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Basophils, IgE, and Autoantibody-Mediated Kidney Disease

Xavier Bosch,* Francisco Lozano, ‡ Ricard Cervera, ‡ Manuel Ramos-Casals, ‡ and Booki Min§

Basophils are of interest in immunology due to their ability to produce a Th2-signature cytokine, IL-4, following activation. A new understanding of the role of basophils in immunity shows novel functions at a cellular level through which basophils influence adaptive immunity. This review summarizes new advances in basophil biology and discusses new roles for basophils in human disease, especially in the mediation of the pathogenesis of lupus nephritis. Recently, basophils have been shown to contribute to self-reactive Ab production in systemic lupus erythematosus and may enhance pre-existing loss of B cell tolerance, suggesting that basophils, IL-4, and IgE mediate the pathogenesis of lupus nephritis by promoting the Th2 environment and activating autoreactive B cells. In addition to envisaging exciting therapeutic prospects, these novel findings open the way for the study of basophils in other autoimmune and renal diseases. The Journal of Immunology, 2011, 186: 6083–6090.

Asophils are bone marrow-derived basophilic granulocytes that contain large cytoplasmic granules and two- to three-lobed nuclei. They constitute <0.3% of the total nucleated cells in the bone marrow and are the least abundant granulocytes found in the circulation (1). Since the discovery of basophils >130 y ago, they have been implicated in many types of allergic inflammatory responses. Earlier studies using a guinea pig model of cutaneous hypersensitivity found that basophils reach tissue sites, where they are triggered by Ags to release mediators (2). Basophils also have been shown to confer resistance against ectoparasite infections (3). During Amblyomma americanum tick infection in calves, significant decreases in feeding are associated with cutaneous basophil infiltration and blood basophilia (4). Transfer of anti-basophil serum abolishes resistance to tick infection in guinea pigs (5). Nevertheless, a tool to identify or selectively purify basophils has not been available until recently. Studies in the last 7 y have made significant progress in identifying the biologic functions of basophils, a list that continues to grow (see below for details). Surface phenotypes to analyze and purify basophils have been characterized extensively: FcεRI+ CD49b+ CD203c+ Thy1+ c-Kit+ FcγR+ CD45intermediate (6). Animal models to study basophil functions in vivo have been developed. Most importantly, genetically engineered basophil-deficient animals have been generated recently (7, 8). We now are beginning to understand novel functions of basophils at the cellular level through which they influence adaptive immunity. This review summarizes new advances in basophil biology and novel roles of basophils in human disease, particularly their mediation in the pathogenesis of lupus nephritis (LN).

IL-3 is a key factor for basophil development

IL-3 is involved in the differentiation of early precursors into fully mature basophils in the bone marrow and spleen (9, 10). Because basophil differentiation is controlled at a transcriptional level by differential expression of two key transcription factors, C/EBPα and GATA2 (11), IL-3 may regulate expression of these factors, influencing fate decision during early development. IL-3 deficiency results in significant defects in the generation of basophils in the course of Th2 immunity (12, 13). Nonetheless, the basal production of basophils in naïve IL-3–deficient mice is similar to that in wild-type mice (12). Therefore, the role of IL-3 in basophil development during steady-state conditions and immune responses is likely to differ. Basophil differentiation in steady-state conditions could be IL-3–independent; however, IL-3 becomes the major factor enhancing basophil generation in the bone marrow under Th2-associated inflammatory conditions (13).

Factors involved in basophil activation

The list of factors that positively and negatively regulate basophil activation continues to grow (Fig. 1). The primary action of IL-3 on mature basophils is to enhance IL-4 pro-
through interaction with the VH3 region of IgE (31). Com-
induces IL-4 and IL-13 release from human basophils.

Ags from pathogens also modulate basophil func-
tions.

Ag-presenting dendritic cells (DCs) provide IL-12, which
then program activated naïve CD4 T cells to Th1 lineage
cells, the source of initial IL-4 necessary to initiate Th2
differentiation remains elusive. Studies using cytokine-reporter
mice (4met or G4 mice) identified basophils as potential
candidates for the role of Th2 inducers (37, 38). In vitro, the
stimulation of naïve CD4 T cells in the presence of basophils
promotes Th2 differentiation without exogenous addition of
IL-4 (39). A key mechanism of basophils that supports Th2
differentiation operates via IL-4, because basophils deficient
in IL-4 or IL-4 neutralization lack or abolish basophil-
mediated Th2 differentiation (Fig. 1).

Unlike CD4 T cells, CD8 T cells stimulated in the presence
of basophils produce high levels of IL-10, which is not ob-
served when T cells are stimulated by other APCs (40). Because
basophils express MHC class I molecules, they directly in-
teract with and promote IL-10 expression in CD8 T cells.
The IL-4 neutralization abolishes basophil-mediated IL-10 ex-
pression; however, rIL-4 alone does not induce IL-10 in CD8
T cells, suggesting an additional factor in this process. IL-6
has a synergistic effect on CD8 T cell IL-10 expression when
cocultured with IL-4, although IL-6 alone had no effect (40).

Basophils also can enhance B cell IgE production in vitro
through the production of Th2 cytokines and CD40L ex-
pression (41, 42). It was reported recently that basophils effi-
ciently capture intact Ags and enhance B cell activation,
particularly B cell proliferation and Ig production (43). Both
IL-4 and IL-6 produced by basophils are key cytokines that
optimize CD4 T cell-dependent B cell help (40). In vivo,
basophil-mediated effects on B cells are critical to mount
protective humoral immunity against bacterial infection (44).
In humans, circulating IgD binds to basophils and induces
CD8 T cells, the source of initial IL-4 necessary to initiate Th2
differentiation, the controversy

Basophil functions in vivo

Th1 CD4 T cells mainly produce IFN-γ, protecting hosts
from intracellular pathogens, and factors inducing Th1 dif-
ferentiation have been identified, including IL-12, IFN-γ,
and transcription factor T-bet (36). Th2 CD4 T cells produce
IL-4, IL-5, and IL-13, protecting hosts from extracellular
pathogens. IL-4 and transcription factor GATA3 are key Th2-
inducing factors. Unlike Th1 immunity, in which activated
Ag-presenting dendritic cells (DCs) provide IL-12, which
then program activated naïve CD4 T cells to Th1 lineage
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Basophil functions as APCs and the controversy

Studies show that basophils play critical roles as APCs during
Th2-type responses (Fig. 1). Basophils uptake exogenous

FIGURE 1. Potential functions of basophils stimulated via multiple path-
ways are illustrated. LT, leukotriene; PAMP, pathogen-associated molecular
pattern; TSLP, thymic stromal lymphopoietin; IPSE.
Basophil-deficient animals: new functions revealed

A transgenic mouse, Mcpt8Cre, was generated by expressing the Cre recombinase gene under the control of the Mcpt8 gene. Basophil numbers were constitutively lower in this animal, while other leukocytes, such as peritoneal mast cells, remained intact. In vivo Th2 responses, including alumn-induced allergic lung inflammation, alumn-induced humoral immune responses, and Ig-mediated passive systemic anaphylaxis, were induced normally. Furthermore, primary Th2 immune responses against infection with the intestinal nematode Nippostrongylus brasiliensis were not impaired without basophils (49), which is consistent with our recent report (50). In contrast, protective memory immune responses against secondary N. brasiliensis infection were impaired significantly (49). Interestingly, lung infiltration of Th2-type CD4 T cells and eosinophils following N. brasiliensis infection was not altered; instead, eosinophil recruitment into the draining mediastinal lymph node was diminished greatly without basophils, suggesting that they may contribute to eosinophil recruitment (51).

Basophil mobilization: a key step for basophil function in vivo

In steady-state conditions, the primary locations of basophils are the bone marrow and the circulation, while basophils are found very rarely in secondary lymphoid tissues. A key step that allows basophils to contribute to Th2 immune responses is their transient mobilization into secondary lymphoid tissues. Basophils within draining lymph node nodules are observed in many in vivo immune responses: immunization with parasite Ags, such as papain (29) and house dust mite Ags (48), and infection with N. brasiliensis (50), S. mansoni (47), T. muris (46), and ticks (7). Recruitment is found only in draining lymphoid tissues, suggesting active immune responses. IL-3 plays a crucial role in this recruitment process (50). Because IL-3 is produced primarily by activated T cells (13), Ag-induced T cell activation within local lymphoid tissues seems to be the primary underlying factor. In addition, recruitment is transient, only found between days 3 and 4 post-Ag challenge (29, 50). It is unclear how IL-3–derived basophil recruitment is tightly controlled, although IL-3–responsive cells have been shown to be bone marrow–derived cells (50). Likewise, recruited basophils are in close contact with T cells within the T cell zone (29). Basophils may function as APCs (24, 45, 46) and/or produce IL-4, creating an optimal microenvironment favoring Th2 differentiation. Basophils express chemokine receptors, including CCR1, CCR2, CCR3, CXCRI, CXCR3, and CXCR4 (52). A microarray study of basophils isolated from the lungs of N. brasiliensis-infected mice showed that CCR2 is highly expressed on basophils (38). Whether IL-3–dependent basophil recruitment is chemokine-dependent and, if so, which chemokines are involved in basophil recruitment remains to be determined.

Basophils: from allergy to autoimmunity

Because basophils play an immunomodulatory role, provoking Th2 cell differentiation in vivo, it could be suggested that they...
also might play a leading role in immune diseases other than allergies. In addition to the finding of peripheral basophilia and constitutive Th2 skewing of CD4 T cells in lyn−/− mice, basophil involvement also is reported in autoimmune urticaria, where autoantibodies to the high-affinity receptor FceRIα induce basophil activation (53, 54). A Th2 component is well-described in autoimmune urticaria, and basophils contribute to the development of autoimmune symptoms through their immunomodulatory and effector responses. Reports show that, in some murine models, mast cells contribute to autoimmune arthritis (55). In this and other autoimmune diseases, mast cell effector and immunomodulatory functions initiate inflammation, whereas the enhancement of inflammation may be due to Th1 and Th17 cell responses. These CD4 T cell subsets are thought to be the primary effector cells involved in chronic inflammation in experimental autoimmune encephalomyelitis, a model of human multiple sclerosis, experimental autoimmune uveitis, a model of human posterior uveitis, and collagen-induced arthritis, a murine model of human rheumatoid arthritis (RA) (56).

Although IgE is recognized as a human Th2 marker, some reports describe increased levels of IgE in the setting of Th1 and Th17 responses in patients with autoimmune diseases (57–59). Although the significance of Th1- and Th17-driven responses in the development of autoimmunity is evident, it seems improbable that Th2 responses do not contribute to the disease. Furthermore, allergy and autoimmunity share various features, such as manifestations associated with autoantibody production and circulating immune complex (CIC) formation (60). Studies report a common structure of some allergens and autoantigens (61) and suggest that numerous environmental allergens have common structural conformations with self-antigens, which could explain the development of autoimmune diseases, such as chronic urticaria. However, as discussed later, increased IgE levels are not associated with increased allergic disease in other autoimmune diseases, such as systemic lupus erythematosus (SLE) (57).

The recent finding that IgD-mediated basophil activation by a yet unidentified receptor is relevant to some chronic auto-inflammatory diseases, such as hyper IgD syndrome, TNFR-associated periodic syndrome, and Muckle-Wells syndrome (44), suggests that this activation could be involved in B cell homeostasis and the production of Abs.

SLE as a paradigm of autoimmune disease

SLE is characterized by functional changes in B and T cells, monocytes, plasmacytoid DCs, and granulocytes, autoantibody deposition at inflammation sites, and increased circulating cytokine and chemokine levels. In LN, immune complexes deposited in glomeruli include IgG, IgM, and IgA autoantibodies, which are directed against ubiquitous nuclear Ags, especially dsDNA, possibly leading to kidney failure and death (62). Mechanisms contributing to LN pathogenesis include those mediated by Th1 and Th17 cells (63).

Although humoral responses produced by self-reactive Abs act as effector mediators of LN and IgE autoantibodies have been observed in some cases, the manner of Th2 cell and B cell activation in LN pathogenesis remains unclear (62).

Role of T cells and cytokines in the pathogenesis of SLE and LN

In SLE, T cells provide “excessive help” to B cells and mount inflammatory responses while producing low levels of IL-2 (63). Defective IL-2 production in T cells could explain the known reduction in cytotoxic activity, defective regulatory T cell function, and decreased activation-induced cell death in SLE patients (64). Helper CD4 T cells are vital components of immune responses in SLE; after differentiation, CD4 T cell effector functions correlate with the profiles of the cytokines that they secrete (65).

Amplified Th1, Th2, Th17, and follicular helper T cell responses are related to autoantibody production in murine and human SLE, and their effector cytokines may mediate target-organ inflammation. The cytokine response might reflect the primary activation pathway, which could be governed by genetic factors, and/or a specific environmental trigger (65, 66).

As mentioned, studies show a reduction in the amount and/or function of regulatory T cells in SLE patients and lupus-prone mice (67). Regulatory T cells have a reduced capacity to suppress CD4 T cell proliferation in active lupus compared with those from inactive lupus or healthy controls (68).

In addition to Th1, Th17, and regulatory T cells, reports suggest a role for Th2 cells in SLE (68–70). The strong humoral response in SLE indicates that there may be a Th2 component, with reports showing increased IgE and the presence of self-reactive IgE in the serum from some SLE patients, with no increase in allergy (71, 72). However, it is unclear whether Th2 cytokines, such as IL-4, and IgE contribute to SLE and which cell type may be implicated.

The presentation of LN is phenotypically and histologically heterogeneous. Diffuse proliferative glomerulonephritis (DPGN) and membranous glomerulonephritis (MGN) are, morphologically, complete opposites (73). DPGN pathogenesis is associated with a predominance of Th1 cytokines, suggesting that it occurs in a Th1-dominant immune response. Renal tissue from DPGN patients shows increased Th1 cytokine levels, including IFN-γ, and the IFN-γ/IL-4 production ratio correlates with the nephritic histological activity index. In contrast, the ratio is reduced in PBLs of MGN patients, suggesting that Th2-dominant cytokine responses are associated with MGN pathogenesis (74).

IgE in SLE and LN

Studies show that SLE patients without allergy have elevated total IgE and anti-nuclear IgE autoantibody levels, which appear to be related to disease severity (57). Likewise, the presence of IgE in glomerular immune complex deposits in renal biopsies of SLE patients and a murine model of systemic autoimmune disease suggest that they play a role in LN (75). A study of anti-nuclear IgE Ab specificity and cytokine involvement suggests that IgE Abs against cell autoantigens implicated in protein expression, cell proliferation, and apoptosis are observed in SLE patients and that IL-10 may downregulate IgE autoimmune responses in SLE (75).

Lyn, basophils, and Th2

Lyn is one of various Src tyrosine kinases involved in B cell activation. Aged lyn−−/− mice develop an autoimmune disease resembling human SLE (76). lyn−−/− mice have circulating autoantibodies to dsDNA and anti-nuclear Abs (ANAs). Glomerular CIC deposition in these mice results in renal damage and death.
lym−/− mice develop early strong, constitutive Th2 skewing and exacerbated responses to Th2 challenges (77, 78). In addition, B cells from some SLE patients express reduced levels of Lyn kinase (79). Therefore, lym−/− mice are a likely model to study the influence of a Th2 environment on lupus-like nephritis.

The cell types causing Th2 cell differentiation are not clear. Identification of the cell types and molecules responsible for Th2 cell response dysregulation could help to control these responses (34). Although important, factors controlling basophil-mediated Th2 cell differentiation remain unknown. Lyn kinase dampens basophil expression of the transcription factor GATA3 and the initiation and extent of Th2 cell differentiation. Reportedly, lym−/− mice had marked basophilia, a constitutive Th2 cell skewing that was exacerbated by in vivo basophil challenge, produced Abs to normally inert Ags, and did not respond appropriately to a Th1 cell-inducing pathogen. Th2 cell skewing was dependent on basophils, IgE, and IL-4 but independent of mast cells, suggesting that basophil-expressed Lyn kinase exerts regulatory control on Th2 cell differentiation and function (34).

Basophils, IgE, Th2, and LN

Charles et al. (80) recently investigated whether Th2 skewing in lym−/− mice plays a role in the development of late-life lupus-like nephritis and whether similar characteristics exist in SLE patients. They found that the Th2 phenotype contributes to lupus-like nephritis in lym−/− mice and is associated with LN in human SLE. Basophils and self-reactive IgE were identified as key players in renal disease. In mice, basophil depletion or a lack of IL-4 or IgE led to reduced autoantibody production and preserved renal function. Therefore, without basophils, autoantibody levels might not be sufficient to cause renal disease.

Charles et al. (80) studied the role played by the Th2 environment in the development of an SLE-like phenotype using mice deficient in IgE and Lyn, IL-4 and Lyn, or mast cells and Lyn, respectively. As reported (77), IgE contributes to increased mast cell levels in lym−/− mice, suggesting that it plays a role in mast cell survival (81). However, neither IL-4 nor IgE was associated with basophilia in mice, and the lupus-like nephritis seen was, therefore, dependent on IgE and IL-4 but not on mast cells. Basophil depletion in lym−/− mice aged >32 wk substantially decreased ANA and reduced splenic plasma cells and the renal proinflammatory environment. Basophils supported splenic plasma cells and enhanced the production of autoantibodies in an IL-4– and IgE-dependent manner, resulting in kidney damage.

Charles et al. (80) also determined whether self-reactive IgE is observed in murine circulation, whether they activate FcεRI-bearing basophils, resulting in Th2 cytokine expression, and whether IgE or IgG immune complexes stimulate basophil IL-4 production. Although IgE immune complexes induced basophil IL-4 production, IgG immune complexes did not.

Circulating basophils had increased CD62L expression, which permits leukocyte homing to peripheral lymphoid tissues. A lack of IL-4 or IgE inhibited CD62L expression on circulating basophils. Large amounts of basophils were present in the spleen and lymph nodes, where the proportion of basophils was reduced markedly in IL-4− or IgE-deficient but not in mast cell-deficient settings. Lymph node basophils expressed membrane-associated BAFF, showing a possible role for lymph node basophils in B cell survival and differentiation. In addition, basophils from mice lymph nodes and spleen had high expression of MHC II. Higher expression of MHC II and/or BAFF in the lymph nodes and spleen could permit communication with T and B cells.

SLE patients had high numbers of C1q-reactive CICs, which activate the classical complement pathway and were increased markedly in mild and active disease. SLE patients also showed high total IgE and self-reactive dsDNA-specific IgE levels, which were associated with active LN. IgGs directed against IgE also were found in sera in SLE patients, with significantly increased levels correlating with active disease.

Basophils from all of the SLE patients had high CD203c expression compared with that of healthy controls, indicating basophil activation. CD62L and HLA-DR expression also was elevated on SLE basophils and correlated with greater disease activity. The number of total circulating basophils was reduced in SLE patients and was associated with immunosuppressive therapy but not with basophil activation.

Interpretation and caveats

Charles et al. (80) showed that basophils contribute to self-reactive Ab production in SLE and could enhance pre-existing loss of B cell tolerance. The development of lupus-like disease in lym−/− mice depended on the presence of IL-4 and IgE, whose absence reversed the Th2 skewing seen in these mice. IgG anti-dsDNA and ANA titers and CIC levels also were reduced in mice deficient for IgE and Lyn, and IL-4 and Lyn, respectively, demonstrating that autoantibody production in lym−/− mice was, at least partly, reliant on the Th2 environment. Therefore, these results demonstrate the participation of basophils, IgE, and IL-4 in the maintenance of autoantibody production in lym−/− mice and indicate that the Th2 environment contributes to the autoimmunity. They also show that, in some settings, basophils are strong inducers of Th2 cell differentiation, thus connecting the “allergic” environment to the development of autoimmune diseases, such as SLE, although the suggestion that basophils are necessary for Th2 cell differentiation must be inferred with caution. Research is limited on this topic, and the crucial test of challenging mice with a Th2 Ag in the complete absence of basophils remains to be done.

Although this study by Charles et al. (80) increases the understanding of LN pathogenesis, it has some limitations. IgE autoantibodies are found only in one third of SLE patients (75). Therefore, it is unlikely that the lym−/− mouse models SLE in most patients. However, it is known that IFN-γ, the primary Th1 cytokine, can negatively regulate both basophils and IL-4 production; therefore, it remains to be determined whether the 30% of SLE patients with high IgE ANA levels would respond to therapeutic basophil modulation, as suggested by this study in lym−/− mice (65).

It is also unclear whether the reported upregulation of BAFF on basophils depends on FcεRI engagement or needs concomitant TLR9 engagement or, alternatively, BAFF produces basophil-mediated class switching and Ig production (44). Activated basophils migrate to peripheral lymphoid organs, but the manner and site of interaction with T or B cells remain to be elucidated.
Finally, Charles et al. (80) observed a significant decrease in the number of circulating basophils in SLE patients, which was associated with increased disease activity, findings consistent with basophil homing to the secondary lymphoid tissues. A reduced number of circulating basophils was not observed in lyn−/− mice, although the mice had peripheral basophilia, which was not observed in patients. In lyn−/− mice, dysregulation of basophil proliferation probably covers circulating basophil depletion after basophil homing to the secondary lymphoid tissues.

**Therapeutic implications**

This study suggests that reducing circulating levels of self-reactive IgE or dampening basophil activity could have therapeutic benefits in LN. Therefore, determining whether basophil reduction or inactivation early in the disease course could defer or rescue the early development of LN is of substantial interest.

A recent phase 3 multicenter, placebo-controlled trial in patients with active SLE found that belimumab, a mAb against BAFF, is safe and efficacious (62, 82). Belimumab, besides affecting B cells, might deplete basophils (which contain membrane-bound BAFF), suggesting that it could be of help in some LN patients, perhaps combined with treatments suppressing IgE production.

The study showed that IgE immune complexes activate basophils and that removing self-reactive IgEs forming functional C1c2 prevents renal disease. As circulating IgE levels are decreased, omalizumab, a mAb binding to human IgE and decreasing FcεRI expression on basophils (83), may provide therapeutic benefits in SLE patients with increased levels of IgE. This approach could be tested easily, because omalizumab is used currently to treat asthma and allergic rhinitis and seems to be well tolerated (80, 81).

**Future directions**

The variety of basophil immunoregulatory activities explains why their pharmacological modulation by specific inhibitors or regulators is actively pursued, especially in allergic diseases. This approach may be used fairly soon in other pathologic conditions, including autoimmunity, as illustrated by the recent finding of basophil activation by anti-citrullinated protein Abs (ACPs) in the serum of RA patients (84). Schuerwegh et al. (84) showed that IgE-bearing basophils from ACPA-positive RA patients are activated directly on exposure to citrullinated Ags, probably reflecting the presence of FcεRI-bound IgE–ACPs on basophil surfaces. Identification of this activation pathway mediated by IgE–ACPs in basophils could lead to innovative therapeutic schemes in RA.

The role of basophils also should be tested in immunemediated renal disorders other than LN. A memory-type immune response prevails in transplantation and various autoimmune diseases with the constant presence of alloantigens/autoantigens. Together with specific Abs, these Ags may activate basophils, which may enhance ongoing humoral immune responses and further boost Ig production (85).

Although studies suggest that basophils may play a role in transplant rejection, studies using consistent methods of detecting basophils and determining their activation in some renal disorders are required. Basophils should be studied in minimal-change disease and focal segmental glomerulosclerosis, where T cells and allergy/atopy are believed to play a major role, and Th2 skewed cytokine profiles have been recognized (85). Basophils, as inducers of Th2 immune responses and an important source of IL-4, could initiate disease and play a role in sustaining Th2-immune responses. Basophils also should be assessed in diseases driven by Ig directed against defined kidney structures (e.g., anti-glomerular basement membrane disease) or deposited in the glomeruli (e.g., membranous nephropathy) or driven by systemic vasculitis (e.g., anti-neutrophil cytoplasmic Ab-associated vasculitis), in which basophils may contribute to the generation and maintenance of high levels of specific Ig and, eventually, to disease progression.

**Conclusions**

Although our knowledge of the immunomodulatory and effector functions of basophils remains imperfect, it can be stated that, in addition to their role in allergy and host defense against parasites, basophils can promote Th2 cell differentiation and amplify the humoral immune response. Their role in autoimmune diseases is not clear, but the studies reported here provide a persuasive argument for a role in the amplification of LN rather than disease initiation. Essential requirements are autoreactive IgE-dependent basophil activation, IL-4 production by basophils, and promotion of Th2 cell differentiation. This does not negate the proven roles of Th1, Th17, and the loss of regulatory T cell function in the development of autoimmunity but rather suggests that the robust humoral constituent of autoimmune diseases, such as SLE, requires basophils to reach the autoantibody production levels that produce renal disease. These novel findings open the way for the study of basophils in other autoimmune and renal diseases. Future studies also may show whether basophil-mediated immune activation is linked to other SLE-prone mouse models in addition to lyn−/− mice.

**Disclosures**

The authors have no financial conflicts of interest.

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