Pathogenic and protective roles of B cells and antibodies in patients with chronic rhinosinusitis

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Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nose and sinuses that affects up to 12% of the population in Europe and the United States. This complex disease is likely driven by multiple environmental, genetic, and inflammatory mechanisms, and recent studies suggest that B cells might play a critical role in disease pathogenesis. B cells and their antibodies have undisputed roles in health and disease within the airway mucosae. Deficient or inadequate B-cell responses can lead to susceptibility to infectious disease in the nose, whereas excess antibody production, including autoantibodies, can promote damaging inflammation. Thus, patients with B-cell defects often have either chronic or recurrent acute infections, and this can be associated with nonpolypoid CRS. In contrast, many patients with CRS with nasal polyps, which is less likely to be driven by pathogens, have excess production of local immunoglobulins, including autoreactive antibodies. These B-cell responses activate complement in many patients and likely contribute to immunopathogenic responses. A better understanding of the B cell–associated mechanisms that drive disease in patients with CRS should be a high priority in the quest to understand the pathogenesis of this disease. (J Allergy Clin Immunol 2018;141:1553-60.)

Key words: *Antibodies, antibody deficiency, autoimmunity, chronic rhinosinusitis, B cells, immunodeficiency, mucosal immunity*

Abbreviations used

BAFF:	B-cell activating factor of the TNF family
BAFF-R:	B-cell activating factor of the TNF family receptor
CRS:	Chronic rhinosinusitis
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
CVID:	Common variable immunodeficiency
EBI2:	EBV-induced protein 2
GC:	Germinal center
GPA:	Granulomatous polyangiitis
ICOS:	Inducible costimulator
NF-κB:	Nuclear factor κB
sIgA:	Selective IgA
SLO:	Secondary lymphoid organ
TACI:	Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TLO:	Tertiary lymphoid organ

The sinonasal mucosa is the first epithelial surface encountered by inhaled microbes and allergens.[1] B cells and their immunoglobulins play an active role in surveillance of this mucosal barrier and protection against infectious diseases.[2,3] B cells can directly recognize and respond to pathogens through their surface-bound immunoglobulins (also known as the B-cell receptor), and they help other immune effector cells recognize and respond to pathogens through secretion of antibodies that interact with Fc receptors expressed on immune effector cells.[4] In addition, B cells play important roles in T_H cell activation and can produce a variety of cytokines and effector molecules that can contribute to the host response against pathogens. However, when B-cell responses are not properly regulated, they can lead to disease.

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nose and sinuses that persists for at least 12 weeks and affects up to 12% of the population in Europe and the United States.[5] CRS is often divided into 2 subtypes, chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP), based on clinical findings. Patients with CRSwNP generally have more severe radiographic disease and a greater propensity for recurrence after sinus surgery but make up a smaller proportion of all patients with CRS.[6] Classically, these 2 phenotypic forms of CRS were thought to be driven by distinct inflammatory mechanisms; however, recent evidence suggests that both forms of CRS can be characterized by

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Terms in boldface and italics are detailed in the glossary on page 1554.

a variety of inflammatory endotypes.[7-9] CRS is a complex disease that is likely driven by multiple environmental, genetic, and inflammatory mechanisms, and many recent studies indicate that B cells can play a critical role in the pathogenesis of this disease.[10] This review will highlight recent evidence that supports a role for B cells and antibodies in the pathogenesis of CRS.

B CELLS AND ANTIBODIES IN THE UPPER AIRWAYS AND SINUSES

B-cell activation in the mucosa

B cells are thought classically to recognize their cognate antigen and become activated in ***secondary lymphoid organs (SLOs)*** through the ***germinal center (GC) reaction***. After they leave the SLOs, activated B cells can then traffic to sites of inflammation and participate in inflammatory responses. The details of these classic B-cell activation mechanisms have been covered extensively elsewhere and are beyond the scope of this review.[11] Importantly, B cells can also be activated directly at sites of inflammation, including the airways.[10] Mucosal-associated lymphoid tissues have been well characterized, especially Peyer patches in the gut and the Waldeyer ring (eg, tonsils and adenoids) in the airways.

Rabbits and rats also have constitutive bronchus-associated lymphoid tissue and nasal-associated lymphoid tissue, but these tertiary lymphoid organs (TLOs) are largely absent in healthy murine and human airways.[12] However, the formation of TLOs can be induced in the airways by inflammation, and inducible bronchus-associated lymphoid tissue has been shown to be critical for the optimal response to and clearance of pathogens and even tumors in human subjects.[13,14] The structures of follicles within TLOs are similar to those found in SLOs, although they tend to be less well organized.[10] Because of this lack of organization and possibly reduction in clonal selection (see below), it has been speculated that TLOs might allow for activation of autoreactive B- and T-cell clones, which could contribute to chronic inflammation or development of autoimmunity.[15,16] Although TLOs in the airways are associated with protective immune responses, their presence is also associated with chronic inflammatory diseases, including asthma and COPD, as well as autoimmiunity.[12]

B cells in patients with CRS

Although B cells and plasma cells have been described in the inflammatory infiltrate in patients with CRS,[17] the specificity and pathogenic potential of these B cells remained underexplored until recently. Early immunohistologic studies demonstrated increased expression of the B-cell marker CD19 and the plasma cell marker CD138 in tissue from patients with CRSwNP,[18] which

GLOSSARY

ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODIES (ANCAs): Autoantibodies specific for different enzymes contained within primary granules of neutrophils and macrophages. c-ANCA and p-ANCA refer to the patterns seen on immunofluorescences studies (cytoplasmic and perinuclear, respectively). The c-ANCA pattern is usually caused by antibodies to serine proteinase 3 and is found in patients with granulomatosis with polyangiitis. The p-ANCA pattern is typically caused by antibodies to myeloperoxidase.

CD180: Also known as RP105, a cell-surface molecule that associates with MD-1 to form a complex that functions as a Toll-like receptor that recognizes LPS from gram-negative bacteria.

FOLLICULAR DENDRITIC CELLS: Cells that reside primarily in the light zone of germinal centers and display antigen. Together with follicular T_H cells, they help promote the survival of B cells with the highest affinity receptors.

GERMINAL CENTER (GC) REACTION: See De Silva and Klein[11] for details. Briefly, lymph nodes have T cell– and B cell–rich zones. B-cell zones form lymphoid follicles in the cortex. Primary follicles do not have GCs. Secondary follicles contain GCs. Activated T_H cells migrate to the edge of a primary follicle to meet and activate B cells. B cells then migrate into the follicle and proliferate. Isotype switching and affinity maturation occur in the GCs. B cells then differentiate into plasma cells and memory B cells.

IL-21: The signature cytokine of follicular T_H cells. IL-21 is required for germinal center development. IL-21 also induces B-cell apoptosis that is only averted if the B cell is rescued by high-affinity receptors for antigen.

INCOMPLETE PENETRANCE: In complete penetrance everyone with a pathogenic genotype expresses the disease. In incomplete penetrance only some will express the disease, indicating other genetic or environmental factors must be present. Penetrance represents the probability of disease when a pathogenic genotype is present. One of the more common clinical examples of penetrance variability is seen in women with breast cancer susceptibility mutations of the *BRCA* genes: both mutations and other factors, such as family history and ethnicity, determine disease probability.

RECOMBINATION-ACTIVATING GENE (RAG): Lymphoid-specific proteins important in lymphocyte antigen receptor gene rearrangement. RAG1 and RAG2 create double-stranded DNA breaks in immunoglobulin and T-cell receptor genes to allow for V(D)J recombination, a process that randomly generates V(D)J exons that will code for the variable regions of antigen receptor proteins. V(D)J recombination allows for development of a diverse array of antigen receptors on B and T cells.

SECONDARY LYMPHOID ORGANs (SLOs): Lymphoid tissue in which lymphocyte responses to foreign antigens are triggered and enhanced. SLOs include lymph nodes, the spleen, the cutaneous immune system, and the mucosal immune system. Lymph nodes promote the initiation of adaptive immune responses to antigens. Red pulp areas of the spleen contain macrophages that assist with removing aging and/or damaged blood cells, immune complexes, and opsonized microbes. The white pulp contains high numbers of lymphocytes and promotes adaptive responses to blood-borne antigens.

SWITCHED MEMORY B CELLS: Memory B cells are derived from germinal center reactions. They are capable of prolonged survival caused by expression of the antiapoptotic protein Bcl-2. CD40 on B cells binding to CD40 ligand (CD40L) on T cells is critical for memory B-cell formation. Mutations in CD40 or CD40L results in hyper-IgM syndrome. Memory B cells are identified by the surface markers CD19 and CD27. Switched memory B cells refers to B cells that have undergone antibody class-switching and are often designated as $CD19^+CD27^+IgD^-IgM^-$ cells.

TYPE 2 INNATE LYMPHOID CELLs (ILC2s): Many articles, as well as a recent review in the *Journal*, have explained how innate lymphoid cells (ILCs) are emerging as key contributors to the pathogenesis of inflammatory disease. ILC2s produce type 2 cytokines, such as IL-4, IL-5, IL-9, and IL-13, on stimulation with epithelium-derived cytokines, such as IL-33, IL-25, and TSLP.

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