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The deleterious role of basophils in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus is a complex autoimmune disease of multifactorial origins. All compartments of the immune system appear to be affected, at least in some way, and to contribute to disease pathogenesis. Due to an escape from negative selection autoreactive T and B cells accumulate in SLE patients leading to the production of autoantibodies mainly raised against nuclear components and their subsequent deposition into target organs. We recently showed that basophils, in an IgE and IL-4 dependent manner, contribute to SLE pathogenesis by amplifying autoantibody production. Here, we summarize what we have learned about the deleterious role of basophils in lupus both in a mouse model and in SLE patients. We discuss which possible pathways could be involved in basophil activation and recruitment to secondary lymphoid organs during SLE, and how basophils may amplify autoantibody production.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of multifactorial origin including genetic, hormonal and environmental factors. This disease can affect multiple organs including skin, joints, heart, central nervous system and kidneys. Involvement of the latter leads to lupus nephritis (LN) affecting 40 to 60% of SLE patients. It is considered as one of the most severe manifestations as it may evolve to end-stage renal failure [1]. It is widely admitted that SLE pathogenesis is associated with a break in tolerance of apoptotic bodies, particularly nuclear antigens, leading autoreactive T and B cells to expand. They produce autoreactive antibodies mainly raised against nuclear components such as double stranded DNA (dsDNA) or RNA-binding protein Smith (Sm), Ro (SS-A) and La (SS-B) antigens…[1]. These autoantibodies will form circulating immune complexes (CIC) when bound to their antigens and complement factors. Deposition of these CICs in the target organ promotes a chronic inflammatory response, leading ultimately to tissue damage and organ dysfunction [1]. It is well established that disease activity and especially lupus nephritis activity correlate with autoantibody titers [2]. Like for most other autoimmune diseases, specific or curative therapy for SLE do not exist, and flares of the disease are contained by aggressive immunosuppressive treatments [3].

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Basophils as immune regulators

Representing less than 1% of circulating white blood cells, basophils have long been ignored apart from their involvement in allergic diseases and parasitic infections as they express the high affinity IgE receptor (FcεRI) in its tetrameric isoform ($\alpha\beta\gamma_2$) like mast cells. However, new insights about their role in immune regulation have emerged in the past few years [4]. Following stimulation with a number of stimuli, basophils can secrete large amounts of cytokines (mainly IL-4 and IL-6), upregulate particular molecules at their surface with activating functions (such as MHC class II, BAFF, APRIL…) to influence a wide array of immune cells [4]. Basophils can promote T-helper type 2 CD4+ cells (Th2) differentiation [5,6], inhibit Th1 differentiation [7], act as antigen presenting cells for CD8+ T cells via MHC class I [8] and for CD4+ T cells via the upregulation of MHC class II [9–12]. If the latter point is controversial in the literature [13,14], a recent report by Otsuka *et al.* demonstrated that basophils were required for the induction of Th2 immunity to haptens and peptide antigens [9]. Basophils have been also described as components involved in the B cell class switch towards Th2-type immunoglobulins (IgG1, IgG2b and IgE), plasma cell differentiation and survival, as well as to support the humoral memory response [15–17]. Basophils also interact with the myeloid compartment since they cooperate with dendritic cells in a papain-induced Th2 differentiation model [18]. They also promote monocyte differentiation into M2 macrophage [19] and inhibit inflammatory responses by inducing FcγRIIb expression on monocytes through dendritic cell (DC)-induced IL-33 stimulation [20]. Basophils have been shown to promote the recruitment of immune cells at the site of inflammation during IgE-mediated chronic allergic inflammation [21] and in acquired immunity against ticks [22]. Their immunomodulatory actions have led to the identification of basophils as deleterious contributors to some human non-atopic diseases such as certain autoinflammatory syndromes (Hyper IgD syndrome (HIDS), TNF receptor-associated periodic syndrome (TRAPS)…) [23] and autoimmune diseases (SLE) [15].

Immune dysregulations in SLE

As a complex systemic autoimmune disease, SLE has been extensively studied both in animal models and in patient samples. T cell involvement in lupus pathogenesis has been well documented and regulatory T cells, Th1, Th2, Th17 and T follicular helper cell (T_{FH}) components of the disease have been, at least partially, described [24]. As a break in tolerance is clearly occurring, regulatory T cells have been studied [25]. In animal models, the Th1/Th2 balance has been shown to be central for disease development and the way it affects organs, especially the kidney [26]. The Th1 component of the disease has been associated with tissue damage and was also shown to participate to the chronic inflammatory environment in affected organs [1,27]. IL-17 levels correlate with disease activity and IL-17 producing T cell number are increased in the periphery and in the kidneys of SLE patients [28]. IL-17 participates in increasing the survival and the proliferation of B cells, and their differentiation into antibody secreting cells in germinal centers [28,29]. T_{FH}-like cells are detected in the periphery of active SLE patients [30] and associated with SLE development in mouse models [31].

Plasmacytoid dendritic cells (pDCs) are well studied for their involvement in SLE, particularly for the type I interferon signature, which has been observed both in SLE patients and mouse models. CICs and TLRs stimulate type I interferon production by pDCs and promote autoantibody production [32–34]. When stimulated by nucleic acid-containing immune complexes (NA-ICs), neutrophils may play a central role in the amplification of the disease by extruding DNA webs associated with alarmin peptides when dying via a phenomenon called NETosis (Neutrophil Extracellular Traps, NET). These newly available NA-ICs activate pDCs to amplify type I interferon production by these cells [35,36].

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With the help of autoreactive T cells and other humoral stimulators described above, autoreactive B cells mature as autoreactive plasma cells and subsequently produce autoantibodies [24]. This central humoral component of pathogenesis leads to the formation of CIC and their deleterious effects. Presence of overreactive and dysregulated B cells in SLE have led to the development of immunotherapies targeting this cell compartment (Rituximab, anti-CD20 depleting antibody, Belimumab, anti-Blys/BAFF blocking antibody…) [24]. However, clinical trials using these monoclonal antibodies showed very limited benefits for the patients, likely due to trial designs and regulations [24]. Together with elevated total IgE titers in SLE patient serum as compared to the general population (see below) [37], a Th2 component of the disease appears to be critical for full disease development. Detailed review of current knowledge concerning SLE pathogenesis is reviewed in reference [24].

Basophils and the Th2 environment in a spontaneous model of murine lupus

Lyn is a Src family kinase member that functions both as a positive and negative regulator in a wide variety of immune receptor signaling. Lyn is expressed in all hematopoietic cells with the exclusion of T cells [38]. Lyn deficient animals have a strong susceptibility to Th2 challenges and develop in their late life an SLE-like disease including its kidney component [39–41]. Lyn is a key negative regulator of BCR signaling. This feature is thought to be central for the loss of tolerance that occurs in aged mice [38]. We recently showed that these mice also develop a peripheral basophilia responsible for a profound Th2 bias in an IgE- and IL-4-dependent manner. Knocking-out the *Igh-7* (IgE) gene, the *Il-4* gene or depleting basophils in Lyn deficient animals could indeed reverse this Th2 bias [5]. Aged $Lyn^{-/-}$ mice acquire autoantibodies against nuclear antigens and CIC deposit in the kidney, leading to the development of end-stage renal disease and loss of kidney function [39,40]. We verified whether the early basophil-dependent Th2 bias of these mice was responsible for the autoimmune phenotype observed in aged animals. Our data showed that autoreactive IgE (anti-Nuclear Antigen (ANA) and anti-dsDNA) accumulated in CIC from $Lyn^{-/-}$ mice [15]. Furthermore, these IgE-containing immune complexes (IC) were able to strongly induce IL-4 production by basophils. Adding IgE or IL-4 deficiency to the $Lyn^{-/-}$ mice, despite a still present basophilia, led to the development of a much milder disease with decreased autoantibody titers and CIC deposition, rescuing the kidney function [15]. Basophils from aged $Lyn^{-/-}$ mice had an activated phenotype and were able to accumulate in secondary lymphoid organs (SLO). SLO-accumulated basophils expressed MHC class II molecule and a membrane-bound form of the B cell activating factor BAFF explaining how they could, in addition to their production of IL-4 and IL-6, interact with the T and B cell compartments [15]. Moreover, short-term antibody-mediated basophil depletion led to a dramatic decrease in kidney pro-inflammatory cytokine concentrations and in autoantibody titers. The latter effect was due to basophil-dependent support of (autoreactive) plasma cell survival in SLO [15]. Altogether, these data allowed us to conclude that basophils and the Th2 environment (through IgE- and IL-4-dependent mechanisms) were key contributors for lupus-like disease in the $Lyn^{-/-}$ mouse model. Basophil-deficient animal models have recently been reported and will allow to confirm basophil contribution in other spontaneous or inducible SLE mouse models [22,42].

Basophils and the Th2 environment in human disease

Evidences for a Th2 component in the human disease have been reported. Indeed, elevated levels of circulating IgE in SLE patients have been documented without being associated with a higher incidence of atopic diseases[37]. Autoreactive IgE raised against dsDNA could be detected in sera of SLE patients. Interestingly, their titers correlated with the SLE disease

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activity index (SLEDAI) and even more prominently in patients with active nephritis [15]. Such autoreactive IgE had already been described in the early 80's and were known to be present at the surface of basophils [43]. However, no degranulated phenotype is observed in SLE patient basophils (*unpublished data*). These SLE patient basophils also had an activated phenotype exhibiting an upregulated surface expression of CD203c and HLA-DR molecules. Lyn, which is a negative regulator of mouse basophil proliferation [5], had normal expression levels in circulating basophils of SLE patient [15]. This explains why the basophilia observed in the $Lyn^{-/-}$ mouse model is not observed in SLE patients who show a marked basopenia that correlates with disease activity. These basophils had an upregulated CD62L (L-selectin) surface expression suggesting transendothelial migration capabilities for recruitment into SLO. This was supported by the observed accumulation of basophils in SLE patient SLO (spleen and lymph nodes) whereas control biopsies did not show any staining [15]. Since autoreactive IgE titers increase with disease activity, and especially with the activity of lupus nephritis, it is reasonable to assume that IgE concentration into CICs increases as well, suggesting that the Th2 component of the disease is particularly strengthened during flares. As in other renal pathologies, flares are thought to be associated with benign viral infections able to skew the immune system towards a Th2 humoral response [1]. This would correlate as well with the basopenia which is aggravated during active phases of the disease. However, CICs do not contain only IgE. Indeed, CICs contain autoantibodies from all other isotypes: IgM, IgG, IgA and IgD ([1] *and unpublished data)*. Basophils are armed to bind several isotypes (IgG, IgE, IgA and IgD) which can induce positive or negative signals [23,44,45]. For instance, FcεRI triggers activating signals and FcγRIIb triggers inhibitory signals when co-engaged [44]. The extent of the CIC-mediated basophil activation therefore results from the integration of these different signals which, in all SLE cases we observed, does not lead to basophil degranulation *(unpublished data)*. However, basophils are stimulated enough to produce cytokines and to upregulate stimulatory molecules on their surface. They can then provide a strong support to autoreactive B and T cells to amplify autoantibody and CIC production [15]. Chemotactic signals (ligands and receptors) responsible for the peripheral basopenia observed in SLE patients and for basophil addressing to SLO remain to be identified.

Basophil activation pathways in SLE

As indicated above, murine and human data led us to propose the following working hypothesis: basophils, due to their permanent, systemic and low intensity stimulation, amplify autoantibody production and CIC formation by supporting both autoreactive T and B cells in SLO [46]. This hypothesis supports the notion that basophils have a deleterious role in lupus pathogenesis. Whereas we demonstrated a clear correlation between autoreactive IgE titers in patients and the activation status of their basophils, together with the marked basopenia, it is possible that many other stimuli might impact on these cells in lupus pathogenesis. As summarized in Table 1, basophils are known to express a wide variety of receptors, the ligands of which have been described as being upregulated in SLE patient serum. By the same approach, chemokine receptors expressed by basophils, the ligands of which are dysregulated in SLE patients are listed in Table 1 together with their known effects on basophils. All these receptors and their respective ligands could participate to basophil recruitment into SLO and/or at the site of chronic inflammation during SLE and hence contribute to the deleterious role of basophils in SLE. Another example of possible basophil activation pathway in SLE concerns aberrant immune responses to dsDNA, RNA and other nuclear components which occur during SLE pathogenesis. An elegant study by Marichal *et al.* showed that the Th2 bias induced by alum-adjuvant based immunizations is in fact due to the DNA released by cell death [47]. Since basophils express TLR-9 [48], direct basophil stimulation by excessive self-antigen concentrations (dsDNA via NETosis and apoptotic bodies…) could occur. Similarly, TLR-2, which is expressed on basophils as

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well, could trigger an activation signal via low molecular weight hyaluronan derived from the inflamed site [49] and/or be engaged by a concomitant pathogenic infection. These events involving TLRs could amplify the deleterious role of basophils in SLE.

Putative pathways for additional deleterious function of basophils in SLE

As we demonstrated in the *Lyn*$^{-/-}$ mouse model, basophils act on T and B cell compartments via the production of IL-4, BAFF and MHC class II surface expression, promoting Th2 differentiation and autoantibody production [15]. However, as described above, basophils may act on the immune system in multiple ways. Some possible pathways by which basophils could contribute to the amplification of autoantibody production and to SLE pathogenesis in general are summarized in Figure 1. For instance, basophils have been shown to represent key players in the amplification of Th17 differentiation in vitro when co-cultured with T cells and lung or mucosal epithelial cells from patients with chronic inflammatory diseases [50,51]. By promoting Th17 differentiation and by the possibility of being indirectly activated by IL-17A, basophils could promote Th17 cell activity during SLE. On the other end, basophils can produce retinoic acid, promoting Th2 and inhibiting Th1 and Th17 differentiations [52]. Thus, activated basophils could influence in many ways the Th1 and Th17 components during SLE pathogenesis.

Concluding remarks

In summary, research data obtained in recent years largely support a deleterious role of basophils in SLE pathogenesis. This involves autoreactive IgEs included in CICs that activate basophils, but also other factors dysregulated during SLE, which could influence the basophil activation status and their recruitment to SLO. Identifying these factors and analyzing basophil-mediated effects on the immune system during SLE pathogenesis should offer new diagnostic and prognostic tools. It has become clear that targeting basophil or involved basophil-activating factors represent valuable strategies to develop new therapeutic approaches in SLE. Will the targeting of autoreactive IgE allow to break the amplification loop of autoantibody production supported by basophils? Could immunotherapy allowing basophil depletion be an efficient new approach to prevent flares of the disease? These questions are likely to be central in our investigations in the coming years.

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Highlights

- Basophils and Th2 environment contribute to systemic lupus erythematosus pathogenesis.
- Basophil activation could occur through different stimuli during lupus.
- Basophils amplify autoantibody production by supporting autoreactive B cell maturation and plasma cell survival.
- Basophil-mediated T cell differentiation could be induced through various signals.

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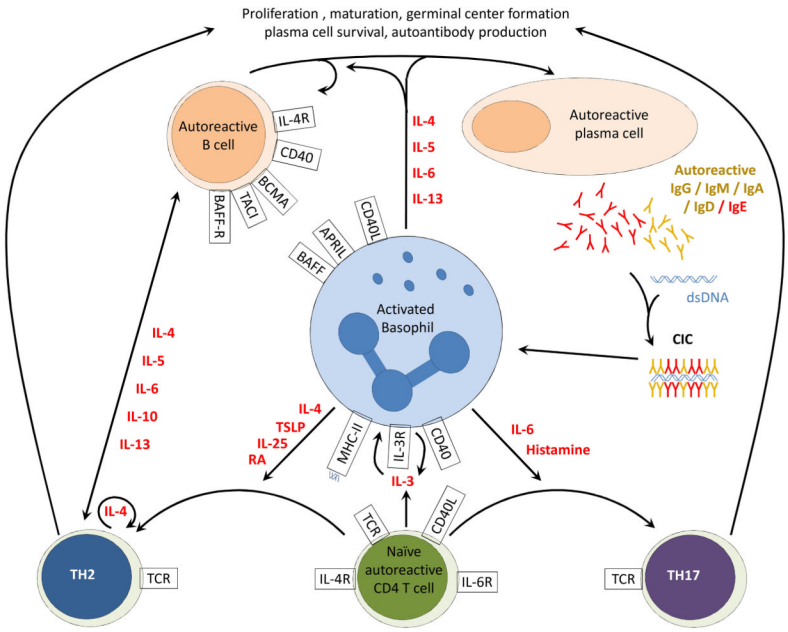

Figure 1. Deleterious interactions between basophils, B and T cells during SLE

Autoreactive T and B cells trigger autoantibody production and CIC formation during SLE. Activated basophils migrate to lymph nodes where they can interact with both B and T cells. Through secretion of IL-4, IL-6, IL-5, IL-13 and membrane expression of CD40L, BAFF and APRIL, basophils interact with the B cell compartment. They induce autoreactive B cell proliferation, class switch (towards IgG, IgA and IgE), maturation, plasma cell survival and autoantibody production via relevant receptors expressed on B and plasma cells. Basophil-expressed CD40 and MHC class II can activate naïve T cells via CD40L and T cell receptor (TCR) respectively. Activated T Cells secrete IL-3 which induces basophils to secrete IL3 to sustain their own activation and survival. Basophils can drive the Th17 differentiation by secreting IL6 and histamine. Th17 cells promote germinal center formation and support autoantibody production. Through IL-4, Thymic stromal lymphopoietin (TSLP), IL-25 and retinoic acid secretion, together with MHC class II and CD40 surface expression, basophils induce Th2 differentiation of CD4+ T cells. Once primed by basophils, Th2 cells secrete large amounts of IL-4 to support their own generation. This IL-4, together with IL-5, IL-6, IL-10, IL-13 and cell-cell interactions drive autoantibody production by the B cell compartment.

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Table 1

Basophil Receptors and their dysregulated ligands in SLE

Molecule dysregulated in Human SLE	Basophil- expressed receptor involved	Effect on basophils	References for SLE	References for the effects on basophils
CCL2 (MCP-1)	CCR1 and/or CCR2	Marginal IL-4 and LTC4 secretion, Histamine release, migration	[53]	[54–58]
CCL3 (MIP-1α)	CCR1 and/or CCR5	Migration	[53,59,60]	[54,55,57]
CCL5 (RANTES)	CCR3 (CCR1 and CCR5)	Migration	[59,60]	[55,56,58]
CCL7 (MCP-3)	CCR1, CCR2, CCR3, CCR5	Migration to SLO	[53]	[18]
CCL8 (MCP-2)	CCR1, CCR2, CCR3, CCR5	Migration	[53]	[55]
CCL17 (TARC)	CCR4	Skin recruitment	[53]	[61]
CCL19 (MIP-3β)	CCR7	Migration	[53]	[62]
CCL21 (6Ckine)	CCR7	Migration	[53]	[62]
CXCL1 (Gro-α)	CXCR2	Activation and Migration	[59]	[57,63]
CXCL2 (Gro-β)	CXCR2	Activation and Migration	[59]	[57,63]
CXCL8 (IL-8)	CXCR1, CXCR2	Histamine release and migration	[53]	[57]
CXCL12 (SDF-1α)	CXCR4	Migration	[64]	[56,57]
IL-18	IL-18R	IL-4 and IL-13 secretion	[53,59]	[65]
IL-33	T1/ST2	IL-4, -8, -13 and LTC4 secretion, priming and adherence	[66,67]	[65,68,69]
Leptin	Leptin receptor	Survival, migration, degranulation, IL-4 and IL-13 secretion	[70]	[71]
VEGF	VEGFR2	Migration	[72]	[73]
PGD2	CRTH2	Priming, activation and migration	[74]	[75,76]
PGD2	DP1	Inhibition	[74]	[75,76]
Low molecular weight Hyaluronan	TLR-2	Priming, IL-4 and IL-13 secretion	[77]	[49,78]

CCL: CC chemokine

CCR: CC chemokine receptor

CXCL: CXC chemokine

CXCR: CXC chemokine receptor

CRTH2: Chemoattractant receptor homologous molecule expressed on T helper type 2 cells, Prostaglandin D2 receptor 2, DP2

DP1: Prostaglandin D2 receptor 1

LTC4: leukotriene C4

MCP: Monocyte chemotactic protein

MIP: Macrophage inflammatory protein

PGD2: Prostaglandin D2

RANTES: Regulated on Activation, Normal T cell Expressed and Secreted

SDF: Stromal cell-derived factor

TARC: Thymus and activation regulated chemokine

TLR: *Toll*-like receptor

T1/ST2: IL-33 receptor

VEGF: Vascular endothelial growth factor

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