Editorial: Btk—friend or foe in autoimmune diseases?

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B cells are critical players in the development of a broad range of autoimmune diseases, including systemic lupus erythematosus, type I diabetes, rheumatoid arthritis, and multiple sclerosis. In addition to the secretion of autoantibodies, B cells can potentiate autoimmunity by several additional means, such as their function as APCs and the secretion of proinflammatory cytokines. Also, the successful use of B cell-depletion therapies for the treatment of autoimmune disorders has supported the fundamental role of B cells in the development and sustaining of autoimmunity. All of these factors lead to a growing interest in understanding how autoreactive B cells develop and how their activation is controlled in health and disease. In the current issue of the Journal of Leukocyte Biology, Nündel and colleagues [1] provide new insight into these questions by exploring the role of Btk signaling in autoreactive B cell development and activation in response to nucleic acid-associated autoantigens.

Systemic autoimmune diseases are frequently associated with the production of autoantibodies that recognize nuclear or cytosolic cellular components. Cellular debris derived from dying cells is likely to induce activation of autoreactive B cells and subsequent production of autoantibodies. In this context, the activation of autoreactive B cells that express low-affinity receptors for nucleic acids (or nucleic acid-associated autoantigens) is prompted by signals that originate from the engagement of TLRs with nucleic acids [2]. Hence, in addition to BCR stimulation, the binding of RNA- or DNA-containing antigen to the BCR leads to receptor internalization and delivery of antigen to intracellular compartments containing TLR7 and TLR9. As a model system to understand development and activation of these autoreactive B cells, Nündel and colleagues [1] take advantage of mice expressing a prototypic RF BCR, encoded by heavy and light-chain, site-directed transgenes (AM14 mice). These mice possess a highly homogeneous B cell pool, in which essentially all B cells express the same BCR. RF B cells have a low-affinity receptor and proliferate in response to IgG2a immune complexes that incorporate DNA or RNA. Therefore, AM14 mice allow evaluation of the effect of individual signaling molecules in the homeostasis, differentiation, and activation of autoreactive B cells, irrespectively of BCR specificity.

Among the many molecules involved in BCR signaling, Btk is known to be essential for B cell activation and differentiation in both mouse and humans. As such, mutations in Btk result in XLA in humans and xid in mice. Importantly, xid mice, Btk-deficient mice, and XLA patients show a reduction in mature peripheral B cells [3]. In general, mutations in components of the BCR-Btk pathway result in a loss of follicular B cells and comparative preservation of MZ B cells. Accordingly, Nündel and colleagues [1] show that whereas Btk-sufficient RF B cells develop into a homogeneous follicular B cell population, Btk deficiency leads to an increased proportion of RF B cells with a MZ phenotype. Therefore, the loss in signal strength derived from Btk deficiency favors differentiation of the MZ compartment. Interestingly, AM14-xid mice show a marked increase in the number of MZ precursors relative to the number of MZ B cells, suggesting that Btk could be required for survival of MZ RF B cells. Nevertheless, it is worth mentioning that some clones of transgenic B cells that recognize self-antigens have shown a requirement for Btk for differentiation to MZ B cells [4–6]. Consequently, although MZ B cells seem to be able to differentiate in the absence of Btk, it is possible that some clones (maybe with very low BCR affinity) might need Btk signaling to enter and/or survive in the MZ B cell pool. In addition to the altered splenic B cell populations, xid and Btk-deficient mice show a severe drop in the numbers of CD5 B1 peritoneal B cells and remarkably low levels of circulating IgM and IgG3 [3]. Interestingly, Btk-sufficient AM14 mice lack CD5 B1 peritoneal B cells and display low levels of serum IgM compared with WT counterparts. Depletion of Btk in AM14 mice induces a further drop in IgM, suggesting that Btk could affect circulating IgM levels separately from the contribution of B1 cells.
xid mice and Btk-deficient mice fail to respond to immunization with type 2 thymus-independent antigens, and accordingly, peripheral B cells from these animals are unresponsive to BCR crosslinking [3]. The same holds true for RF7 Btk-deficient B cells that remain unresponsive to anti-IgM(F(ab)2) stimulation in vitro. However, stimulation of B cells from AM14-xid mice with nucleic acid-containing IgG2a-immune complexes resulted in several rounds of B cell proliferation (Fig. 1). In line with this, Btk-deficient B cells from mice carrying the 56R anti-DNA Ig transgene have been shown to be able to proliferate in response to CpG-containing DNA fragments [4]. In summary, these data indicate that coengagement of the BCR and TLR can bypass the need of Btk for B cell proliferation, suggesting a Btk-independent mechanism for activation of autoreactive B cells. In this regard, it would be interesting to address whether other parameters, resulting from autoreactive B cell activation (i.e., cytokine secretion, antigen presentation capacity), are affected by Btk expression and how this may condition the development of autoimmune pathologies.

The precise role of Btk in autoimmune processes is difficult to decipher, as Btk takes part in myriad signaling pathways, and it has a broad cellular expression within the hematopoietic compartment. Nonetheless, several lines of evidence suggest that regulation of Btk levels and/or function can affect the development of autoimmunity. For instance, when autoimmune-prone MLR mice are crossed with xid animals, the resulting offspring show delayed disease development, although the xid gene does not prevent the autoimmune phenotype completely [7]. In line with this, administration of Btk inhibitors reduces the levels of autoantibodies and the development of kidney disease in MLR mice [8]. It is worth mentioning that in those settings, Btk function is abolished in the different APCs, and the precise contribution of Btk, specifically on B cells, to the development of autoimmunity is difficult to interpret. Notably, a transgenic mouse model that targets overexpression of Btk to B cells has been reported recently [9]. These animals display spontaneous B cell activation, secretion of antinuclear antibodies, and development of a lupus-like autoim-

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**Figure 1. Effect of Btk expression in autoreactive B cell activation.** WT B cells proliferate in response to anti-IgM stimulation in vitro, whereas Btk-deficient B cells remain unresponsive to such stimulation. However, both Btk-sufficient and -deficient B cells proliferate in response to nucleic acid-containing autoantigen, although Btk-deficient cells show a less-robust response than their WT counterparts.
immune pathology, implying a direct role for Btk in setting the threshold for autoreactive B cell activation and/or differentiation. Additionally, it should be borne in mind that on top of its role in BCR signaling, Btk becomes activated by a broad range of receptors, and it has been proposed to participate in many different processes, including cytokine signaling, TLR signaling, and integrin-mediated adhesion. In this line, Btk-deficient cells show decreased IL-10 production following stimulation with multiple TLR ligands, suggesting a potential regulatory role for Btk [10]. Further studies will help in the understanding of the requirement for Btk function in specific signaling pathways (within different cell types) and their precise contribution to the development of autoimmunity.

Finally, an interesting remark of the present manuscript is the observation that activation of autoreactive B cells in response to BCR/TLR7 and BCR/TLR9 results in different degrees of B cell proliferation and survival. These data point to disparities in the signaling cascades and/or regulatory mechanism underlying coengagement of BCR and TLR7/TLR9. Although the molecular mechanisms that explain these differences will require further investigation, these results are in line with the contrasting roles that have been suggested for TLR7 and TLR9 in the development of autoimmunity [11]. Indeed, whereas both receptors are located in endosomal compartments and signal through MyD88, they seem to convey opposite effects in murine models of autoimmunity, with TLR7 playing a pathogenic and TLR9 a protective role. Although the data provided by Nündel et al. [1] provide insight into this issue, a more complex picture could be happening in vivo. Many different cell types express TLRs, can respond to nucleic acid-containing immune complexes, and affect the production of autoantibodies. Further research is needed to decipher the complex cellular interactions involved in the activation of autoreactive B cells and to understand the outcome of such processes. Finally, it is important to keep in mind that mouse and human B cells show differences in the expression and function of several TLRs, and the phenotype of xid mice is milder than that of XLA patients. Therefore, in the future, it will be central to address how the findings presented by Nündel et al. [1] can be translated to human autoimmune pathologies.

REFERENCES

KEY WORDS: systemic lupus erythematosus · Toll-like receptor · X-linked immunodeficiency
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