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Local Immunoglobulin Production in Nasal Tissues: A Key to Pathogenesis in CRSwNP and AERD

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Abstract

Objective: Local activation of B cells and antibody production is important for protective and pathogenic immune responses. There is also evidence that local activation of B cells and antibody production is important in the pathogenesis of chronic rhinosinusitis with nasal polyps (CRSwNP), and a severe subset of this disease, aspirin-exacerbated respiratory disease (AERD). This review aims to summarize these findings and the potential role of B cells and antibodies in disease pathogenesis.

Data Sources: Published literature from PubMed searches

Study Selections: Studies relevant to B cell development and to the role of B cells and antibodies in the pathogenesis of CRSwNP and AERD.

Results: Formation of tertiary lymphoid structures plays a key role in the local activation of B cells and antibody production. This process is important for fighting infections but also contributes to autoimmune disease. There is also evidence to support a role for local B cell activation and antibody production in a variety of allergic diseases. Nasal polyp tissues from patients with CRSwNP and AERD have elevated levels of activated B cell subsets and locally produced antibodies. These locally produced antibodies may contribute to disease pathogenesis in a variety of ways, including activation of innate effector cells, while locally activated B cells may contribute to pathogenesis through the activation of T cells.

Conclusions: More studies are needed to determine the role of B cells and antibodies in driving disease in these patients. However, targeting the processes that drive local B cell activation and antibody production may provide new therapeutic approaches and could help to reduce chronic inflammation.

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I. Introduction

Aspirin-exacerbated respiratory disease (AERD) is an adult onset respiratory disorder characterized by the triad of severe chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic asthma, and pathognomonic upper and lower respiratory reactions to aspirin and other cyclooxygenase (COX)-1 inhibitors[1]. Chronic rhinosinusitis with nasal polyps is a sub classification of chronic rhinosinusitis (CRS) where patients have inflammatory outgrowths of sinus mucosa leading to nasal obstruction and anosmia[2]. Nasal polyps are markedly severe in AERD, often do not respond to standard therapies, and are associated with substantial medical resource utilization[3–5]. Following endoscopic sinus surgery patients with AERD often have rapid recurrence of nasal polyposis, and 85% of patients with AERD have regrowth of nasal polyps within two years of surgery[6].

Nasal polyps in AERD and CRSwNP are characterized by dysregulated epithelium, activated B cells and plasma cells, T helper type 2 (Th2) inflammation, and mast cell and eosinophil infiltration[7–13]. Understanding the mechanisms underlying AERD and CRSwNP are necessary to develop improved diagnostic and therapeutic tools. Recent evidence supports a role for activated B cells and local antibody production in the pathogenesis of AERD and CRSwNP [12–14]. Here we will review the immunobiology of B cell activation and antibody production in secondary and tertiary lymphoid organs, local antibody production in AERD and CRSwNP, and possible mechanisms by which locally produced antibodies may contribute to disease pathogenesis.

II. B cell activation and antibody production in secondary lymphoid organs

Peripheral B cell subsets

B cells develop in the bone marrow through a highly regulated and coordinated process. The details of their development is beyond the scope of this review, but an excellent review of this process has previously been published[15]. While the majority of B cells are B2 B cells, or follicular B cells, two other populations of peripheral B cell subsets also exist and play key roles in early immune responses, the marginal zone B cell and the B1 B cell[16], but these will not be discussed further in this review. Once mature naïve B cells leave the bone marrow, they rapidly undergo two distinct transitional stages in the spleen before they become mature naïve B cells that circulate throughout the body in search of their cognate antigen. Once they encounter their cognate antigen, B cells then undergo the process of maturation and differentiation.

B cell activation and antibody production

B cell activation can occur via either a T cell-dependent or independent mechanism, depending on the nature of the antigen[17, 18]. There are two types of T cell-independent antigens. The first type, called a TI-1 antigen, can activate B cells independently of their B cell receptor specificity, and are commonly composed of TLR agonists such as LPS[19]. At high concentrations, these TI-1 antigens can provide a strong enough signal to induce B cell activation and antibody production, and this mechanism may be relevant in the context of

local inflammation, such as in nasal polyps. The second type, called a TI-2 antigen, is a highly repetitive antigen that can crosslink multiple B cell receptors on the same cell, such as bacterial polysaccharides, which in the presence of pro-inflammatory cytokines, provides sufficient signal to induce activation[19]. In the case of TI-2 antigens, while T cells are not explicitly required, they may provide key activation signals through production of pro-inflammatory cytokines, like IL-2[20]. These additional signals may also be provided through innate immune cells, such as NK cells or dendritic cells[20], and this could also be an important mechanism for B cell activation within the inflammatory environment of nasal polyps.

While TI B cell activation can play an important part in the generation of antibody responses, the majority of antibodies are produced via T cell-dependent activation mechanisms. Classically, this B cell activation occurs in secondary lymphoid organs (SLOs). After their maturation in the bone marrow, mature naïve B cells generally circulate through SLOs due to their high expression of CXCR5, whose ligand CXCL13 is highly expressed by follicular stromal and dendritic cells in SLOs[21, 22]. SLOs, including the lymph nodes, Peyer's patches, and spleen, develop during embryogenesis, are critical for immune homeostasis, and play an important role in the immune response to invading pathogens and inflammation[23]. Importantly, similar mechanisms may contribute to the local activation of B cells and antibody production at sites of inflammation. Once a naïve B cell encounters its cognate antigen, it upregulates expression of CCR7 allowing it to traffic to the T cell zone, where it will receive additional signals from cognate helper T cells that are required for its differentiation and production of antibodies[22]. Cognate antigen encounter also induces expression of co-stimulatory molecules by the B cells, including CD40 and MHCII, which enhance the interactions between cognate B and T cell pairs in the T cell zone[24].

After this initial interaction with Th cells in the T cell zone, B cells can further differentiate into one of 3 subsets: extrafollicular plasmablasts, early memory cells, or germinal center (GC) B cells[16]. The first two of these are formed independently of the germinal center, and therefore produce lower affinity antibodies that are important for controlling early phases of infections, and they are similar to B cells activated by T-independent mechanisms[16]. B cells with BCRs that strongly recognize antigen are more likely to differentiate down the extrafollicular pathway, and these cells are also characterized by expression of Epstein-Barr Virus-Induced protein 2 (EBI2), which prevents them from trafficking back into the follicle, and they generally have a short life span of about 3–5 days[25, 26]. This extrafollicular mechanism may also promote the activation of autoreactive B cells and production of autoantibodies at local sites of inflammation[27].

GC B cells, on the other hand, maintain expression of CXCR5 and traffic back into the follicle to participate in the GC reaction[28]. During this phase, B cells with the highest affinity BCRs will be selected for survival, undergo somatic hypermutation, and class switch recombination to generate high affinity IgG, IgA and IgE antibodies. These positively selected B cells will eventually exit the GC reaction as either long-lived memory B cells or plasma cells. Memory B cells will continue to circulate throughout SLOs and can be rapidly re-activated upon secondary encounter with their cognate antigen to become antibody-secreting plasma cells or new memory cells. Plasma cells can traffic to sites of inflammation

to produce large quantities of high-affinity antibodies needed to control infections, or they can traffic to the bone marrow where they can survive for years in specialized niches and continually produce high affinity antibody that can be found in the circulation. While these mechanisms of B cell activation and antibody production have been well-established and are critical for the generation of protective immune responses to a variety of infections, there are other mechanisms that can contribute to B cell activation and antibody production at local sites of inflammation. These local activation events may play a critical role in the control of infections, such as influenza, but they may also contribute to the pathogenesis of a variety of inflammatory diseases and will be discussed in detail below.

III. Tertiary lymphoid structures have a role in local immunoglobulin production during acute inflammation

As discussed above, B cells generally become activated in SLOs through the GC reaction and subsequently traffic to sites of infection or inflammation to participate in the immune response, which results in formation of memory B cells and plasma cells that produce high affinity antibodies[29]. In contrast, tertiary lymphoid organs (TLOs), which are also referred to as ectopic lymphoid tissues, are not generated during embryonic development, but are induced by antigenic stimuli including infections, environmental insults, and self-antigens (Figure 1). Both the gut and the airways are common sites for the development of TLOs, referred to as gut- and bronchus-associated lymphoid tissues, respectively (GALT and BALT), in response to inflammation[30, 31]. Homeostatic chemokines and cytokines that are important for the formation of SLOs have also been shown to be necessary for formation of TLOs, including IL-7, CCL19, CCL20, CCL21, and CXCL13[32-35]. These homeostatic chemokines and cytokines can be induced in nonlymphoid tissues during periods of inflammation or infection, and they may help to recruit lymphocytes to the inflamed tissue[34]. B cells accumulate within TLOs in GC-like structures and can express high levels of activation induced cytidine deaminase, one of the key enzymes required for antibody class switching[33, 36]. Further, TLOs can form memory B cells that can be rapidly re-activated following reinfection[37]. The structure of TLOs is less organized than SLOs[16], possibly resulting in reduced clonal selection and subsequent activation of autoreactive B- and T-cell clones, which may contribute to the development of inflammation or autoimmunity, similar to extrafollicular B cell responses[31, 38].

IV. Local antibody production CRSwNP, and AERD

Local antibody production in type 2 disease

It is well established that formation of TLOs can facilitate the local activation of B cells and antibody production that can contribute to control of infection as well as autoimmunity[31, 39]. This mechanism has also been implicated in the pathogenesis of type 2 inflammatory diseases, such as allergic rhinitis, asthma and CRSwNP. In allergic rhinitis, local B cell activation results in the activation of class switching to not only IgE, but also multiple IgG isotypes[40–42]. Interestingly, it has also been shown that this local class switching is elevated during the pollen season in pollen-allergic patients but is generally absent outside of the pollen season in those same patients[43]. This suggests that the local production of IgE plays a

key role in driving allergic symptoms in these patients. Similarly in asthma, it has been demonstrated that local class switching to IgE occurs in the lungs, and that this IgE is functional and can induce the degranulation of mast cells *in vitro*[42, 44, 45]. Further, there is evidence for local class switching to IgA in asthmatic lungs, which may also play a role in the activation of eosinophils in disease[46]. Not surprisingly then, there is also evidence for local class switching to IgE in the gut of patients with peanut allergies[47]. A recent study utilized high throughput sequencing of antibodies obtained from gut biopsies and found evidence for local class switching to IgE in the gut of food allergic patients[48]. Interestingly, while many groups have shown that IgG^+ B cells can be induced to undergo an additional round of class switching, called sequential switching, to IgE after local activation, this study found evidence that IgA^+ B cells can undergo similar sequential switching events to become IgE-expressing cells[48].

Local antibody production in CRSwNP and AERD

Both CRSwNP and AERD are characterized by local type 2 inflammatory environments. Over the last several years there has been accumulating evidence to support a key role for the local activation of B cells and antibody production in the pathogenesis of CRSwNP and AERD. Early studies found evidence for increased expression of B cell and plasma cell markers in nasal polyp tissues based on gene expression and IHC analyses[8, 49]. Later studies using flow cytometry analysis also found evidence for elevated levels of B cells, plasma cells, and plasmablasts in nasal polyps from CRSwNP patients[12, 14]. This work also found that plasmablasts in CRSwNP nasal polyps were more likely to be extrafollicular, based on their expression of EBI2, and that B cells from nasal polyps were potent antibody-secreting cells[12]. More recently, it has been shown that nasal polyps from AERD patients have even higher frequencies of plasma cells, in addition to elevated levels of antibodies, compared to polyps from CRSwNP patients[13]. The plasma cells in polyps from AERD patients were also more likely to express the IL-5Ra, suggesting that IL-5 may play an important role in their activation and/or antibody production[13]. In addition to elevated levels of antibody-secreting cells, elevated expression of germline transcripts, which are markers of local class switching events, have been reported in nasal polyps from CRSwNP patients[12, 50, 51]. Other studies have provided evidence that some of the local production of antibodies may be driven by super antigens derived from *Staphylococcus aureus* (SA)[8, 51–53]. These studies have demonstrated a link between levels of SA enterotoxins and IgE levels in nasal polyps, and they have identified enterotoxin-specific antibodies, which may play a role in promoting inflammation in some patients[54]. Altogether, these studies suggest that local switching not only to IgE, but also to IgG and IgA, may play important roles in the pathogenesis of nasal polyposis.

V. Local nasal polyp immunoglobulins may contribute disease pathogenesis

Immunoglobulin mediated activation of Fc receptor-expressing innate immune effector cells

Given the increased local production of nasal polyp immunoglobulins in AERD, specifically IgE and IgG4, understanding the role these immunoglobulins have in disease pathogenesis may provide greater understanding of underlying immune dysregulation in AERD (Figure 2). One possible role of locally produced immunoglobulins in CRSwNP and AERD pathobiology is activation of Fc receptor-expressing innate immune effector cells. Locally generated IgE may lead to activation of mast cells, basophils, and other FcεRI-bearing effector cells in the nasal polyp tissue. Analysis of microparticles has shown increased activation of mast cells and basophils in subjects with AERD compared to aspirin-tolerant subjects with CRSwNPs[55]. It is known that mast cells infiltrate the nasal polyp tissue and bronchial mucosa in patients with AERD[56–58]. Mast cells release inflammatory mediators such as tryptase, histamine, leukotrienes, and prostaglandin(PG) D_2 at high levels at baseline in AERD, and they are further activated during aspirin-induced reactions[7, 59–61]. Subjects with AERD who have the highest levels of urinary PGD-M, a metabolite of PGD_2, have the most severe aspirin-induced reactions[7], indicating that mast cell-derived PGD_2, and other products of mast cell activation, likely contribute to the upper and lower airway tissue inflammation and bronchoconstriction seen in AERD. Further, previous studies have shown that use of drugs such as cromolyn and nedocromil, can block chronic inflammation and aspirin-induced reactions in AERD[62, 63].

The cause of mast cell activation in AERD is unknown. As discussed above, patients with AERD have elevated serum[64] and nasal[13] IgE levels but lack classic atopy[64]. Recent studies have reported that treatment with omalizumab, a monoclonal antibody that binds IgE, decreases products of mast cell activation including PGD-M and leukotriene E4 in subjects with AERD[65] and blunts aspirin-induced reactions[66]. These findings support a role for local IgE in driving the persistent mast cell activation in AERD. A recent study found that patients with AERD who have the highest nasal polyp IgE levels have the most rapid nasal polyp recurrence[13]. Polyclonal nasal polyp IgE has been shown to induce histamine release in nasal polyp tissue fragments, suggesting that the polyclonal IgE is functional[53]. Taken together, these findings suggest that tissue IgE could be instrumental to the mast cell and basophil activation in the nasal polyp tissue of subjects with AERD.

Subjects with recurrent nasal polyposis have elevated total nasal polyp IgA and IgG[14, 52], which may also mediate nasal polyp inflammation through Fc receptor signaling. Significant tissue eosinophilia is characteristic of nasal polyposis in AERD[67–69]. Drugs targeting IL-5, a key survival factor for eosinophils, have shown promise in the treatment of nasal polyposis and AERD[70–72]. While many factors contribute to the dense tissue eosinophilia in the nasal polyps of patients with AERD, IgA may play a role in sustaining eosinophil survival[73] and may lead to eosinophil degranulation[74] further exacerbating nasal polyp inflammation in AERD. Similarly, IgG isotypes may contribute to nasal polyp pathogenesis through multiple mechanisms. IgG isotypes may direct local complement activation in nasal polyp tissue[75],

activate innate effector cells including macrophages and dendritic cells through Fc receptor signaling[76], and lead to tissue destruction through auto-antibodies[77].

IgG4 is elevated in the serum[78] and polyp tissue[13, 79] of subjects with AERD and is associated with an inferior post-operative course after endoscopic sinus surgery and longer duration of nasal polyposis[13, 79]. Yet, the role that IgG4 plays in nasal polyp pathogenesis, if any, is not well understood. IgG4 is thought to have an immunoregulatory role in patients with allergic sensitization[80] and may reflect chronic antigen exposure[81], as occurs in the upper airway where there is constant contact with microbial organisms and airborne allergens. IgG4 is also seen in pathologic conditions such as IgG4-related disease[81] and eosinophilic esophagitis[82], although the pathologic role of IgG4 in these disease is not well defined. IgG4-related disease can manifest as chronic rhinosinusitis leading to fibrotic disease in the sinuses[83, 84], and B cells play a prominent role in IgG4-related disease as evidenced by $IgG4^+$ plasma cell infiltration in affected tissues and clinical response to B-cell depleting therapies[85]. Another explanation of the relationship between local IgG4 production and worse disease outcomes in AERD could be that $IgG4^+$ cells represent an intermediate step in class switching to IgE[86] and do not have a direct pathologic effect themselves. Future study of the role of IgG4 in AERD may help to further our understanding of its role underlying disease pathogenesis.

Immunoglobulin mediated complement activation leading to destruction of epithelial barrier

TLOs are associated with a variety of autoimmune and inflammatory diseases[31], possibly due to reduced organization of TLOs compared to SLOs and impaired clonal selection. In the sinonasal mucosal tissue of patients with CRS, a number of autoreactive IgG and IgA antibodies have been identified, including antibodies to double-stranded DNA and anti-basement membrane autoantibodies[77, 87, 88]. These autoreactive antibodies are associated with more severe phenotypes of nasal polyposis such as AERD. Antibody-mediated complement activation, as measured by levels of C5b – 9, C4d, and activated C1, is increased in the nasal polyp tissue[89]. Activated compliment product deposition occurs linearly on the epithelial basement membrane, suggesting the possibility that complement-mediated epithelial destruction is caused by anti-basement membrane antibodies[89]. Given the association of nasal polyp autoreactive antibodies and elevated tissue eosinophilia, IgE, and more severe nasal polyposis, further investigation of autoreactive antibodies in AERD is an important area for future study.

Immunoglobulin facilitated antigen presentation to T cells

In allergic disease, facilitated antigen presentation is the process by which an antigen-IgE complex is taken up by B cells through the low-affinity IgE receptor (CD23) and is presented to naïve T cells. Following antigen presentation, the naïve T cells undergo differentiation into allergen-specific Th2 cells capable of producing type 2 cytokines such as IL-4 and IL-13. This can further promote the allergic response by stimulating IgE class switching of allergen-specific B cells[90, 91]. Additional type 2 cytokines produced by the Th2 cells, such as IL-5 and IL-9, lead to further migration and activation of effector cells such as eosinophils, basophils and mast cells to the site of inflammation[92, 93]. Shami et al

demonstrated that polyclonal IgE idiotypes in nasal polyp tissue complex with antigen to bind to CD23 on the surface of B cells, and they can elicit facilitated antigen presentation and subsequent proallergic T-cell response[94]. By depleting IgG from nasal homogenates, they also showed an increase in IgE-allergen binding to B cells through CD23, resulting in greater FcεRI-mediated basophil activation and subsequent histamine release[94]. As discussed above, inhibiting signaling of the type 2 cytokines IL-4 and IL-13, has shown efficacy in the treatment of nasal polyposis and AERD[95, 96]. Facilitated antigen presentation by IgE in the nasal polyp tissue of patients with AERD may have a role in nasal polyp pathogenesis and merits further investigation.

VI. Implications for management of CRSwNP and AERD

Many patients with CRSwNP and AERD are unable to achieve sufficient disease control with standard medical and surgical therapies, requiring revision surgery and high-dose corticosteroids to control inflammation. Given that locally produced nasal polyp immunoglobulins may facilitate disease pathogenesis in CRSwNP and AERD, modification with therapeutics targeting local nasal tissue immunoglobulins and/or B cells and plasma cells is of interest.

One area that may be amenable to therapeutic modification is targeting local IgE driven by *S. aureus* super antigens by treating the underlying *S. aureus* infection [8, 53]. Van Zele et al. conducted a 12 week, randomized, double-blind, placebo-controlled study of oral methylprednisolone compared to oral doxycycline and found that both regimens led to some reduction in nasal polyp size compared to placebo. They did not assess *S. aureus* colonization or IgE to staphylococcal enterotoxins but did find that total nasal IgE levels were lower in the subjects treated with methylprednisolone compared to doxycycline[97]. Studies of anti-staphylococcal topical therapies have been conducted in subjects with CRS but have not been conducted specifically in subjects with nasal polyposis[98, 99]. Further study of antimicrobial therapies to eradicate *S. aureus* are required to assess how this impacts staphylococcal enterotoxin-mediated inflammation.

Several monoclonal antibodies approved for severe asthma and/or CRSwNP are known to affect serum and tissue IgE levels. Dupilumab, a fully human monoclonal antibody targeting IL-4Rα, a shared receptor subunit between IL-4 and IL-13, reduces nasal polyp size, improves sinonasal symptoms and sense of smell, and reduces the need for oral corticosteroids and/or surgery in patients with CRSwNP[95]. In a post hoc analysis of a phase II study of dupilumab vs placebo in subjects with CRSwNP, the subgroup of patients with aspirin sensitivity on dupilumab had significant improvement in nasal polyp score and sense of smell compared to placebo[96]. While the inhibition of IL-4 and IL-13 can modify type 2 inflammation in multiple ways, it is known to reduce serum IgE levels in patients with CRSwNP and asthma, and nasal secretion and nasal polyp tissue IgE levels in patients with CRSwNP [95, 100, 101]. Omalizumab, a monoclonal antibody targeting IgE, has also been shown to reduce nasal polyp size and nasal congestion and lead to improvement of sinonasal symptom scores and sense of smell in subjects with CRSwNP[102, 103]. In a study of 21 adults with AERD, 12 months of treatment with omalizumab reduced levels of urinary LTE4 and PGD-M. In addition, subjects with AERD had reduction in sinonsal symptom scores[65]. The

use of monoclonal antibodies to target IgE and other local tissue antibodies requires further study with biomarker-based endotyping and responder analyses to allow for optimization of biologic selection in patients with CRSwNP.

Autoantibodies have been identified in nasal polyp tissue and are associated with more severe disease [77, 87, 88]. Therapies specifically targeting nasal polyp B cells and plasma cells have not been studied for treatment of CRSwNP. Rituximab, a monoclonal antibody targeting CD20 [104, 105], is known to reduce autoantibodies in multiple autoimmune diseases. While rituximab has not been studied for treatment of CRSwNP, it has been used to treat sinus manifestations of IgG4-related disease [84]. Further understanding of autoantibodies in the nasal polyp tissue of patients AERD and CRSwNP may lead to the identification of new therapeutic targets in patients with refractory disease.

VI. Conclusions

Activation of B cells and production of antibodies at local sites of inflammation plays a critical role in both protective and pathogenic B cell responses. There is accumulating evidence that highly activated B cell subsets are elevated in the nasal polyp tissues of CRSwNP and AERD patients. Moreover, the local production of antibodies likely plays a key role in the pathogenesis of these diseases, via multiple mechanisms. More studies are needed to determine the precise role of B cells and antibodies in driving disease in these patients. However, targeting the processes that drive this local B cell activation and antibody production may provide new therapeutic approaches for these patients and could help to reduce chronic inflammation.

Acknowledgments

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Abbreviations

AERD	Aspirin-exacerbated respiratory disease
BALT	Bronchus-associated lymphoid tissue
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyps
EBI2	Epstein-Barr virus-induced protein 2
GALT	Gut-associated lymphoid tissue
GC	Germinal center
iBALT	Induced bronchus-associated lymphoid tissue
ILF	Isolated lymphoid follicle
SA	Staphylococcus aureus

SLO	Secondary lymphoid organ
TLO	Tertiary lymphoid organ

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Key Messages

- Local activation of B cells plays a key role in both protective and pathogenic immune responses
- Local production of IgE has been shown to play an important role in the pathogenesis of allergic disease
- Aspirin-exacerbated respiratory disease (AERD) is a severe subset of chronic rhinosinusitis with nasal polyps (CRSwNP) and both diseases are characterized by elevations in activated B cell subsets and antibodies in nasal polyp tissues
- Local production of antibodies in AERD and CRSwNP may contribute to disease pathogenesis through multiple mechanisms

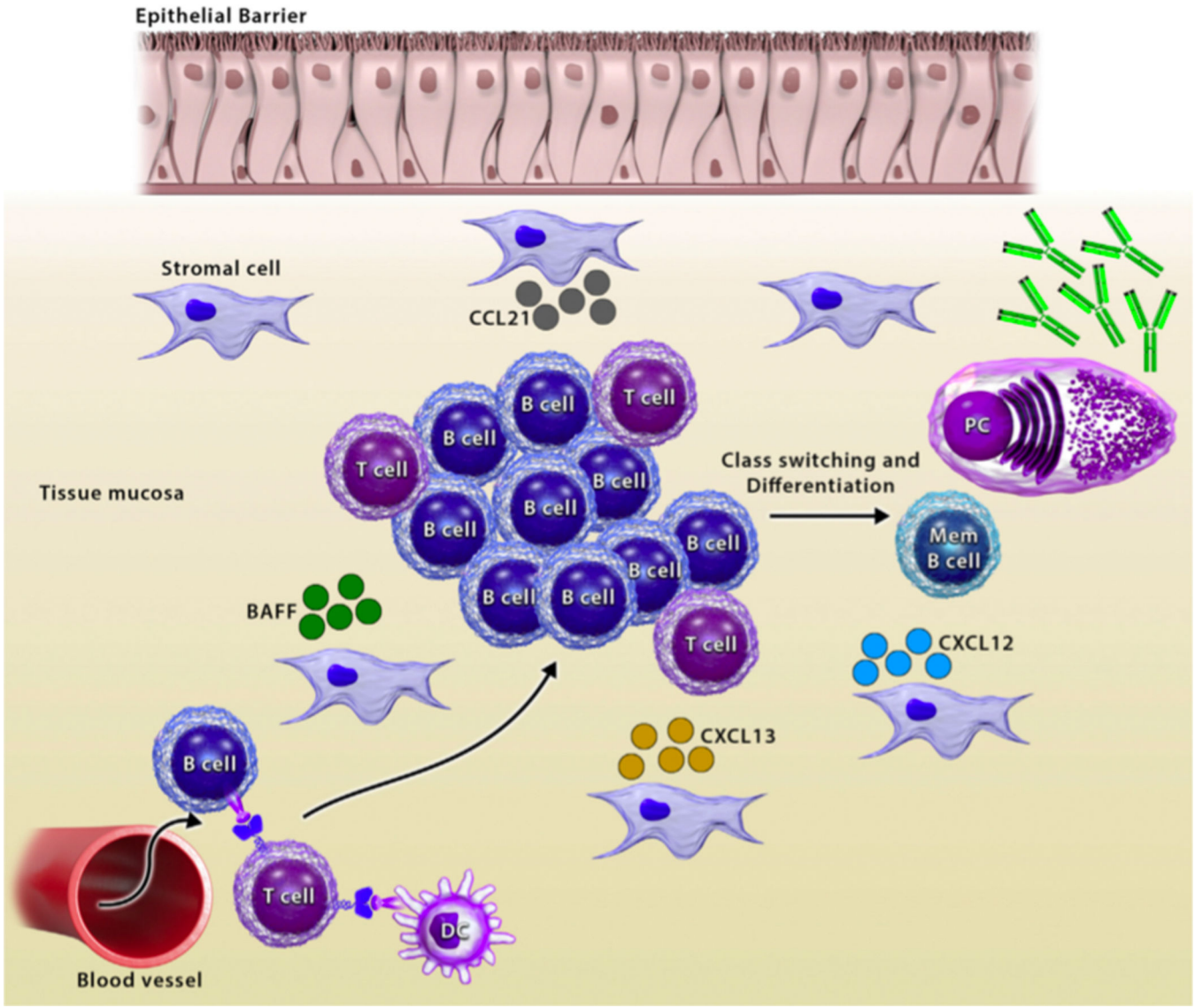

Figure 1.

Formation of tertiary lymphoid structures. Lymphocytes are recruited into the tissue via chemokines. T cells are activated by dendritic cells (DCs), and they activate B cells, along with cytokines, like BAFF. Activated B and T cells form lymphoid aggregates where B cells proliferate, undergo class switching, and differentiate.

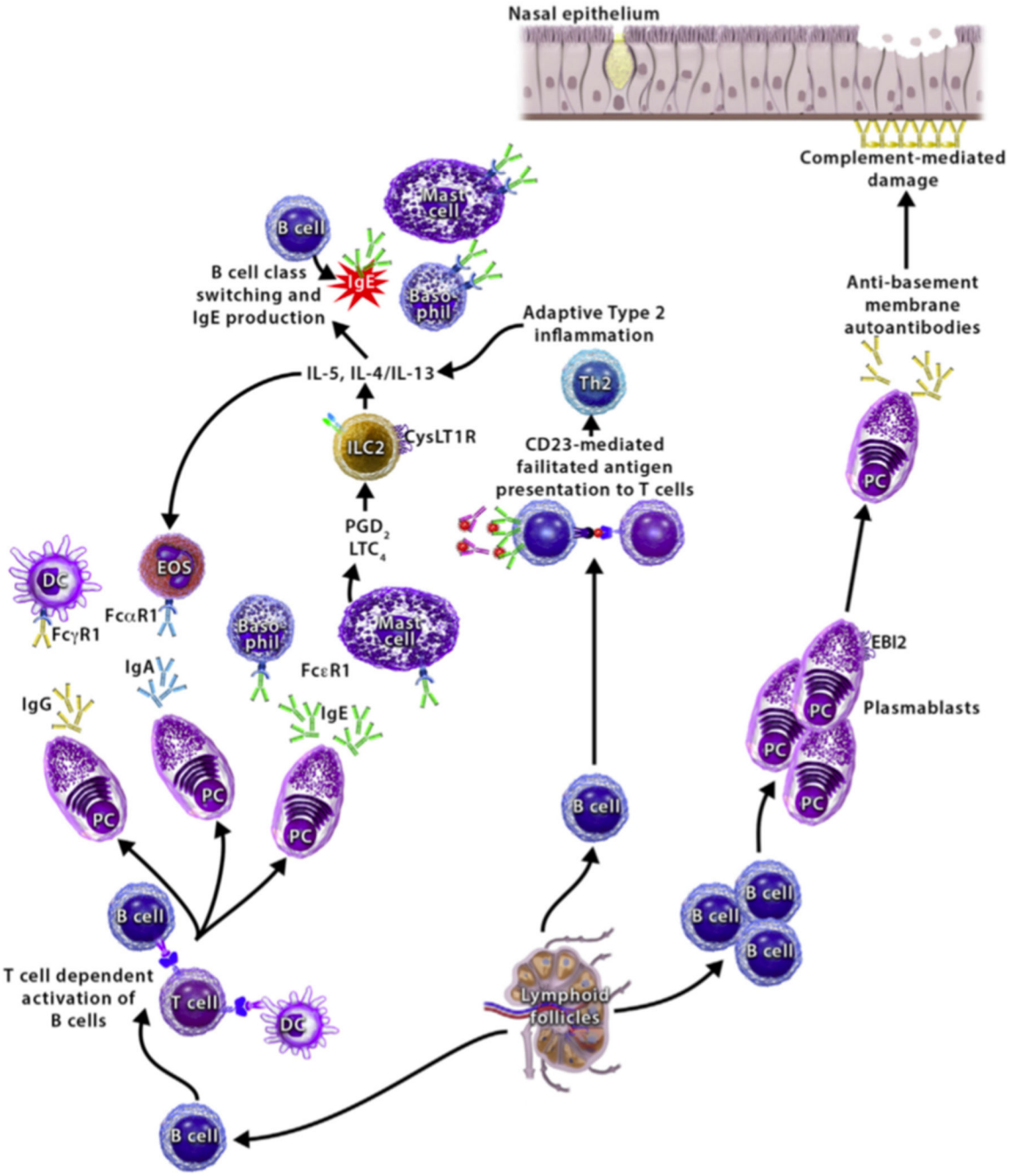

Figure 2.

Mechanisms of local antibody production in nasal polyps. (Left) locally produced antibodies activate innate effector cells, furthering type 2 inflammation. (Center) CD23-mediated facilitated antigen presentation by local B cells activates Th2 cells. (Right) autoreactive B cells and plasma cells produce autoantibodies leading to complement-mediated epithelial cell damage.