

REVIEW

We are memory: B-cell responses in allergy and tolerance

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The significance of B-cell memory in sustaining IgE-mediated allergies but also ensuring the development of long-term allergen tolerance has remained enigmatic. However, well-thought murine and human studies have begun to shed more light on this highly disputed subject. The present mini review highlights important aspects, like the involvement of IgG1 memory B cells, the meaning of low- or high-affinity IgE antibody production, the impact of allergen immunotherapy, or the relevance of local memory established by ectopic lymphoid structures. Based on recent findings, future investigations should lead to deeper knowledge and the development of improved therapies treating allergic individuals.

Keywords: allergy · B-cell memory · ectopic lymphoid structures · IgE

Introduction

The phrase “*We are memory*” exemplifies how a human being and its behavior is essentially determined through recollections [1]. Indeed, it also illustrates a fundamental principle of the immune system ensuring our existence by protecting us against harmful while at the same time staying tolerant toward harmless encounters. Here, B-cell (BC) memory plays a decisive part [2–4]. Its establishment rests on the cognate interaction of antigen-primed BC and T-follicular helper cells (Tfh), which express CD40 ligand and secrete cytokines like IL-21 and IL-4. This results in BC proliferation and differentiation into short-lived plasma cells, secreting IgM or isotype-switched antibodies of low affinity, memory BC (B_{mem}) of (primarily) IgM isotype, and GC forming BC [5–7]. Antigen-specific communication of the latter with follicular DCs and Tfh leads to affinity maturation, mostly by somatic hypermutation (SHM), and the development of both highly affine plasmablasts and less strongly affine B_{mem} . This well-coordinated process serves the evolution of markedly antigen-specific, long-lasting immunological memory, provided by both B_{mem} , which can

be promptly activated in a secondary immune response, and long-living plasma cells secreting up to 10 000 antibodies per second [8].

BC memory in IgE-mediated allergies

As important as memory is for a protected interaction with our environment, it may also function as a troublemaker, causing unwanted adverse reactions. In neuropsychology, “*misremembering*” means that a memory may become distorted or reconstructed, provoking an inappropriate emotional response [1]. Yet this term can also be referred to the development of aberrant immune responses leading to autoimmunity or allergies, the former caused by the erroneous recognition of self as foreign, the latter expressed by sensitization to a formerly innocuous-graded environmental substance. In the case of immediate-type allergy, this misdirected immune response results in the production of IgE antibodies, which after crosslinking as surface-bound antibodies on basophils and mast cells lead to the release of inflammatory mediators and clinical symptoms like urticaria, angioedema, rhinitis, bronchial asthma, or anaphylactic shock. IgE-mediated allergies can persist for long times eliciting severe anaphylactic reactions even after decades without allergen contact [9–11].

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Notably, studies on BM transplantation recipients confirmed that IgE memory can even be transferred to another individual [12, 13]. However, compared to the prototypical pathway of IgG BC memory development, animal and clinical investigations revealed that preservation of IgE-dependent immune responses is characterized by striking differences [14, 15] (Fig. 1).

IgE GC are transient, with IgE BC showing impaired BC receptor function and expression, a short form of membrane IgE with decreased signaling strength, and reduced number of costimulatory surface molecules, which predispose them to low-affinity plasma cell differentiation and apoptosis rather than developing into IgE B_{mem} [16–18]. A remarkable study confirmed former data gained from helminth infection models [19], showing that IgG1 GC B_{mem} serves as the main precursor of long-living IgE plasma cells [20]. While IgE B_{mem} were almost undetectable in lymphoid organs (but not totally absent), IgG1 B_{mem} could be subdivided into two subsets, a GC forming CD80⁺CD73⁺ population, of which selected clones of high-affinity IgG rapidly differentiated into IgE plasma cells, whereas pro-GC double-negative IgG1 B_{mem} gave a delayed rise to mainly low-affinity IgE plasma cells. Evolution of IgE rather than IgG1 plasma cells was dependent on T-cell (TC) help and IL-4/IL-13. Notably, only IgE from the first subset were pathogenic in a passive cutaneous anaphylaxis model [20]. While there still seem to be IgE plasma cells generated through direct isotype switch (from IgM to IgE), markedly affinity-matured IgE plasma cells are derived from GC IgG1 BC by indirect switching (from IgM over IgG1 to IgE; [15]). However, IgE plasma cell survival is not unlimited and exclusively sufficient in maintaining allergic responses, as a study utilizing a peanut-allergic mice model revealed that persistent IgE memory is critically dependent on Th2-promoted restimulation of B_{mem} [21]. Thus, the establishment of proallergic IgE memory in mice comprises a unique differentiation process, of which decisive parts are (i) the development of antigen-specific IgG1 GC BC, (ii) affinity maturation by SHM and differentiation into IgG1 B_{mem}, (iii) the selection of high-affinity IgG1 B_{mem} clones and generation of isotype-switched long-living plasma cells, which secrete highly antigen-specific IgE antibodies mediating anaphylaxis, and (iv) Th2-supported boost of IgG1 B_{mem}.

Several findings suggest that IgE memory in humans comprises similar principles. In atopics, IgE synthesis is preceded by or associated with marked IgG production against the same allergen, respectively [22, 23], and shows “molecular footprints” of sequential switching via IgG [24]. A recent study provided further evidence demonstrating by in vitro culturing of tonsil BC with IL-4 and anti-CD40 that the majority of IgE plasma cells were generated from IgG BC, which exhibited enhanced long-form membrane IgE expression, indicating increased survival [25]. In a technically demanding investigation, peripheral blood single IgE⁺ cells were successfully isolated from peanut allergic patients (but not healthy controls) with transcriptome analysis showing that—similar to mice and unlike the cells with other isotypes—the majority were IgE plasmablasts determined for plasma cell differentiation by expression of *PRDM1*, *XBPI1*, and *IRF4* ([26] and reviewed in [27]). Further exploration revealed several cellular

features known from murine IgE memory composition, like the presence of short-lived plasmablast characteristics (specifically, immature gene expression status, reduced activation, and survival capacity) and a compromised ability for B_{mem} development (loss of membrane IgE), although a few IgE B_{mem} could be identified. Another interesting finding, a convergent evolution was noticed in the IgE profiles of different individuals, which showed high-affinity maturation to the same allergens.

BC memory in tolerance induction and maintenance

Recent studies examined memory responses elicited during tolerance induction in allergic individuals treated with allergen immunotherapy (AIT). AIT, comprising the repeated administration of increased allergen dosages, elicits pronounced immunological alterations, that is, a transitional boost of allergen-specific IgE, a continued increase of allergen-blocking IgG antibodies (mainly of the IgG4 isotype), the transient induction of regulatory TC, and a gradual loss of pathogenic Th2 cells [28–30]. A randomized, placebo-controlled longitudinal trial investigated the temporary IgE increase in patients receiving sublingual grass pollen AIT and showed that this was accompanied by a boost of short-lived IgE plasmablasts [31]. Utilizing next-generation sequencing, two clonally related BC populations of IgE plasmablasts and IgG B_{mem} (termed IgG_E B_{mem}) were detected, similarly expanding and condensing, which exhibited analog profiles of SHM. As most of the IgG_E B_{mem} contained ϵ -germline transcripts, these results clearly point to the selection of high-affinity matured allergen-specific IgG clones as precursors of the IgE response by sequential switching to IgE plasmablasts also in humans, as already described in mice. As similar clones were found in nasal biopsies, this selection process might occur in peripheral tissues as well and not solely in secondary lymphoid organs (see local BC memory). However, since only 20% of the analyzed clones represented IgG_E B_{mem}, these data do not exclude the simultaneous existence of long-living IgE B_{mem} as another source of human IgE memory.

Single IgG B_{mem} of various isotypes were additionally described in this investigation, notably IgG4 B_{mem}, potentially representing an AIT-induced BC subset required for the establishment of long-term allergen tolerance. However, the significance of an IgG memory response for the stable development of immunological tolerance was not the focus of this study. Another study tried to address this question by determining different BC subpopulations by flow cytometry analysis in patients treated with ryegrass pollen sublingual AIT [32]. Here, the frequency of IgG2 and IgG4 B_{mem} were found to increase during an observation period of 3 years. However, since no allergen-specific BC analysis was performed, the meaning of these findings remains unclear. As IgG B_{mem} are very important in ensuring long-term pathogen protection induced by vaccination, it would be interesting to learn more about how allergen-targeted IgG memory is shaped by AIT in the direction of providing long-term allergen tolerance rather than maintaining IgE B_{mem} responses.

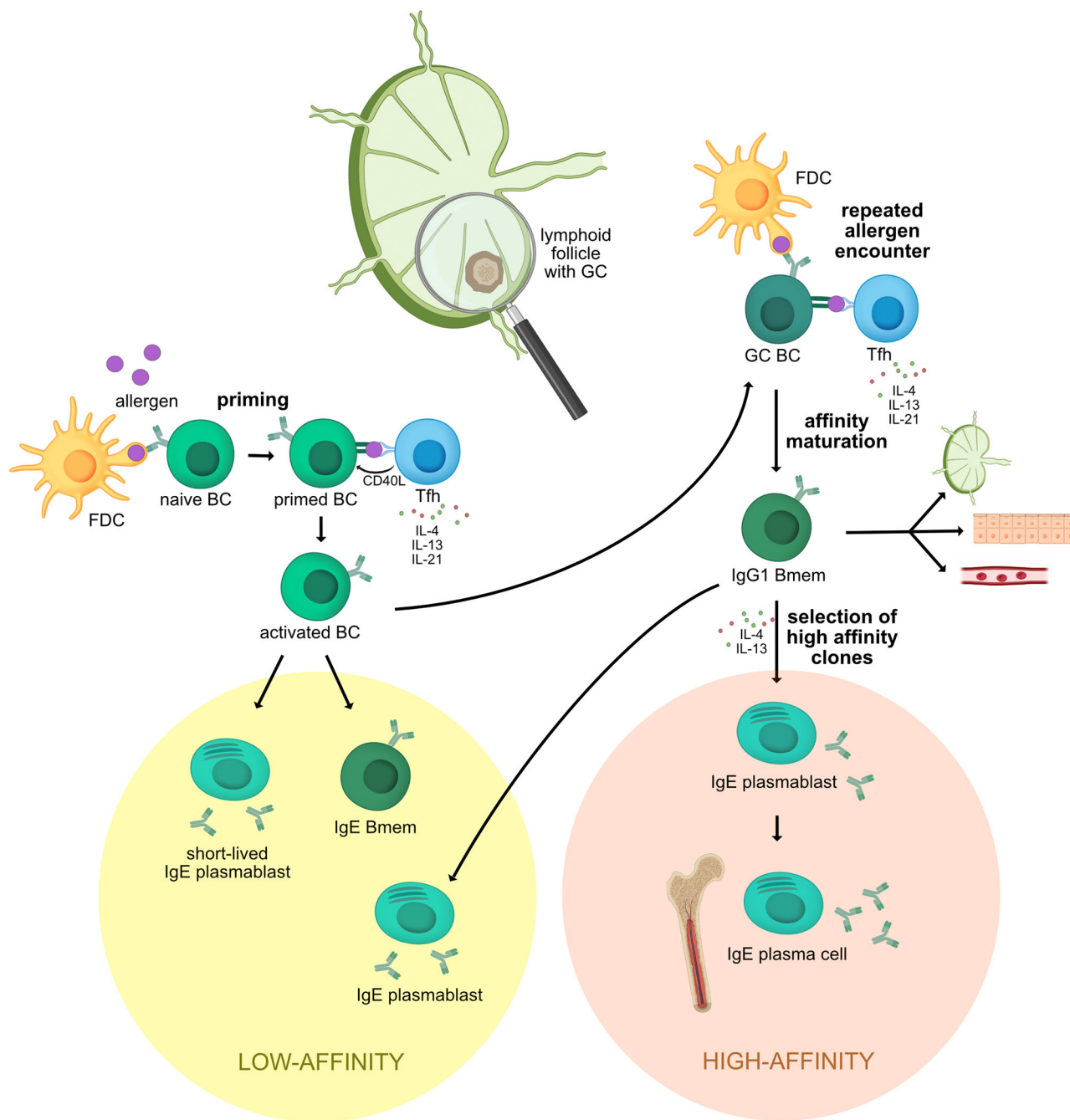


Figure 1. IgE memory in lymphoid follicles. Priming of naïve B cells (BC) by allergen-presenting follicular dendritic cells (FDC) and T-follicular helper cells (Tfh), which secrete IL-21, IL-4, and IL-13, lays ground for different manifestations of IgE memory (as schematically illustrated in this figure). A rather transient form is generated by BC showing shortened membrane IgE with decreased signaling strength, which differentiates into short-lived plasmablasts and a few B-memory cells (B_{mem} ; yellow circle). They produce low-affinity IgE antibodies, which are mainly derived from direct isotype switching (IgM/IgD→IgE). Repeated allergen encounters lead to the formation of germinal centers (GC) by Tfh and allergen-specific BC, which produce IgE primarily generated by indirect isotype switching (IgM/IgD→IgG→IgE). Somatic hypermutation results in the development of IgG1 B_{mem} , which can either circulate in the peripheral blood, settle in peripheral tissues (see Fig. 2) or rather stay in the lymphoid follicle. Here, upon new allergen contact, they might contribute to short bursts of low-affinity IgE or the establishment of long-lasting, strongly pathogenic high-affinity IgE synthesis (red circle), promoted by the type 2 cytokines IL-13 and IL-4 and sustained by selected clones of IgE plasmablasts, which become long-living plasma cells after entering the BM. Thus, both IgG1 B_{mem} and IgE plasma cells are the two major players ensuring the maintenance of IgE-mediated allergies.

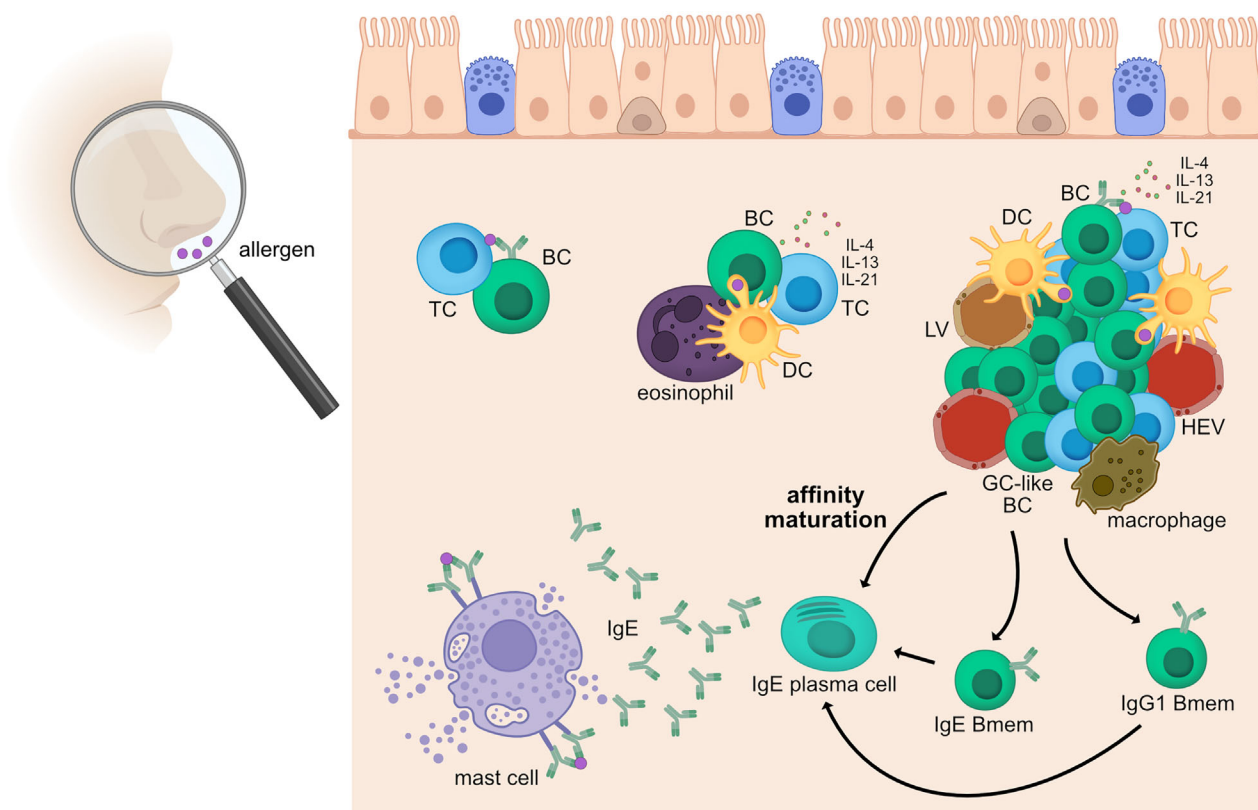


Figure 2. IgE memory in peripheral tissues. After their development in secondary lymphoid organs (see Figure 1), IgE and IgG1 B memory cells (B_{mem}) might migrate to peripheral tissues, supporting local IgE memory responses by differentiating into IgE secreting B cells (BC). However, IgE memory might also develop directly in these tissues. Upon allergen contact and concomitant inflammatory signals, BC and TC may establish different forms of ectopic lymphoid structures (ELS) in skin, gastrointestinal, or respiratory mucosa. These range from simple encounters of BC and TC to arrangements of BC, TC, DCs, and other immune cells to complex structures resembling germinal centers (GC) of lymphatic follicles by encompassing lymphatic vessels (LV) and high endothelial venules (HEV). Stimulated by IL-21 and the type 2 cytokines (IL-4 and IL-13) allergen-specific BC can undergo proliferation, somatic hypermutation and class-switching to IgE, generating IgE plasma cells, IgE B_{mem} or IgG B_{mem} . These cells provide an allergen-specific IgE memory, allowing a rapid response to environmental allergen exposure, which results in local IgE production. Fixation of allergens by IgE on the surface of mast cells results in clinical symptoms elicited by degranulation and the release of inflammatory mediators.

Local BC memory

Recent evidence suggests that BC memory is not only established and modified in the GC of LN but can also be shaped in peripheral tissues and actively modulate local immune responses [33, 34]. Here, propagated by chronic inflammatory signals, BC together with other cell types may form so-called tertiary lymphoid organs, also termed ectopic lymphoid structures (ELS) [35, 36]. Their organization ranges from simple TC–BC aggregates to architecturally complex, highly organized GC-like configurations associated with lymphoid neogenesis and high endothelial venules (Fig. 2) [37–39]. Unlike the usually diffuse pattern of inflammatory infiltrates, the generation of ELS seems to be governed by a set of lymphangiogenic signals and the intricate interplay of tissue-resident, stromal, and infiltrating immune cells [40–42]. In these structures, BC can become activated in response to an environmental stimulus in an antigen-specific manner and undergo SHM with class switching, affinity maturation, and plasma cell differentiation to produce high-affinity antibodies at the site of the

encounter [43, 44]. Variable types of TC and innate lymphoid cells (ILC) have been detected in ELS, which are reported to play an important part in orchestrating their formation. Due to their plasticity, they may also exert Tfh-like functions needed for the establishment of high-affinity matured B_{mem} and plasma cells. While this seems especially the case for IL-17-producing cells, there are also data pointing to IL-4-producing type 2 TC and ILC, namely LTi/CCR6⁺ ILC3 [34, 40, 45, 46].

Immunological findings both in humans and animal studies indicate that ELS might also be important in IgE-mediated allergies. In patients with allergic rhinitis, adaptive immune receptor repertoire sequencing lay ground for evidence of allergen-driven SHM in the nasal mucosa during seasonal allergen exposure [17]. Furthermore, mucosal IgE plasmablasts, which have undertaken affinity maturation in the process of their development in situ, are fully functional in peripheral tissue in humans [47, 48] and may become long-lived IgE plasma cells after migration to the BM as suggested by murine studies [49]. However, data on to what extent short- and long-lived plasma cells contribute to

IgE production in humans, especially in local tissues, is limited [50, 51].

In addition, mRNA analysis revealed class-switch recombination to IgE in the nasal or bronchial mucosa of patients with either allergic rhinitis or asthma, pointing to local IgE production in these tissues [43, 52] with evidence of sequential switching via IgG1 [53]. Similar observations have been made in the gastrointestinal tract in peanut allergy patients [54]. Another human study suggested that a specific set of CD27⁺ IgE B_{mem} might even be generated independently of TC help in the periphery [24]. In an OVA-allergic murine asthma model, allergen-specific BC and TC⁺/– DCs (together with eosinophils) were not only detected in bronchial LNs but also—albeit at a low percentage (4%)—in chronically inflamed lung tissue, where they aggregated to clusters [55]. Interestingly, more than 6 weeks after the last allergen challenge, BC were still in close contact with TC, with many of them demonstrating features of B_{mem}-like class-switched isotypes and SHM including CD80⁺CD73⁺ IgG1 BC. The TC showed similarities to Tfh with the expression of IL-21 and IL-4 but also type 2 cytokines like IL-5, IL-10, and IL-13. Notably, a distinct Tfh13 population expressing high levels of IL-13, IL-4, and IL-5 and reduced amounts of IL-21 compared to other Tfh (but still more than non-Tfh) has been detected both in mice and humans, which, by secreting IL-13, was critical for the synthesis of high-affinity, anaphylactogenic IgE antibodies [56].

Thus, in contrast to the original belief that B_{mem} differentiation and IgE plasmablast formation is solely confined to the GC of secondary lymphoid organs, memory IgE responses appear to be established in the ELS of peripheral tissues such as the respiratory and gastrointestinal mucosa. It has been proposed that in a subgroup of patients with allergic rhinitis allergen-specific IgE antibodies are solely produced in the nasal mucosa, as these individuals show only local allergen reactivity (demonstrated by positive nasal allergen challenge but negative skin test results) [57]. Further studies are needed to shed more light on the immunological endotype of this clinical entity termed “local allergy.” Since ELS are involved in the development and/or maintenance of IgE-mediated allergies, they might also present significant structures for tolerance induction. Allergen-specific IgG as well as IgA antibodies have been detected in the nasal mucosa of patients with allergic rhinitis treated by AIT [58]. Thus, ELS producing increased amounts of allergen-blocking IgG or IgA could outcompete persisting local IgE clones [59].

Future perspectives

BC memory plays an important role in IgE-mediated allergies and the (therapeutic) development of tolerance. With ELS emerging as an additional area—besides secondary lymphoid organs—shaping humoral immune responses and a potential BC equivalent to residential TC memory [60], several interesting questions arise regarding their role in allergy and the establishment of allergen tolerance: Do they constitute a redundant counterpart to GC in lymphoid follicles or have an autonomous function? What deter-

mines their development and their impact on allergic diseases? Do they make a difference in patients experiencing a relapse of allergic rhinitis after being successfully treated by AIT? And could they serve as a promising, easily accessible target for ensuring long-term allergen tolerance? Well-thought immunologic translational studies are, thus, needed to shed more light on this novel and fascinating subject of memory.

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Abbreviations: AIT: allergen immunotherapy · BC: B cell · B_{mem}: memory B cell · ELS: ectopic lymphoid structures · ILCs: innate lymphoid cells · SHM: somatic hypermutation · TC: T cell · Tfh: follicular T helper cell

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