgE has an important role in allergic reactions as, when it binds to the surface of mast cells and basophils, it triggers their degranulation, thus releasing various chemical mediators, such as biogenic amines, proteases, cytokines and proteoglycans [2,4,5]. There are three IgE receptors; Fc epsilon RI (high affinity), Fc epsilon RII or CD23 (low affinity), and galectin-3 [6]. In humans, two forms of Fc epsilon RI receptors have been described: the tetrameric receptor is mainly expressed in tissue-based basophils and mast cells [2,4,6], while the trimeric receptor is expressed in dendritic cells, neutrophils, eosinophils, monocytes, Langerhans cells, platelets, and intestinal and bronchial epithelial cells [4,6,7].

Some studies have proposed the term “autoallergy” to refer to autoimmune processes mediated by IgE autoantibodies [6]. There are two types of IgE in SLE: autoreactive IgE and non-autoreactive IgE (Table 1). Autoreactive IgE have been associated with increased SLE activity and lupus nephritis (LN), and promote the production of interferon (IFN) alpha by plasmacytoid dendritic cells (pDC) [1,8–10]. Non-autoreactive IgE correlate negatively with the Lupus Erythematosus Activity Index (SLEDAI) and inhibit the release of IFN by pDC [1,4,11]. Studies have reported that 30–50% of SLE patients present autoreactive IgE directed against dsDNA (mainly), Ro/SSA, La/SSB and Sm [9,11,12], anti dsDNA IgE have been found in all lupus subtypes [10] and have been associated with SLE disease activity [1,5,8–10,13] and kidney involvement [8–10].

Autoreactive IgE are suggested to regulate basophils, pDC and IFN alpha to trigger acquired and innate immune responses by generating autoantibodies [1,4,14]. Activation of basophils by immune complexes with autoreactive IgE amplifies the production of autoantibodies [3]. Pan et al. found that increased activation of peripheral basophils by autoreactive IgE correlated with increased autoantibody production and disease activity in patients with SLE [15]. Activated basophils interact with autoreactive B and T cells to amplify the immune response (Fig. 1). B cells mature and differentiate into autoantibody-producing plasma cells through the secretion of IL-4, IL-6, IL-5, IL-13 and the membrane expression of CD40L, BAFF and APRIL [13,15], while T cells differentiate into Th17 through IL-6 and histamine, and Th2 lymphocytes through IL-4, thymic stromal lymphopoietin, the superficial expression of MHC class II, CD40L, IL-25 and the secretion of retinoic acid [3,4,16–18].

Henault et al. reported that, in pDC/B cell cultures stimulation with anti-dsDNA IgE antibodies promoted B cell proliferation and their differentiation to plasma cells [10]. IFN alpha production by

pDC is induced and sustained by immunocomplexes containing IgE autoantibodies [1]. IFN alpha promotes the activation, proliferation and differentiation of B cells in plasma cells that produce antibodies. Massive IFN secretion by pDC induces IFN gamma production by natural killer (NK) cells, amplifying the inflammatory response [19].

Reducing autoreactive IgE levels and inhibiting their receptor or increasing non-autoreactive IgE are promising therapeutic objectives in the management of SLE [1,4]. Omalizumab is an anti-IgE monoclonal antibody that reduces circulating IgE, including autoreactive IgE, and prevents their binding to the Fc epsilon RI receptor [1,4,20], in a clinical trial with sixteen subjects with SLE and a SLEDAI-2K score of ≥ 4 and elevated autoreactive IgE antibody levels, omalizumab decreased disease activity and reduced IFN release [21]. The pro-apoptotic molecule Bcl-2 homologous antagonist killer (BAK) and the C epsilon 3 domain of IgE have been designed to form a fusion molecule, which, in vitro, efficiently reduces cells expressing Fc epsilon RI [22]. A reduction in basophils and pDC has also been achieved with an anti-IL3R alpha cytotoxic antibody, with efficient in vitro results [23]. The gut microbiota and helminths may participate in the optimal functioning of the regulatory pathways involved in immune tolerance [1,4,24], since the products they secrete could have an immunomodulatory effect, helminths promote a Th2 immune response with increased production of non-autoreactive IgE, this avoids the Th1 or Th17 immune response involved in the pathogenesis of SLE, favors the proliferation of anti-inflammatory M2 macrophages, decreases the synthesis of proinflammatory cytokines such as IFN gamma or tumor necrosis factor alpha, and promotes the production of immunosuppressive cytokines such as IL-10 or transforming growth factor beta by regulatory T lymphocytes. These helminth functions have led to a new therapeutic approach in SLE – helminth-based immunotherapy [1,4,25,26].

Table 1
Differences between autoreactive IgE and non-autoreactive IgE.

Autoreactive IgE	Non-autoreactive IgE
Increased SLE activity	Correlates negatively with SLEDAI
Promotes the release of IFN	Inhibits IFN release
Stimulate LN	Suppresses the inflammatory process of the disease

SLE: Systemic lupus erythematosus; IFN: Interferon; LN: lupus nephritis; SLEDAI: Lupus Erythematosus Activity Index.

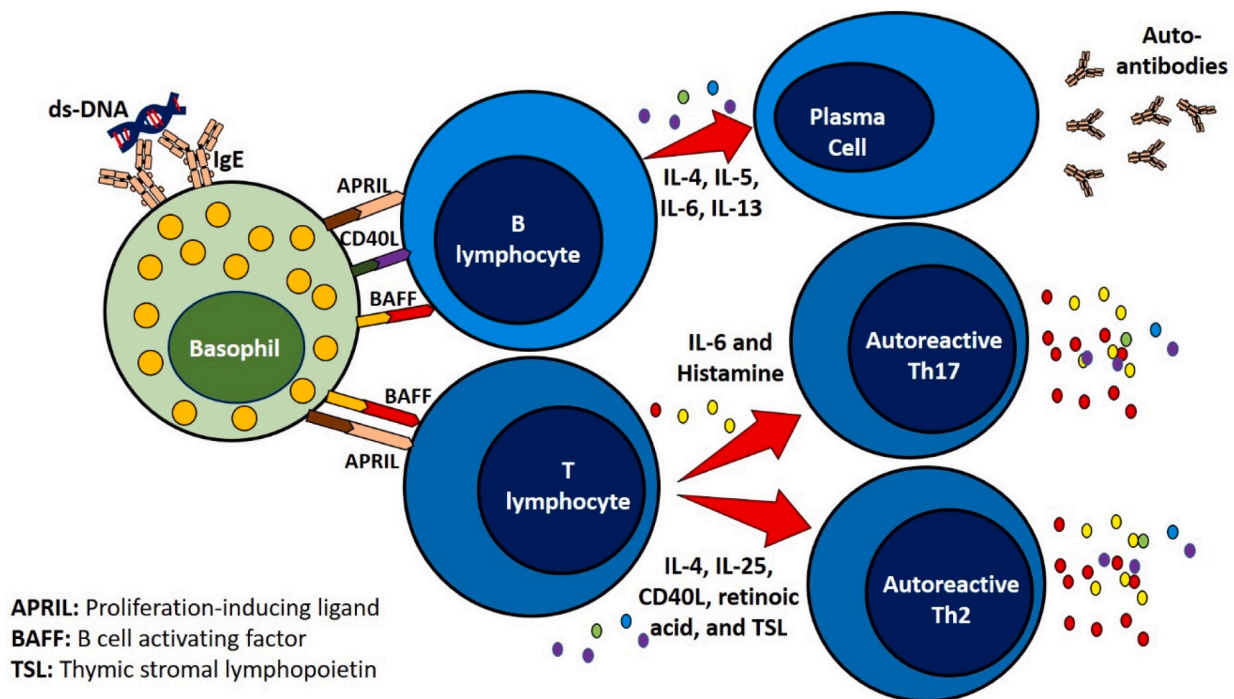


Fig. 1. Activated basophils by autoreactive IgE, promote B and T lymphocyte differentiation.

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Mario García-Carrasco^{a,b}, Salvador Macías-Díaz^c, Claudia Mendoza-Pinto^{a,b,z}, Pamela Munguía-Realpozo^b, Ivet Etchegaray-Morales^b, José Luis Gálvez-Romero^d, José Carmelo Peña-Pérez^a, Roberto Berra-Romani^e, Álvaro Montiel-Jarquín^f, Socorro Méndez-Martínez^g

^a Systemic Autoimmune Diseases Research Unit CIBIOR, Hospital de Especialidades, UMAE, Instituto Mexicano del Seguro Social, Puebla, Mexico

^b Rheumatology Department, School of Medicine, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico

^c Internal Medicine Service, Hospital General de Zona N° 1, Instituto Mexicano del Seguro Social, Pachuca, Hidalgo, Mexico

^d Clinical Research Department, Regional Hospital, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Puebla, Mexico

^e Department of Biomedicine, School of Medicine, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico

^f Research in Health Unit, UMAE, Instituto Mexicano del Seguro Social, Puebla, Mexico

^g Research in Health Coordination, Instituto Mexicano del Seguro Social, Puebla, Mexico

* Corresponding author at: 2004 2 Norte, Puebla 72000, Mexico.
E-mail address: cmp_26@yahoo.com.mx (C. Mendoza-Pinto).