

What Is the Source of Serum Allergen-Specific IgE?

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Published online: 13 April 2013
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Abstract Immunoglobulin E (IgE), the key effector element in the induction and propagation of allergic diseases, is the least abundant antibody class. In allergic patients, class switch recombination to IgE in B cells is induced by allergen contact in conjunction with T cell interaction and a Th2 cytokine environment. With regard to future therapeutic approaches, the sites of IgE production in human subjects and the nature and characteristics of IgE-producing cells are of great interest. In this context, it has been shown that allergen-specific IgE levels can be boosted by contact with allergens via the respiratory mucosa of the nose. Also, it has been proposed that allergy effector organs (e.g., the nasal mucosa and the lung) may be important sites of IgE production in allergic patients. IgE-producing cells have also been found in the blood, but their numbers are extremely low. Transfer of specific sensitization during bone marrow transplantation indicates the presence of IgE-producing B memory cells or plasma cells also in the bone marrow. This review summarizes data on the induction of IgE production, IgE memory and the sites of IgE production in human allergic patients.

Keywords IgE · Immunoglobulin · Allergy · Antibody production · Memory · B cell · Memory cell · Plasma cell

Abbreviations

Ig	Immunoglobulin
CD	Cluster of differentiation
PBMCs	Peripheral blood mononuclear cells
IL	Interleukin

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Th2 T helper 2
mRNA Messenger ribonucleic acid

Introduction

The presence of immunoglobulin (Ig) E antibodies in the blood represents the hallmark of IgE mediated allergy, a disease that affects more than 20 % of the population in industrialized countries [1]. Typical manifestations of allergic disease such as allergic rhinitis, conjunctivitis, asthma and anaphylaxis are caused by mediator release from mast cells and basophils upon crosslinking of receptor bound IgE by its cognate antigen. IgE's primary, evolutionary function however is the immune defense against parasitic worms and certain protozoan parasites [2], which play only an ancillary role in modern westernized societies. In individuals who are infected with these organisms, total IgE levels are usually substantially higher than in allergic patients [3].

IgE is the least abundant of all serum immunoglobulins, representing only 0.0005 % of the total free serum Igs in non-atopic adults [4]. However, the presence of elevated levels of allergen-specific serum IgE against otherwise harmless environmental antigens is strongly associated with atopic disease and thus represents an important tool in allergy diagnosis [4]. The half-life of free serum IgE is rather short in comparison to other immunoglobulin classes—12 h in mice [5] and 2–3 days in humans [6, 7]. Although the survival of IgE antibodies can be markedly increased by binding to its high affinity receptor, FcεRI, or its low affinity receptor, CD23 [8], it has to be produced continuously in order to maintain its serum levels.

The investigation of IgE production and metabolism in humans is hampered by the small numbers of IgE-producing cells in blood, nasal mucosa or tonsils, which are relatively easy to obtain from allergic patients [9•, 10–12]. Therefore, our knowledge of the location and precise mechanisms of IgE production and of the metabolism of IgE-producing cells is mostly based on extrapolations of data obtained in

mouse models and in in-vitro systems using peripheral blood mononuclear cells (PBMCs) or tonsil-derived B cells. Mouse models are often a well-suited surrogate for studying mechanisms of human diseases and have been crucial for the investigation of human immunology [13•, 14]. However, with regards to mouse models for allergy, there is a major problem: Mice do not naturally develop allergies, and thus several rounds of intraperitoneal systemic sensitization with high amounts of model antigens such as ovalbumin with aluminum hydroxide as an adjuvant are required to achieve allergic responses, as defined by IgE and IgG₁ induction, in mice [15]. These models of systemic sensitization do not correspond well to the mechanism of allergic sensitization in humans, where allergy is usually initiated by the uptake of only minute amounts of allergen via mucosal surfaces. In fact, it has been proposed that it is a critical feature of allergic sensitization that the absence of strong antigenic stimulation by allergens due to their small doses or the lack of danger signals allows IgE-switched B cells to escape elimination [16]. Methods of sensitization of mice via the respiratory tract have been described [17], but were not used in most mechanistic mouse allergy studies. In addition, the protocols used for sensitization of mice via the respiratory tract also use very high allergen doses, which are not comparable to the amounts of allergens that allergic patients are normally exposed to [17–19]. Thus, differences between mice and men need to be borne in mind when extrapolating mouse data regarding IgE production.

This review will reconsider the current knowledge on how IgE is produced and will discuss potential locations of IgE production (listed in Table 1), mainly focusing on those studies that have investigated IgE production in human subjects.

Steps towards Allergen-Specific IgE Production

After leaving the bone marrow, mature IgM- and IgD-bearing B cells with specificity for allergens become activated upon recognition of their cognate antigen. Subsequently, they interact with T cells, which have previously

been activated by allergen presentation through professional antigen-presenting cells. The cytokines interleukin (IL)-4 and IL-13 produced by activated T helper 2 (Th2) cells promote the class switch to IgE [20]. Whether the switch to IgE occurs directly or via other switch stations is a matter of debate [13•, 21, 22]. In mice, both direct class switch via IgM as well as sequential class switch via IgG₁ intermediates has been described [23]. It has been proposed that affinity maturation is abetted in clones that undergo sequential class switching [23, 24]. In humans, switching to IgE can occur apparently either directly or via IgG of all four classes [25–27]. Switching via S γ was demonstrated in a human cell line [28] as well as in nasal mucosal samples from allergic patients [27]. In a group of children from a birth cohort who acquired allergy during their first 7 years of life, indices of both direct and sequential class switching were observed [29].

The IgE Memory Response in Human Allergic Patients

In sensitized patients, allergen-specific IgE memory can be strongly boosted by contact with small amounts of allergen via the respiratory tract [30, 31]. Nasal provocation on 2 subsequent days using an allergen dose that corresponds to the natural exposure to allergen during 1–2 days at the height of the pollen season [19, 31] is sufficient to induce an increase of IgE of 30 % [30] or 40 % [31] as compared to baseline levels.

It has been shown that the sensitization profile, which is often established during early childhood [29, 32], does not change substantially over many years [33•]. A study that investigated the IgE variable regions of patients with birch pollen allergy over a period of 4 years revealed that the repertoire of IgE variable regions used by B cells was limited in this patient population and did not change over four periods of repeated exposure to the relevant allergen [34•]. Whether IgE memory in human allergic patients is due to the existence IgE memory cells or is sustained by long-lived IgE plasma cells and a pool of IgG memory B cells with specificity for allergens that switch to IgE production upon allergen contact is currently under debate [13•, 16, 21, 22, 35, 36]. While this question has been diligently investigated in mouse models, it is difficult for technical reasons to directly address in human patients. So far, only a few sites in the human body have been thoroughly investigated directly for the presence of cells involved in allergen-specific IgE memory. The following paragraphs will give an overview of studies investigating this topic.

Are There IgE-Producing Cells in the Human Blood?

Although IgE antibodies and their role in allergic disease were first described in 1967 [37], the source that

Table 1 Identification of IgE-producing cells in human tissues

	Reference
Blood	[9•, 10, 35, 38–42]
Nasal mucosa	[11, 26, 27, 53, 57–59]
Adenoids	[60–62]
Tonsil	[12, 63, 64]
Lung	[65–68]
Spleen	[74]
Bone marrow	[76–81]

continuously replenishes serum IgE levels is still far from clear. Early efforts to identify and characterize IgE-producing cells in humans focused on blood- or tonsil-derived B cells, as these cells were easily accessible. These studies gave first insights into which cellular and soluble factors regulate IgE synthesis. Initial observations from in vitro cultures of unfractionated PBMCs showed that the cells from allergic patients spontaneously secreted allergen-specific IgE [38–41]. It was shown that this represented at least partly newly synthesized IgE as addition of protein synthesis inhibitors reduced the level of IgE present in the supernatant of the cultures [39, 41]. IL-4, mostly secreted by T cells, was found to be a crucial cytokine for the induction and amplification of IgE synthesis [42–44]. However, IL-4 was only a potent inducer of IgE synthesis if applied in the presence of T-cell help [42, 43, 45] or upon addition of CD40 ligand or anti-CD40 antibodies as a surrogate of T cell help [42, 45–48]. Interestingly, although total IgE production was increased up to 20 times by the addition of IL-4 and anti-CD40 to in vitro cultures of allergic patients, no rise in allergen-specific IgE production was observed in culture supernatants [35]. The finding that IL-4 does not promote previously established specific IgE production is corroborated by results from a mouse model that showed that while anti-IL-4 treatment substantially interfered with de-novo allergic sensitization, it did not interfere with IgE production in already established allergy [36].

Although in vitro cultures of PBMCs gave the first insights into the mechanism of IgE production, attempts to isolate and characterize IgE-producing cells from peripheral blood have one major constraint: Allergen-specific lymphocytes are extremely rare in the blood and are thus hard to identify with commonly used techniques such as flow cytometry. Using tetramer staining for a major birch pollen allergen—Bet v 1—epitope, the frequency of Bet v 1-specific CD4 T cells was estimated between 1 in 10^4 to 10^6 among circulating CD4 T cells outside the pollen season and between 2–5 in 10^3 CD4+ T cells during the season [49]. However, the frequency of IgE + plasma cells was observed to be even much lower: 1 in 10^4 PBMCs is thought to be a plasma cell as defined by positive staining for the common plasma cell marker CD138+ in the flow cytometer [10]. Only a mean of 0.32 % of this small plasma cell fraction was found to be IgE + plasma cells in atopic patients [10]. In non-atopic donors, the frequency of IgE + plasma cells was only 0.06 % among total plasma cells [10].

It appears unlikely that such a small number of cells could constantly produce as much allergen-specific IgE as is needed to arm mast cells and basophils for their effector function. In this context, our group showed that only approximately 0.2 % of the serum IgE is newly produced by blood-derived plasma cells [9•]. All these findings indicate that there are few IgE-producing cells in the blood, but that

the majority of IgE-producing cells in human allergic patients reside elsewhere.

IgE Production at Target Organs for Allergy

In previously sensitized allergic patients, respiratory contact with relevant allergens is followed by a substantial systemic rise of specific IgE antibodies [31, 50–52]. It has been proposed that this allergen-contact induced rise of IgE antibodies may arise locally in the nasal mucosa. The presence of allergen-specific IgE in nasal secretions of allergic patients was already described in 1979 [53]. In the same study it was shown that the proportion of IgE antibodies specific for respiratory allergens as compared to total IgE was higher in nasal secretions than in the blood, thus suggesting local IgE production [53]. Since then, other studies have shown the presence of allergen-specific IgE antibodies in nasal polyps of patients that did not have the same IgE specificities in the blood [54]. The clinical relevance of local IgE antibodies is shown by recent clinical studies that revealed that a substantial number of rhinitis patients without allergen-specific serum IgE and with negative skin prick test reactions mounted a positive response to specific allergens in nasal provocation tests and also have specific IgE antibodies in nasal secretions [55, 56]. Nasal mucosal biopsies from symptomatic allergic rhinitis patients but not from non-allergic controls contained increased numbers of IgE-positive B cells and plasma cells and allergen-specific plasma cells [57]. To investigate whether these IgE-producing cells derived from more distant lymphatic tissue or whether they were resident to the nasal mucosa and performed class switch to IgE locally, biopsies of nasal mucosa from allergic patients were challenged ex vivo with allergen [11, 26, 27, 58, 59]. Interestingly, not only local synthesis of ϵ germline transcripts [58, 59] but also ϵ circle transcripts as signs of mature IgE synthesis [26, 27] could be detected in the biopsies upon allergen challenge.

Upon inhalation of airborne allergens, not only the nasal mucosa but also other lymphatic tissue of the airways, such as the adenoids and the tonsils as part of the Waldeyer's lymphatic ring, are potential sites of allergen encounter. In this context, tissue homogenates of adenoids of atopic children showed higher levels of total and allergen-specific IgE compared to non-atopic children [60]. Using immunohistochemical staining, IgE + cells were identified mainly in the extrafollicular area of the adenoids of atopic subjects, whereas adenoids of healthy controls contained only very few IgE + cells [61]. Those IgE + cells were identified mainly as plasma cells and macrophages using double staining for IgE and the plasma cell marker CD138 or the macrophage marker CD68, respectively [62]. Furthermore, tonsil-derived PBMCs also produced IgE when cultured in

vitro and stimulated with pokeweed mitogen [63, 64]. The presence of allergen-specific IgE in the sputum of house dust mite-sensitized asthmatic patients indicates that local IgE production may also occur in the lung of patients suffering from allergic asthma [65]. Analysis of IgE transcripts of a bronchial biopsy of a polysensitized asthmatic patient indicated that IgE-synthesizing B cells can also occur in the lung of humans [66]. However, class switch recombination to IgE has been observed in bronchial biopsies of both atopic and non-atopic asthmatic patients but not in atopic control subjects not suffering from asthma [67, 68]. Thus, local IgE synthesis in the lung seems to be one characteristic of asthma regardless of the atopic status of the patient.

Spleen and Bone Marrow – Reservoirs of Long-Lived Plasma and Memory Cells?

In humans, memory B cells and plasma cells have been shown to reside in the white pulp of the spleen [69–71]. The longevity of these cells is for example demonstrated by a study that showed that vaccinia virus-specific memory B-cells could be found in the spleen of patients decades after smallpox had been eradicated [72]. IgE-producing cells were detected in the spleen of aerosol-challenged mice that had previously been made allergic systemically with ovalbumin [73]. Whether this also applies for human allergic patients is so far not clear, as data on the presence of IgE-producing cells in human spleen are rare. One report analyzing the spleen of an atopic patient sensitized to house dust mite, who died from an asthmatic attack, showed that IgE was also produced in the spleen of allergic patients [74]. However, the nature of the IgE-producing cells and the specificity of the IgE antibodies produced were not reported.

In mice, the transfer of bone marrow from immunized mice bearing memory for a certain allergen into irradiated mice is a widely used technique to prove the presence of memory or long-lived plasma cells [75]. In humans, similar data are available from patients with leukemia or aplastic anemia who underwent bone marrow transplantation. Some case reports and small studies investigated the effect of transferring bone marrow from an atopic donor into a non-atopic recipient [76–81]. The results are ambiguous. In some case reports, non-atopic recipients receiving bone marrow from atopic donors developed sensitization profiles similar to those of their donors [76–79]. However, it has also been shown that not all recipients acquire the allergy of their donors [80] and that some of the patients also acquire de novo allergic sensitizations in addition to those transferred from the donor [81]. Thus, IgE memory seems to be transferable; however, to which extent and which cells – long-lived plasma cells or memory B cells – are responsible remain to be addressed.

Conclusions and Future Prospects

One problem in the search for IgE-producing cells is that even basic knowledge on human lymphoid organs with regard to their architecture and especially cellular composition is lacking. However, recently the group of Donna L. Farber presented a paper in which the distribution of human T cell subsets in various lymphatic human tissues was diligently assessed, thus making an important contribution toward a better understanding of the compartmentalization of lymphoid organs within the human body [82•]. Similar studies comparing the lymphatic tissue in allergic and non-allergic human patients remain to be performed.

While mice studies have the limitation that allergy does not occur naturally in this species, this restriction does not apply to other animals, for example, dogs or horses, in which allergy is a frequent veterinarian problem [15]. Investigating such “animal patients” would allow studying IgE production in animals that become sensitized to allergens via the respiratory tract in a manner similar to human allergic patients.

The quest for IgE-producing cells is still worthwhile to develop future therapeutic approaches aiming to cure the disease where it is caused, i.e., at the sites where IgE is produced, rather than merely treating its symptoms.

Acknowledgments This study was supported by grant SFB04613 of the Austrian Science Fund (FWF).

Conflict of Interest Julia Eckl-Dorna has received grant support via an FWF SFB04613 grant.

Verena Niederberger has received grant support via SFB04613 of the Austrian Science Fund (FWF), has served as a consultant for Biomay, and has had travel/accommodations expenses covered/reimbursed by GlaxoSmithKline and Stallergenes.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Wuthrich B, Schindler C, Leuenberger P, Ackermann-Liebrich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss study on air pollution and lung diseases in adults. *Int Arch Allergy Immunol*. 1995;106(2):149–56.
2. Erb KJ. Helminths, allergic disorders and IgE-mediated immune responses: where do we stand? *Eur J Immunol*. 2007;37(5):1170–3.
3. Turner KJ, Feddema L, Quinn EH. Non-specific potentiation of IgE by parasitic infections in man. *Int Arch Allergy Appl Immunol*. 1979;58(2):232–6.
4. Hamilton RG, Adkinson Jr NF. Clinical laboratory assessment of IgE-dependent hypersensitivity. *J Allergy Clin Immunol*. 2003;111(2 Suppl):S687–701.

5. Vieira P, Rajewsky K. The half-lives of serum immunoglobulins in adult mice. *Eur J Immunol.* 1988;18(2):313–6. doi:10.1002/eji.1830180221.
6. Meno-Tetang GM, Lowe PJ. On the prediction of the human response: a recycled mechanistic pharmacokinetic/pharmacodynamic approach. *Basic Clin Pharmacol Toxicol.* 2005;96(3):182–92.
7. Waldmann TA, Iio A, Ogawa M, McIntyre OR, Strober W. The metabolism of IgE. Studies in normal individuals and in a patient with IgE myeloma. *J Immunol.* 1976;117(4):1139–44.
8. Achatz G, Lamers M, Cramer R. Membrane bound IgE: the key receptor to restrict high IgE levels. *Open Immunol J.* 2008;1:25–32.
9. •• Eckl-Dorna J, Pree I, Reisinger J, Marth K, Chen KW, Vrtala S, et al. The majority of allergen-specific IgE in the blood of allergic patients does not originate from blood-derived B cells or plasma cells. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol.* 2012;42(9):1347–55. doi:10.1111/j.1365-2222.2012.04030.x. *This paper shows that only a small percentage of free serum IgE is produced by IgE-producing plasma cells present in the blood.*
10. Horst A, Hunzelmann N, Arce S, Herber M, Manz RA, Radbruch A, et al. Detection and characterization of plasma cells in peripheral blood: correlation of IgE + plasma cell frequency with IgE serum titre. *Clin Exp Immunol.* 2002;130(3):370–8.
11. Smurthwaite L, Walker SN, Wilson DR, Birch DS, Merrett TG, Durham SR, et al. Persistent IgE synthesis in the nasal mucosa of hay fever patients. *Eur J Immunol.* 2001;31(12):3422–31.
12. Ostergaard PA. Tonsillar IgE plasma cells predict atopic disease. *Clin Exp Immunol.* 1982;49(1):163–6.
13. •• Xiong H, Curotto de Lafaille MA, Lafaille JJ. What is unique about the IgE response? *Adv Immunol.* 2012;116:113–41. *This comprehensive and recently published review thoroughly discusses recent findings on IgE production in various mouse models.*
14. Mestas J, Hughes CC. Of mice and not men: differences between mouse and human immunology. *J Immunol.* 2004;172(5):2731–8.
15. Zosky GR, Sly PD. Animal models of asthma. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol.* 2007;37(7):973–88.
16. Aalberse RC, Platts-Mills TA. How do we avoid developing allergy: modifications of the TH2 response from a B-cell perspective. *J Allergy Clin Immunol.* 2004;113(5):983–6.
17. Shinagawa K, Kojima M. Mouse model of airway remodeling: strain differences. *Am J Respir Crit Care Med.* 2003;168(8):959–67.
18. Andersson K, Lidholm J. Characteristics and immunobiology of grass pollen allergens. *Int Arch Allergy Immunol.* 2003;130(2):87–107.
19. Schappi GF, Taylor PE, Pain MC, Cameron PA, Dent AW, Staff IA, et al. Concentrations of major grass group 5 allergens in pollen grains and atmospheric particles: implications for hay fever and allergic asthma sufferers sensitized to grass pollen allergens. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol.* 1999;29(5):633–41.
20. Geha RS, Jabara HH, Brodeur SR. The regulation of immunoglobulin E class-switch recombination. *Nat Rev Immunol.* 2003;3(9):721–32.
21. Davies JM, Platts-Mills TA, Aalberse RC. The enigma of IgE(+) B-cell memory in human subjects. *J Allergy Clin Immunol.* 2013;131(4):972–6.
22. Dullaers M, De Bruyne R, Ramadani F, Gould HJ, Gevaert P, Lambrecht BN. The who, where, and when of IgE in allergic airway disease. *J Allergy Clin Immunol.* 2012;129(3):635–45.
23. Erazo A, Kutchukhidze N, Leung M, Christ AP, Urban Jr JF, Curotto de Lafaille MA, et al. Unique maturation program of the IgE response in vivo. *Immunity.* 2007;26(2):191–203.
24. Xiong H, Dolpady J, Wabl M, Curotto de Lafaille MA, Lafaille JJ. Sequential class switching is required for the generation of high affinity IgE antibodies. *J Exp Med.* 2012;209(2):353–64.
25. Mills FC, Mitchell MP, Harindranath N, Max EE. Human Ig S gamma regions and their participation in sequential switching to IgE. *J Immunol.* 1995;155(6):3021–36.
26. Takhar P, Smurthwaite L, Coker HA, Fear DJ, Banfield GK, Carr VA, et al. Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *J Immunol.* 2005;174(8):5024–32.
27. Cameron L, Gounni AS, Frenkiel S, Lavigne F, Vercelli D, Hamid Q. S epsilon S mu and S epsilon S gamma switch circles in human nasal mucosa following ex vivo allergen challenge: evidence for direct as well as sequential class switch recombination. *J Immunol.* 2003;171(7):3816–22.
28. Mills FC, Thyphronitis G, Finkelman FD, Max EE. Ig mu-epsilon isotype switch in IL-4-treated human B lymphoblastoid cells. Evidence for a sequential switch. *J Immunol.* 1992;149(3):1075–85.
29. Niederberger V, Niggemann B, Kraft D, Spitzauer S, Valenta R. Evolution of IgM, IgE and IgG(1–4) antibody responses in early childhood monitored with recombinant allergen components: implications for class switch mechanisms. *Eur J Immunol.* 2002;32(2):576–84.
30. Niederberger V, Ring J, Rakoski J, Jager S, Spitzauer S, Valent P, et al. Antigens drive memory IgE responses in human allergy via the nasal mucosa. *Int Arch Allergy Immunol.* 2007;142(2):133–44. doi:10.1159/000096439.
31. Egger C, Horak F, Vrtala S, Valenta R, Niederberger V. Nasal application of rBet v 1 or non-IgE-reactive T-cell epitope-containing rBet v 1 fragments has different effects on systemic allergen-specific antibody responses. *J Allergy Clin Immunol.* 2010;126(6):1312–5 e4.
32. Orgel HA, Hamburger RN, Bazalal M, Gorris H, Groshong T, Lenoir M, et al. Development of IgE and allergy in infancy. *J Allergy Clin Immunol.* 1975;56(4):296–307.
33. • Lupinek C, Marth K, Niederberger V, Valenta R. Analysis of serum IgE reactivity profiles with microarrayed allergens indicates absence of de novo IgE sensitizations in adults. *J Allergy Clin Immunol.* 2012;130(6):1418–20 e4. *A 10-year study in human subjects using micorarrayed allergens to investigate how the allergen-specific IgE response evolves over time.*
34. • Marth K, Novatchkova M, Focke-Tejkl M, Jenisch S, Jager S, Kabelitz D, et al. Tracing antigen signatures in the human IgE repertoire. *Mol Immunol.* 2010;47(14):2323–9. *This study analyzes the IgE variable sequences in allergic patients sensitized against Bet v 1 over a period of 4 years.*
35. Steinberger P, Bohle B, di Padova F, Wrann M, Liehl E, Scheiner O, et al. Allergen-specific IgE production of committed B cells from allergic patients in vitro. *J Allergy Clin Immunol.* 1995;96(2):209–18.
36. Hahn C, Teufel M, Herz U, Renz H, Erb KJ, Wohlleben G, et al. Inhibition of the IL-4/IL-13 receptor system prevents allergic sensitization without affecting established allergy in a mouse model for allergic asthma. *J Allergy Clin Immunol.* 2003;111(6):1361–9.
37. Ishizaka K, Ishizaka T. Identification of gamma-E-antibodies as a carrier of reaginic activity. *J Immunol.* 1967;99(6):1187–98.
38. Tjio AH, Hull WM, Gleich GJ. Production of human immunoglobulin E antibody in vitro. *J Immunol.* 1979;122(5):2131–3.
39. Fiser PM, Buckley RH. Human IgE biosynthesis in vitro: studies with atopic and normal blood mononuclear cells and subpopulations. *J Immunol.* 1979;123(4):1788–94.
40. Romagnani S, Del Prete GF, Maggi E, Troncone R, Giudizi GM, Almerigogna F, et al. In vitro production of IgE by human peripheral blood mononuclear cells. II. Cells involved in the spontaneous IgE production in atopic patients. *Clin Exp Immunol.* 1980;42(3):579–88.
41. Romagnani S, Maggi E, Del Prete GF, Troncone R, Ricci M. In vitro production of IgE by human peripheral blood mononuclear

- cells. I. Rate of IgE biosynthesis. *Clin Exp Immunol*. 1980;42(1):167–74.
42. Maggi E, Del Prete GF, Parronchi P, Tiri A, Macchia D, Biswas P, et al. Role for T cells, IL-2 and IL-6 in the IL-4-dependent in vitro human IgE synthesis. *Immunology*. 1989;68(3):300–6.
 43. Pene J, Rousset F, Briere F, Chretien I, Bonnefoy JY, Spits H, et al. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons gamma and alpha and prostaglandin E2. *Proc Natl Acad Sci U S A*. 1988;85(18):6880–4.
 44. Gauchat JF, Aversa G, Gascan H, de Vries JE. Modulation of IL-4 induced germline epsilon RNA synthesis in human B cells by tumor necrosis factor-alpha, anti-CD40 monoclonal antibodies or transforming growth factor-beta correlates with levels of IgE production. *Int Immunol*. 1992;4(3):397–406.
 45. Gascan H, Gauchat JF, Aversa G, Van Vlasselaer P, de Vries JE. Anti-CD40 monoclonal antibodies or CD4+ T cell clones and IL-4 induce IgG4 and IgE switching in purified human B cells via different signaling pathways. *J Immunol*. 1991;147(1):8–13.
 46. Jabara HH, Fu SM, Geha RS, Vercelli D. CD40 and IgE: synergism between anti-CD40 monoclonal antibody and interleukin 4 in the induction of IgE synthesis by highly purified human B cells. *J Exp Med*. 1990;172(6):1861–4.
 47. Spriggs MK, Armitage RJ, Strockbine L, Clifford KN, Macduff BM, Sato TA, et al. Recombinant human CD40 ligand stimulates B cell proliferation and immunoglobulin E secretion. *J Exp Med*. 1992;176(6):1543–50.
 48. Zhang K, Clark EA, Saxon A. CD40 stimulation provides an IFN-gamma-independent and IL-4-dependent differentiation signal directly to human B cells for IgE production. *J Immunol*. 1991;146(6):1836–42.
 49. Wambre E, Van Overtvelt L, Maillere B, Humphreys R, von Hofe E, Ferhat L, et al. Single cell assessment of allergen-specific T cell responses with MHC class II peptide tetramers: methodological aspects. *Int Arch Allergy Immunol*. 2008;146(2):99–112. doi:10.1159/000113513.
 50. Henderson LL, Larson JB, Gleich GJ. Maximal rise in IgE antibody following ragweed pollination season. *J Allergy Clin Immunol*. 1975;55(1):10–5.
 51. Naclerio RM, Adkinson Jr NF, Moylan B, Baroody FM, Proud D, Kagey-Sobotka A, et al. Nasal provocation with allergen induces a secondary serum IgE antibody response. *J Allergy Clin Immunol*. 1997;100(4):505–10.
 52. Niederberger V, Stubner P, Spitzauer S, Kraft D, Valenta R, Ehrenberger K, et al. Skin test results but not serology reflect immediate type respiratory sensitivity: a study performed with recombinant allergen molecules. *J Invest Dermatol*. 2001;117(4):848–51.
 53. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol*. 1979;122(6):2218–25.
 54. Gevaert P, Nouri-Aria KT, Wu H, Harper CE, Takhar P, Fear DJ, et al. Local receptor revision and class switching to IgE in chronic rhinosinusitis with nasal polyps. *Allergy*. 2013;68(1):55–63.
 55. Rondon C, Campo P, Togias A, Fokkens WJ, Durham SR, Powe DG, et al. Local allergic rhinitis: concept, pathophysiology, and management. *J Allergy Clin Immunol*. 2012;129(6):1460–7.
 56. Rondon C, Romero JJ, Lopez S, Antunez C, Martin-Casanez E, Torres MJ, et al. Local IgE production and positive nasal provocation test in patients with persistent nonallergic rhinitis. *J Allergy Clin Immunol*. 2007;119(4):899–905.
 57. KleinJan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J: Off J Eur Soc Clin Respir Physiol*. 2000;15(3):491–7.
 58. Cameron L, Hamid Q, Wright E, Nakamura Y, Christodoulou P, Muro S, et al. Local synthesis of epsilon germline gene transcripts, IL-4, and IL-13 in allergic nasal mucosa after ex vivo allergen exposure. *J Allergy Clin Immunol*. 2000;106(1 Pt 1):46–52.
 59. Durham SR, Gould HJ, Thienes CP, Jacobson MR, Masuyama K, Rak S, et al. Expression of epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. *Eur J Immunol*. 1997;27(11):2899–906. doi:10.1002/eji.1830271123.
 60. Shin SY, Choi SJ, Hur GY, Lee KH, Kim SW, Cho JS, et al. Local production of total IgE and specific antibodies to the house dust mite in adenoid tissue. *Pediatr Allergy Immunol: Off Publ Eur Soc Pediatr Allergy Immunol*. 2009;20(2):134–41. doi:10.1111/j.1399-3038.2008.00756.x.
 61. Papatziolos G, van der Ploeg I, Hemlin C, Patwardhan A, Scheynius A. Increased occurrence of IgE + and FcepsilonRI + cells in adenoids from atopic children. *Allergy*. 1999;54(9):916–25.
 62. Papatziolos G, Van Hage-Hamsten M, Lundahl J, Hemlin C. IgE-positive plasma cells are present in adenoids of atopic children. *Acta Otolaryngol*. 2006;126(2):180–5. doi:10.1080/00016480500265976.
 63. Takenaka H, Kusumi T, Mizukoshi O. In vitro synthesis of IgE antibody by human tonsil mononuclear cells. Preliminary report. *Acta Otolaryngol Suppl*. 1988;454:133–7.
 64. Ohta K, Manzara T, Harbeck RJ, Kirkpatrick CH. Human tonsillar IgE biosynthesis in vitro. I. Enhancement of IgE and IgG synthesis in the presence of pokeweed mitogen by T-cell irradiation. *J Allergy Clin Immunol*. 1983;71(2):212–23.
 65. Nahm DH, Park HS. Analysis of induced sputum for studying allergen-specific IgE antibodies in airway secretion from asthmatic patients. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol*. 1998;28(6):686–93.
 66. Snow RE, Djukanovic R, Stevenson FK. Analysis of immunoglobulin E VH transcripts in a bronchial biopsy of an asthmatic patient confirms bias towards VH5, and indicates local clonal expansion, somatic mutation and isotype switch events. *Immunology*. 1999;98(4):646–51.
 67. Takhar P, Corrigan CJ, Smurthwaite L, O'Connor BJ, Durham SR, Lee TH, et al. Class switch recombination to IgE in the bronchial mucosa of atopic and nonatopic patients with asthma. *J Allergy Clin Immunol*. 2007;119(1):213–8.
 68. Ying S, Humbert M, Meng Q, Pfister R, Menz G, Gould HJ, et al. Local expression of epsilon germline gene transcripts and RNA for the epsilon heavy chain of IgE in the bronchial mucosa in atopic and nonatopic asthma. *J Allergy Clin Immunol*. 2001;107(4):686–92.
 69. Tangye SG, Liu YJ, Aversa G, Phillips JH, de Vries JE. Identification of functional human splenic memory B cells by expression of CD148 and CD27. *J Exp Med*. 1998;188(9):1691–703.
 70. Ellyard JJ, Avery DT, Phan TG, Hare NJ, Hodgkin PD, Tangye SG. Antigen-selected, immunoglobulin-secreting cells persist in human spleen and bone marrow. *Blood*. 2004;103(10):3805–12.
 71. Martinez-Gamboa L, Mei H, Loddenkemper C, Ballmer B, Hansen A, Lipsky PE, et al. Role of the spleen in peripheral memory B-cell homeostasis in patients with autoimmune thrombocytopenia purpura. *Clin Immunol*. 2009;130(2):199–212. Orlando, Fla.
 72. Mamani-Matsuda M, Cosma A, Weller S, Faili A, Staib C, Garcon L, et al. The human spleen is a major reservoir for long-lived vaccinia virus-specific memory B cells. *Blood*. 2008;111(9):4653–9.
 73. Luger EO, Fokuhl V, Wegmann M, Abram M, Tillack K, Achatz G, et al. Induction of long-lived allergen-specific plasma cells by mucosal allergen challenge. *J Allergy Clin Immunol*. 2009;124(4):819–26 e4. doi:10.1016/j.jaci.2009.06.047.
 74. Snow RE, Chapman CJ, Frew AJ, Holgate ST, Stevenson FK. Analysis of Ig VH region genes encoding IgE antibodies in splenic B lymphocytes of a patient with asthma. *J Immunol*. 1995;154(10):5576–81.

75. Slifka MK, Antia R, Whitmire JK, Ahmed R. Humoral immunity due to long-lived plasma cells. *Immunity*. 1998;8(3):363–72.
76. Bellou A, Kanny G, Fremont S, Moneret-Vautrin DA. Transfer of atopy following bone marrow transplantation. *Ann Allergy Asthma Immunol*. 1997;78(5):513–6.
77. Walker SA, Riches PG, Wild G, Ward AM, Shaw PJ, Desai S, et al. Total and allergen-specific IgE in relation to allergic response pattern following bone marrow transplantation. *Clin Exp Immunol*. 1986;66(3):633–9.
78. Desai S, Walker SA, Shaw PJ, Riches PG, Hobbs JR, Wild G, et al. Expression of donor allergic response patterns by bone marrow transplant recipients. *Lancet*. 1984;2(8412):1148.
79. Saarinen UM. Transfer of latent atopy by bone marrow transplantation? A case report. *J Allergy Clin Immunol*. 1984;74(2):196–200.
80. Agosti JM, Sprenger JD, Lum LG, Witherspoon RP, Fisher LD, Storb R, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med*. 1988;319(25):1623–8.
81. Hallstrand TS, Sprenger JD, Agosti JM, Longton GM, Witherspoon RP, Henderson Jr WR. Long-term acquisition of allergen-specific IgE and asthma following allogeneic bone marrow transplantation from allergic donors. *Blood*. 2004;104(10):3086–90.
82. Sathaliyawala T, Kubota M, Yudanin N, Turner D, Camp P, Thome JJ, et al. Distribution and compartmentalization of human circulating and tissue-resident memory T cell subsets. *Immunity*. 2013;38(1):187–97. *This recent study thoroughly assesses the distribution of various T cell subsets in different human lymphatic tissues.*