The roles of basophils in mediating the immune responses

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Abstract
Basophils are the rarest blood cell population and have not been extensively studied. Our understanding of the functions of basophils is limited to their roles as the main effector cells in hypersensitivity reactions. Similar to mast cells, basophils express high-affinity IgE receptor (FceRI), contain granules, and release hypersensitivity-associated mediators (such as histamine). The roles of basophils have not been fully elucidated; however, with the rapid development of monoclonal techniques, high-purity cell sorting techniques, and basophil-deficient mouse models, understanding of the functions and phenotypes of basophils has increased. This facilitates further investigations on the relationships between basophils and host immunity. Basophils are not only involved in mediating the generation of allergic reactions but also play important roles in immunomodulation and are responsible for the onset of infectious, allergic, and autoimmune diseases. In this review, we summarize the progress in understanding the roles of basophils in mediating immune responses with an emphasis on autoimmune diseases, particularly systemic lupus erythematosus and rheumatoid arthritis.

Keywords
basophils, autoimmune diseases, systemic lupus erythematosus, rheumatoid arthritis, immune response

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Introduction
Despite their discovery more than 140 years ago, basophils have not been fully characterized, particularly with respect to their physiological functions. Basophils are present in all vertebrates, suggesting that these immune cells are likely to have essential physiological roles in mammals. Basophils are proposed to be derived from the granulocyte–monocyte progenitor cells (GMPs). Basophil development is completed in the bone marrow, and fully matured basophils circulate in the peripheral blood. Basophils do not proliferate after maturation and have a short lifespan (0–60 h). The cytokines required during each stage of basophil differentiation have not been clarified; however, interleukin (IL-3) has been shown to promote the differentiation and maturation of basophils.

Our current understanding of the physiological roles of basophils is limited to their roles as effector cells in hypersensitivity reactions. Additionally, it is difficult to perform large-scale purification of basophils using antibodies in vitro owing to the low abundance of these cells in the peripheral blood; therefore, investigations on the functions of these cells are challenging. However, cell sorting technology has facilitated the identification of numerous novel biological functions of basophils. For example, basophils are now known to be involved in the secretion of leukotrienes and histamines in response to IgE.
receptor (FceRI)/IgE complex activation during allergic reactions and are involved in mediating innate and adaptive immune responses. Recent studies have shown that activated basophils exhibit increased expression of CD40L, C–C motif chemokine receptor 3, and CD63 on their surface and release large amounts of IL-4 and IL-13, suggesting that basophils may play important roles in other immune responses in addition to IgE-mediated responses.

In this review, we aimed to provide an overview of the recent progress in our understanding of basophil activation, the regulatory roles of basophils with respect to the initiation of T helper type-2 (Th2) cell differentiation and adaptive immune responses, and their functions in rheumatic diseases, particularly systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and rheumatic diseases.

**Origin and distribution of basophils**

Basophils are found in a wide variety of animals, including mammals, reptiles, and birds. Electron microscopy has revealed that the components of the basophil granules have a relatively high electron density and contain heparin, histamine, and leukotrienes, which are involved in mediating type-I hypersensitivity reactions.

The differentiation of basophils is regulated by two transcription factors, C/EBa and GATA binding factor 2. IL-3 is involved in the early growth and development of basophils as it regulates these transcription factors. Previous studies have demonstrated that IL-3 can promote the differentiation of basophils in the bone marrow during Th2 immune responses.

**Mechanisms underlying basophil activation**

Basophil activation is the prerequisite for exerting basophil biological functions. Most studies evaluating the roles of basophils have focused on IgE-mediated hypersensitivity reactions, and basophils have been shown to be activated in response to multiple signaling pathways. Activated basophils can produce various effector molecules (including histamine and leukotrienes), chemokines (IL-4, IL-5, IL-13, IL-6, and tumor necrosis factor [TNF]-α), and cell membrane markers (CD203c and CD63). The classical activation of basophils occurs when a foreign antigen and IgE form an immune complex, which then binds to the high-affinity IgE receptor FceRI. This process triggers the activation of basophils, which release various inflammatory mediators and participate in hypersensitivity reactions.

Through secretion of IL-4 and IL-6, activated basophils can cooperate with Th cells to induce immunoglobulin class switching in B lymphocytes, resulting in the secretion of various immunoglobulins, such as IgM, IgG, and IgA. Basophils can be activated by numerous cytokines including IL-17, IL-18, IL-26, and IL-33. After basophils are activated, these cells constitutively express IL-4. Basophils are a potent source of IL-4, which represents the main cytokine promoting a Th2 lymphocyte polarization. In the context of respiratory inflammation, some authors clearly showed in a murine experimental model that basophils are systemically induced upon allergic stimulation and such an early basophil activation correlates with the Th2 lymphocytes, and basophils participate in the initiation of Th2 adaptive immune response.

Basophil activation mediated by pattern recognition receptors, Toll-like receptors (TLRs), has been extensively studied in recent years. Toll-like receptors are a family of transmembrane signaling receptors capable of selectively recognizing microbial components; this enables them to play an important role in innate immunity. Toll-like receptors contain three domains: extracellular, transmembrane, and intracellular. After recognizing and binding to the corresponding pathogen-associated molecular patterns (PAMPs), TLRs activate intracellular signaling pathways that promote the release of various inflammatory factors and cytokines, thereby linking innate immunity to acquired immunity. The TLR family consists of 11 members; TLR2 is the most widely distributed TLR family member and is primarily expressed on cells representing the first line of host defense, such as B lymphocytes, monocytes, macrophages, neutrophils, and basophils. TLR2 recognizes the most diverse molecules derived from pathogenic microorganisms and their products and functions in noninfectious inflammatory processes. Therefore, further studies on TLR2 have both theoretical and practical significance. Basophils can directly recognize various pathogenic microorganisms via TLRs and are involved in mediating the inflammatory responses. For instance, peptidoglycans, which are TLR2 ligands, can induce the secretion of IL-4 and IL-13 by basophils in vitro. IL-4 can promote the maturation and differentiation of Th2 cells, thereby participating in the Th2 immune response. In addition, the IgE-mediated basophil activation also involves complement receptors (CRs), such as CR1, CR2, and CR3, which can induce histamine secretion by basophils.

CD63 was previously used as a marker of basophil activation. However, recent studies have shown that CD203c as a marker of basophil activation—provides greater sensitivity than CD63 in detecting basophil activation. Currently, flow cytometry is often used to qualitatively determine the CD203c-positive cell count as well as to quantitatively measure the average fluorescence intensity of CD203c to evaluate the degree of basophil activation.
Regulatory roles of basophils with respect to the immune response

Promotion of Th2 responses

The cytokines secreted by activated basophils are involved in mediating the immune responses and immunomodulation. Notably, activated basophils can rapidly secrete IL-4 and IL-13. IL-4 is considered the most important cytokine in the initiation and maintenance of Th2 cell differentiation. IL-4 can be secreted by various types of cells including Th2 cells, eosinophils, mast cells, and basophils that play a role in humoral immunity. IL-4 also plays an important role in regulating the stability and differentiation of Th2 cells and in the formation of memory Th2 cells. Additionally, Th2-type cytokines, such as IL-4 and interferon (IFN)-γ, are upregulated during the co-culture of antigen-stimulated CD4+ T cells and basophils in vitro; these cytokines facilitate the differentiation of CD4+ T cells into Th2 cells. IL-4 can also promote the differentiation of CD4+ T cells into Th2 cells, which secrete IL-4, IL-13, and other Th2-type cytokines. In the early stages of the immune response, re-exposure to antigens triggers the rapid secretion of large amounts of IL-4 by the basophils; in contrast, in late stages, IL-4 is primarily secreted by the memory T cells. Various exogenous lectins have the capacity to activate basophils. Moreover, various ligands, including bacterial peptidoglycans, viral proteins, and fungal mannans, can bind to TLR2 and promote the activation of basophils, which then produce IL-4 and promote the Th2 immune responses. Accordingly, basophils can aggravate the immune response triggered by viral and bacterial infections. Hence, IL-4 secreted by the basophils in the early stage of the immune response plays a key role in initiating and maintaining the Th2 responses, which may accelerate disease progression.

Humoral responses

In humans, basophils serve as enhancers of the humoral response. Exogenous antigens bind to receptors expressed on the basophil surface via IgD and induce the production of IL-4 and B-cell activating factor (BAFF). Through these responses, activated basophils promote immunoglobulin class switching in B lymphocytes (which produce IgD and IgM in the early stages of differentiation), resulting in the secretion of large amounts of IgG, IgM, and IgA, thereby facilitating adaptive immune responses. The types of immunoglobulins elevated in the body may be associated with the types and quantities of the stimulating antigens. After initial exposure to an antigen, basophils express substantial amounts of specific IgE antibodies on their surfaces. After being re-exposed to the antigen, basophils can bind via CD40L to B cells expressing CD40 on their surface and induce the production of high concentrations of immunoglobulins by B cells. Moreover, activated basophils also produce large amounts of IL-4 and IL-6, which promote the differentiation of Th2 cells. Activated Th2 cells secrete IL-4, IL-5, IL-13, and IL-10, promote the proliferation and differentiation of B cells, and stimulate immunoglobulin production by B cells via binding to CD40 expressed on their surface through CD40L, thereby enhancing the humoral immune response.

Immunomodulatory roles of basophils in SLE

Systemic lupus erythematosus is a complex disease that affects multiple organs and is associated with disorders of humoral immunity. Kidney injury occurs in more than 90% of SLE patients, primarily due to immune injury caused by the deposition of immune complexes containing IgM, IgG, and IgA in large quantities in the kidneys. These immune complexes comprise autoantibodies specific to nuclear components (antinuclear antibodies [ANAs]) or nucleic acids double-stranded DNA (dsDNA). Many studies have evaluated the roles played by Th1, Th17, and regulatory T cells in the development of SLE. Additionally, Th2 cells have been shown to have a role in the onset of SLE. Several studies have also assessed the roles of Th2-type cytokines in the development of SLE, and IL-4 and IgE have been shown to play important roles in the pathogenesis of SLE.

Autoreactive antibodies may mediate immune responses in the kidneys of patients with SLE, leading to renal failure and even death. Autoactive IgE is responsible for the onset and progression of diseases, and this phenomenon involves basophil activation, induction of their homing to the lymph nodes, and promotion of Th2 cell differentiation and autoantibody production. Notably, activated basophils can mediate immune responses via IgE-dependent and IgE-independent pathways, and basophils act as the main effector cells in allergic reactions by mediating hypersensitivity reactions via an IgE-dependent pathway. Previous studies have shown that IgE deficiency can delay the progression and alleviate the severity of diseases by decreasing the production of autoantibodies, thereby reducing organ damage. Studies performed in mouse models of SLE have revealed that IgE can significantly reduce the production of autoantibodies and the number of plasma B cells in mice; reductions in IgE significantly decrease the infiltration of immune cells, particularly monocytes, neutrophils, eosinophils, and basophils into organs, whereas IgE deficiency significantly reduces basophil activation in the spleens of mice with SLE. IgE-positive patients with SLE exhibit significantly higher disease activity and higher expression of the basophil activation marker CD203c than IgE-negative patients with SLE. Thus, IgE autoreactivity is closely
associated with basophil activation and may increase the level of disease activity. These findings indicate that basophils can promote the amplification of autoimmune and auto-inflammatory responses via IgE-dependent pathways.

Basophils and the Th2-type environment can promote the progression of SLE and aggravate the severity of lupus nephritis. Autoreactive IgE antibodies can activate basophils by binding to FcεRI receptors expressed on the surface of basophils in tyrosine-protein kinase-deficient aged mice with lupus-like disease. These mice exhibit continuous changes in Th2-type cytokine levels, significantly elevated IL-4 levels, high expression of CD62L (an adhesion molecule)40 and the MHC-II molecule human leukocyte antigen type DR (which is involved in self-antigen presentation) on basophils,41,42 production of large amounts of anti-dsDNA antibodies and other ANAs, and have clearly visible immune-complex deposits in the glomeruli of the kidneys. In contrast, basophil-knockout mice show significantly reduced levels of ANAs and anti-dsDNA antibodies, lower proportions of splenic plasma cells, and alleviation of the pro-inflammatory environment in the kidneys. Although high-affinity FcsRI is expressed by basophils and mast cells, IL-4 and IgE-deficient mice exhibit significantly lower CD62L expression and reduced numbers of basophils in the lymph nodes and spleen. The detection of BAFF receptors expressed on the surface of basophils present in the lymph nodes has also indicated that lymph node basophils may affect the survival and differentiation of B cells. Basophils migrate from the peripheral blood to the lymph nodes and spleen via the expression of CD62L and MHC-II and enable the modulation of B-cell function by secreting cytokines and facilitating immune responses. Examination of clinical specimens has revealed that basophils and autoreactive IgE are important factors responsible for the occurrence of Th2-biased immune responses in patients with SLE.43 Basophils are activated (with high CD203c expression) in patients with SLE; hence, basophil activation may be an important feedback loop that affects the progression of SLE. Therefore, reducing the levels of IgE immune complexes in the blood or the degree of basophil activation may represent a new therapeutic approach for SLE.

Significant reductions in the levels of inflammatory factors (e.g., IL-1β, IL-4, IL-6, IL-13, and IFN-γ) in basophil-knockout mice with SLE have suggested that the alleviation of the pro-inflammatory environment in the kidneys via basophil knockout or reduction of basophil activity may be conducive to the treatment of SLE.44 Therefore, some currently available anti-allergic drugs (such as omalizumab) could exert therapeutic effects against SLE by reducing the IgE levels in the body and the expression of the FcεRI receptor on the surface of basophils.45

We have known the key role of IL-17 in tissue inflammation autoimmunity. It has been found that IL-17 produced by basophils plays an important role in the pathogenesis of lupus. Pan et al. found that the increase of serum autoantibodies in patients with lupus erythematosus is related to basophil activation. The serum levels of autoantibodies and IL-17 were decreased in basophil-depleted MRL-lpr/lpr mice. These findings suggest that basophil activation-dependent autoantibody and IL-17 production may constitute a critical pathogenic mechanism in SLE.46 Wakahara et al. found activated basophils amplified IL-17 release in effector memory T cells (TEM) and enhanced the ERK1/2 signaling pathway, which can result in chronic inflammatory disorders beyond Th2.47

The decreased number of basophils in the peripheral blood of patients with SLE may be attributed to multiple factors, such as inflammatory factor and chemokine-mediated recruitment of basophils from the peripheral blood into tissues. Basophil infiltration into these organs may result in damage to multiple systems, and SLE may therefore affect all body systems. Additionally, the observed apoptosis of T and B lymphocytes and production of pathogenic autoantibodies in large quantities during active SLE indicate that the number of basophils may also decrease due to excessive apoptosis.

Toll-like receptors 2 can mediate basophil activation. Pawar et al. found that mice with lupus nephritis have enlarged spleens and exhibit increased secretion of inflammatory factors (anti-dsDNA antibodies, IL-6, IL-12, and TNF-α), resulting in the exacerbation of the progression of lupus nephritis after exposure to bacterial cell wall components.48

**Potential role of basophils in RA and other rheumatic diseases**

Rheumatoid arthritis is a heterogeneous disease, that is, it cannot be attributed to a single cause. Several studies have evaluated the roles of various inflammatory factors, cytokines, and chemokines in the context of RA onset; however, the pathogenesis of this disease remains unclear. Different clinical subtypes of RA exhibit varying disease durations, prognostic outcomes, and therapeutic outcomes.

Many recent studies have assessed the role of Th1/Th2 imbalance in the onset of RA,49 with special focus on the detection of various cytokines and inflammatory factors in patients with RA. Notably, the dominant cytokines vary across different stages of the disease, resulting in differences in disease duration among patients with RA. In the early stages of the disease, the synovium and synovial fluid of patients with RA are dominated by Th2-type cytokines (IL-4 and IL-13), whereas the Th1-type cytokine IFN-γ dominates the synovium of patients with chronic RA in the late stages.50 Accordingly, many researchers have recently evaluated the physiological roles of basophils in regulating the Th1/Th2 balance. Using a basophil-deficient mouse...
model, researchers have demonstrated that IL-4 is mainly produced by basophils and can induce the early differentiation of Th2 cells and cooperate with dendritic cells to regulate Th2-type immune responses by promoting the differentiation of Th2 cells; and thus is responsible for the development of Th2-associated diseases. Basophils are activated in response to the specific binding of antigens with the IgE receptor FceRI expressed on its surface. Activated basophils can produce Th2-type cytokines, such as IL-4, which promote Th2 cell differentiation, enhance humoral immune responses, and affect the Th1/Th2 balance by reducing the Th1 response; this is the mechanism responsible for the pathogenesis of RA. Qiu Hua et al. have found high levels of IgE-containing circulating immune complexes (IgE-CICs) in the peripheral blood of patients with RA. Because they mainly enrolled older patients (49.5 ± 1.5 years) with longer disease durations, the disease had progressed to moderate and late stages in most patients. Importantly, they found that most patients with RA had elevated serum levels of IFN-γ, and there were no significant differences in the levels of IL-4 between groups with different disease activities, suggesting Th1 dominance in patients with chronic RA. Anti-cyclic citrullinated peptide (CCP) antibodies are relatively specific for RA and are produced by plasma cells in the synovium of patients with RA. Previous studies have shown that CCP can activate the basophils by forming IgE-CICs with FceRI, which is highly expressed on the surface of basophils. Activated basophils release inflammatory factors, such as TNF-α and IL-1, thereby further aggravating RA severity, particularly in patients with severe arthritis and vasculitis complications.

It has been found that basophils also play a role in other rheumatic diseases. TLR2 could mediate basophil activation that induces IgG4 production in IgG4-related disease. This enhancement of IgG4 production has been associated with BAFF and IL-13. Poddighe et al. found that the activation of basophils can induce autoimmune pancreatitis. In addition, recent studies have revealed autoimmune pancreatitis as the initial presentation of IgG4-related disease. Basophils release interferon-α and IL-33 after activation mediate autoimmune pancreatitis and human IgG4-related disease.

Conclusions

Basophils are generally thought to be involved only in hypersensitivity reactions and have often been overlooked because of their low abundance in the blood. With the development of various detection techniques and molecular biology approaches, basophils have been shown to play important roles in innate and adaptive immune responses and in the process of immunomodulation. Despite being the least abundant white blood cells in humans, in-depth analyses of the mechanisms through which basophils mediate the pathogenesis of rheumatic diseases suggest that basophils could represent a novel therapeutic target in patients with rheumatic diseases. Indeed, such diseases may be controlled by blocking receptors involved in basophil activation and limiting the damaging effects of inflammatory mediators and cytokines secreted by basophils on organs. However, this study still has limitations. Basophils significantly express the TLR2 receptor. Up to now, the study of TLR2 mainly focuses on its natural immune function in the infection of bacteria, viruses, fungi, and other pathogens. TLR2 has significant antibacterial and antiviral effects. Most studies focus on the prevention and treatment of sepsis and septic shock, but only few studies focus on the immune system disease. Thus, few researches have studied that whether TLR2 can regulate the release of cytokines and inflammatory factors, affect the balance of Th1/Th2, and participate in the pathogenesis of autoimmune diseases by mediating basophil activation.

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References

1. Dossybayaeva K, Abdulkhayimova D and Poddighe D. Basophils and systemic lupus erythematosus in murine models and human patients. *Biology* 2020; 9(10): 308.
2. Arinobu Y, Iwasaki H, Gurish MF, et al. Developmental checkpoints of the basophil/mast cell lineages in adult murine hematopoiesis. *Proc Natl Acad Sci USA* 2005; 102: 18105–18110.
3. Shen T, Kim S, Do J, et al. T cell-derived IL-3 plays key role in parasite infection-induced basophil production but is dispensable for in vivo basophil survival. *Int Immunol* 2008; 20: 1201–1209.
4. Zhang K, Liu J, Truong T, et al. Blocking allergic reaction through targeting Surface-bound IgE with low affinity anti-IgE antibodies. *J Immunol* 2017; 198(10): 38233834.
5. Knol EF and Gibbs BF. Basophil stimulation and signaling pathways. *Methods Mol Biol* 2014; 1192: 193–203.
6. Falcone FH and Gibbs BF. Purification of basophils from peripheral human blood. *Methods Mol Biol* 2020; 2163: 35–48.
7. Min B, Brown MA and Legros G. Understanding the roles of basophils: breaking dawn. *Immunology* 2012; 135(3): 192–197.
8. Shen T, Kim S, Do JS, et al. T cell-derived IL-3 plays key role in parasite infection induced basophil production but is dispensable for in vivo basophil survival. *Int Immunol* 2008; 20(9): 1201–1209.
9. Lantz CS, Boesiger J, Song CH, et al. Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. *Nature* 1998; 392(6671): 90–93.
10. Chirumbolo S. State-of-the-art review about basophil research in immunology and allergy: is the time right to treat these cells with the respect they deserve? Blood Transfus 2012; 10(2): 148–164.
11. MacGlashan DW Jr. Self-termination/anergic mechanisms in human basophils and mast cells. Int Arch Allergy Immunol 2009; 150(2): 109–121.
12. Bühring H-J, Streble A and Valent P. The basophil-specific ectoenzyme E-NPP3 (CD203c) as a marker for cell activation and allergy diagnosis. Int Arch Allergy Immunol 2004; 133(4): 317–329.
13. Schneider E, Petit-Bertron AF, Bricard R, et al. IL-33 activates unprimed murine basophils directly in vitro and induces their in vivo expansion indirectly by promoting hematopoietic growth factor production. J Immunol 2009; 183: 3591–3597.
14. Smithgall MD, Comeau MR, Yoon BR, et al. IL-33 amplifies both Th1- and Th2-type responses through its activity on human basophils, allergen-reactive Th2 cells. Int Immunol 2008; 20(8): 1019–1030.
15. Poddighe D, Mathias CB, Freyschmidt EJ, et al. Basophils are rapidly mobilized following initial aeroallergen encounter in naïve mice and provide a priming source of IL-4 in adaptive immune responses. J Biol Regul Homeost Ag 2014; 28(1): 91–103.
16. Poddighe D, Mathias CB, Brambilla I, et al. Importance of basophils in eosinophilic asthma: the murine counterpart. J Biol Regul Homeost Ag 2018; 32(2): 335–339.
17. Gernez Y, Waters J, Tirouvanziam R, et al. Basophil activation test determination of CD63 combined with CD203c is not superior to CD203c alone in identifying allergic bronchopulmonary aspergillosis in cystic fibrosis. J Allergy Clin Immunol 2016; 138(4): 11951196.
18. Wack A and Gallorini S. Bacterial polysaccharides with zwitterionic charge motifs: toll-like receptor 2 agonists, t cell antigens, or both? Immunopharmacol Immunotoxicol 2008; 30(4): 761–770.
19. Komiya A, Nagase H, Okugawa S, et al. Expression and function of toll-like receptors in human basophils. Int Arch Allergy Immunol 2006; 140(Suppl 1): 23–27.
20. Sabroe I, Jones EC, Usher LR, et al. Toll-like receptor(TLR) 2 and TLR4 in human peripheral blood granulocytes:a critical role for monocytes in leukocyte lipopolysaccharide responses. J Immunol 2002; 168(9): 4701–4710.
21. Hauswirth AW, Natter S, Ghamnadan M, et al. Recombinant allergens promote expression of CD203c on basophils in sensitized individuals. J Allergy Clin Immunol 2002; 110(1): 102–109.
22. van Panhuys N, Prout M, Forbes E, et al. Basophils are the major producers of IL-4 during primary helminth infection. J Immunol 2011; 186(5): 2719–2728.
23. Oeser K, Maxeiner J, Symowski C, et al. T cells are the critical source of IL-4/IL-13 in a mouse model of allergic asthma. Allergy 2015; 70(11): 1440–1449.
24. Khodoun MV, Orekhova T, Potter C, et al. Basophils initiate IL-4 production during a memory T-dependent response. J Exp Med 2004; 200(7): 857–870.
25. Oh K, Shen T, Le Gros G, et al. Induction of Th2 type immunity in a mouse system reveals a novel immunoregulatory role of basophiles. Blood 2007; 109(7): 2921–2927.
26. Leon-Cabrera S and Flisser A. Are basophils important mediators for helminth-induced Th2 immune responses? A debate. J Biomed Biotechnol 2012; 2012: 274150.
27. Sokol CL, Barton GM, Farr AG, et al. A mechanism for the initiation of allergen-induced T helper type 2 responses. Nat Immunol 2008; 9(3): 310–318.
28. Chen K, Xu W, Wilson M, et al. Immunoglobulin D enhances immune surveillance by activating antimicrobial proinflammatory and B cell-stimulating programs in basophiles. Nat Immunol 2009; 10(8): 889–898.
29. Denzel A, Maus UA, Gomez MR, et al. Basophils enhance immunological memory response. Nat Immunol 2008; 9(7): 733–742.
30. Valencia X, Yarboro C, Illei G, et al. Deficient CD4+CD25high T regulatory cell function in patients with active systemic lupus erythematosus. J Immunol 2007; 178(4): 2579–2588.
31. Peng SL, Szabo SJ and Glimcher LH. T-bet regulates IgG class switching and pathogenic autoantibody production. Proc Natl Acad Sci USA 2002; 99(8): 5545–5550.
32. Charles N and Rivera J. Basophils and autoreactive IgE in the pathogenesis of systemic lupus erythematosus. Curr Allergy Asthma Rep 2011; 11(5): 378–387.
33. Charles N, Hardwick D, Daugas E, et al. Basophils and the T helper 2 environment can promote the development of lupus nephritis. Nat Med 2010; 16(6): 701–707.
34. Bieneman AM, Chichester KL, Chen YH, et al. Toll-like receptor 2 ligands activate human basophils for both IgE-dependent and IgE-independent secretion. J Allergy Clin Immunol 2005; 115(2): 295–301.
35. Dema B, Charles N, Pellefigues C, et al. Immunoglobulin E plays an immunoregulatory role in lupus. J Exp Med 2014; 211(11): 2159–2168.
36. Mukai K, Matsuoka K, Taya C, et al. Basophils play a critical role in the development of IgE-mediated chronic allergic inflammation independently of T cells and mast cells. Immunity 2005; 23(2): 191–202.
37. Hammad H, Plantinga M, Deswarte K, et al. Inflammatory dendritic cells—not basophils are necessary and sufficient for induction of Th2 immunity to inhaled house dust mite allergen. J Exp Med 2017; 207(10): 2097–2111.
38. Kiefer-Biasizzo H, Karasuyama H, Milon G, et al. Critical role of the neutrophil-associated high-affinity receptor for IgE in the pathogenesis of experimental cerebral malaria. J Exp Med 2011; 208(11): 2225–2236.
39. Bühring H-J, Streble A and Valent P. The basophil-specific ectoenzyme E-NPP3 (CD203c) as a marker for cell
activation and allergy diagnosis. *Int Arch Allergy Immunol* 2004; 133(4): 317–329.

40. Seshan SV and Jennette JC. Renal disease in systemic lupus erythematosus with emphasis on classification of lupus glomerulonephritis: advances and implications. *Arch Pathol Lab Med* 2009; 133(2): 233–248.

41. Perrigoue JG, Saenz SA, Siracusse MC, et al. MHC class II-dependent basophil-CD4+ T cell interactions promote T(H)2 cytokine-dependent immunity. *Nat Immunol* 2009; 10(7): 697–705.

42. Sharma M, Hegde P, Aimanianda V, et al. Circulating human basophils lack the features of professional antigen presenting cells. *Sci Rep* 2013; 3: 1188.

43. Bosch X, Lozano F, Cervera R, et al. IgE and autoantibody-mediated kidney disease. *J Immunol* 2011; 186(11): 6083–6090.

44. Sinico RA, Rimoldi L, Radice A, et al. Anti-C1q autoantibodies in lupus nephritis. *Ann N Y Acad Sci* 2009; 1173: 47–51.

45. Lin H, Boesel KM, Griffith DT, et al. Omalizumab rapidly decreases nasal allergic response and FcεRI on basophils. *J Allergy Clin Immunol* 2004; 113(2): 297–302.

46. Pan Q, Gong L, Xiao H, et al. Basophil activation-dependent autoantibody and Interleukin-17 production exacerbate systemic lupus erythematosus. *Front Immunol* 2017; 8: 348.

47. Wakahara K, Baba N, Vu QV, et al. Human basophils interact with memory T cells to augment Th17 responses. *Blood* 2012; 120(24): 4761–4771.

48. Rahul D. Pawar, Liliana,Castrezana-Lopez (Bacterial lipopeptide triggers massive albuminuria in murine lupus nephritis by activating Toll-like receptor 2 at the glomerular filtration barrier. *Immunology* 2009; 128(1 Suppl): e206–221.

49. Schulze-Koops H and Kalden JR. The balance of Th1/Th2 cytokines in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2001; 15(5): 677–691.

50. Gerli R, Bistoni O, Russano A, et al. In vivo activated T cells in rheumatoid synovitis. Analysis of Th1- and Th2-type cytokine production at clonal level in different stages of disease. *Clin Exp Immunol* 2002; 129(3): 549–555.

51. Campbell IK, Miescher S, Branch DR, et al. Therapeutic effect of IVIG on inflammatory arthritis in mice is dependent on the Fc portion and independent of sialylation or basophils. *J Immunol* 2014; 192(11): 5031–5038.

52. Wada T, Ishiwata K, Koseki H, et al. Selective ablation of basophils in mice reveals their nonredundant role in acquired immunity against ticks. *J Clin Invest* 2010; 120(8): 2867–2875.

53. Tang P, Chen Q, Lu J, et al. Relationship between basophils and disequilibrium of disease activity and Th1 response in patients with rheumatoid arthritis. *Chin J Immunol* 2016; 32(5): 702–706.

54. Zhang N, Zhang Z-M and Wang X-F. Correlation analysis between peripheral blood basophils and disease activity in patients with rheumatoid arthritis. *Eur J Immunol* 2018; 16: 1–7.

55. Watanabe T, Yamashita K, Sakurai T, et al. Toll-like receptor activation in basophils contributes to the development of IgG4-related disease. *J Gastroenterol* 2013; 48(2): 247–253.

56. Poddighe D, Dossybayeva K, Bexeitov Y, et al. Basophils in autoimmunity: systemic lupus erythematosus and more? *Autoimmun Rev* 2021; 20(4): 102790.

57. Watanabe T, Minaga K, Kamata K, et al. Mechanistic insights into autoimmune pancreatitis and IgG4-related disease. *Trends Immunol* 2018; 39(11): 874–889.

58. Lartigue A, Colliou N, Calbo S, et al. Critical role of TLR2 and TLR4 in autoantibody production and glomerulonephritis in lpr mutation-induced mouse lupus. *Immunol* 2009; 183(10): 6207–6216.