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RESEARCH HIGHLIGHT

New roots for IgE-producing B cells

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In allergic responses, B cells are driven to undergo an immunoglobulin isotype switch, shifting from immunoglobulin M to immunoglobulin E (IgE) synthesis. This process involves the rearrangement of germline DNA in the immunoglobulin heavy-chain locus and is stimulated by cytokines (IL-4 and IL-13) and CD40 activation, but the biology of the IgE-producing B cells, where they are located when the isotype switch occurs as well if the process involves an intermediate step of rearrangement to IgG1 and later to IgE, is still poorly understood.

IgE are the main soluble effectors required to fight parasite infection, but are also produced during the sensitization phase of allergic reactions. So, despite their protective function, IgE are perhaps better known for their pathogenic role in allergies and the pathway of B cells commitment to IgE production is a critical, yet poorly understood, subject in the physiopathology of atopic diseases.

The main reason for the lack of studies in this area is the relatively low frequency of IgE-producing B cells and the technical difficulties for their detection *in vivo*. Current immunohistochemical methods are both poorly sensitive and relatively inaccurate in detecting IgE-switched B cells.

In a recent study published in *Nature Immunology*, Lawren Wu and collaborators[1] revised the current view that IgE-producing hypermutated B cells mainly arise by sequential switching from an IgG1 cell intermediate after affinity maturation of the latter in germinal centers (GCs), demonstrating that the IgE class switch and affinity maturation can actually occur within GCs.[2]

The group of Lawren Wu took advantage of a novel knock-in mouse model that they had previously developed, in which the green fluorescent protein is conditionally produced at high levels only in IgE-switched B cells.[3] The use of this model allows the direct histochemical visualization of IgE-switched B cells by fluorescence microscopy and their precise spatial/temporal detection within secondary lymphoid tissues during the course of immune responses. Moreover, these cells also produce a recombinant 'tagged' form of membrane-bound IgE, which can be used for confirming fluorescence data by antibody staining. This model overcomes the glitches and biases associated with the indirect immunohistochemical detection of IgE-producing B cells that affected previous studies.

High-affinity IgG1 and IgE are both produced during Th2 responses, but previous studies failed to detect a GC phase for IgE-producing cells, despite evidence of extensive hypermutation and hence affinity maturation for these cells. Several papers debate the maturation pathways of the IgE^+ memory B cells and plasma cells, in fact, switching to IgE initiates in GC, but IgE^+ cells differentiate quickly into plasma cells and are mostly found outside GC areas. In spite of their brief GC phase, IgE antibodies display somatic hypermutation (SHM) and affinity maturation. However, it is possible that IgE-producing cells might undergo SHM outside GCs in extrafollicular sites, and these data can also be supported by the fact that T-independent signals can lead to SHM too.[4]

The current model for the generation of high affinity IgE-producing B cells postulated the necessity of an IgG1 intermediate cell phase during which SHM takes place and a later IgE switch event ('sequential switching model' as described previously[2]). Moreover, on the basis of this hypothesis, it was proposed that IgE-producing plasma cells arise during secondary responses from memory B cells producing high-affinity IgG1 upon switching to IgE.

The data obtained by the group of Lawren Wu challenge this model by providing for the first time the evidence *in vivo* that IgE-switched B cells are present within GCs of mice with wild-type polyclonal B and T cells during the course of the immune response to helminthes infection. Moreover, the authors were able to sort and isolate IgE switched cells with immunophenotypical characteristics of memory cells that, when adoptively transferred in B cell-deficient μMT mice, were able to mount a rapid response and protect recipients from parasite infection.

Since previous studies failed to identify IgE memory B cells, the study of Wu and co-workers provides, for the first time, evidence that cellular IgE memory could reside in the IgE-switched compartment. These new findings have relevant implications for the understanding of the mechanisms of memory IgE B-cell expansion during secondary responses, prompting novel studies aimed at finding therapeutic targets for the treatment of allergic conditions and to design better vaccines and adjuvants to induce protective immune response and to allow tolerance for the allergens.

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1 Talay O, Yan D, Brightbill HD, Straney EE, Zhou M, Ladi E *et al*. IgE^+ memory B cells and plasma cells generated through a germinal-center pathway. *Nat Immunol* 2012; **13**: 396–404.
2 Erazo A, Kutchukhidze N, Leung M, Christ AP, Urban JF, Curotto de Lafaille MA *et al*. Unique maturation program of the IgE response *in vivo*. *Immunity* 2007; **26**: 191–203.
3 Brightbill HD, Jeet S, Lin Z, Yan D, Zhou M, Tan M *et al*. Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice. *J Clin Invest* 2010; **120**: 2218–2229.
4 Puga I, Cols M, Barra CM, He B, Cassis L, Gentile M *et al*. B cell-helper neutrophils stimulate the diversification and production of immunoglobulin in the marginal zone of the spleen. *Nat Immunol* 2011; **13**: 170–180.