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Role of type I interferons in the activation of autoreactive B cells

Kerstin Kiefer¹, Michael A Oropallo², Michael P Cancro², and Ann Marshak-Rothstein¹

¹Department of Medicine, University of Massachusetts School of Medicine, Worcester, MA, USA

²Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Abstract

Type I interferons (IFNs) are a family of cytokines involved in the defense against viral infections that play a key role in the activation of both the innate and adaptive immune system. IFNs both directly and indirectly enhance the capacity of B lymphocytes to respond to viral challenge and produce cytotoxic and neutralizing antibodies. However, prolonged type I IFN exposure is not always beneficial to the host. If not regulated properly IFN can drive autoantibody production as well as other parameters of systemic autoimmune disease. Type I IFNs impact B-cell function through a variety of mechanisms, including effects on receptor engagement, Toll-like receptor expression, cell migration, antigen presentation, cytokine responsiveness, cytokine production, survival, differentiation and class-switch recombination. Type I IFNs are also cytotoxic for a variety of cell types and thereby contribute to the accumulation of cell debris that serves as a potential source for autoantigens. Type I IFN engagement of a variety of accessory cells further promotes B-cell survival and activation, as exemplified by the capacity of type I IFNs to increase the level of B-cell survival factors, such as B lymphocyte stimulator, produced by dendritic cells. Therefore, it is not surprising that the loss of expression of the type I IFN receptor can have dramatic effects on the production of autoantibodies and on the clinical features of systemic autoimmune diseases such as systemic lupus erythematosus.

Keywords

type I IFN; B cell; autoimmunity; SLE

TYPE I IFN PROMOTES B-CELL RESPONSES TO VIRAL INFECTION

The type I interferons (IFNs) are immunoregulatory cytokines that play a pivotal role in viral immunity. Initially identified several decades ago for their capacity to interfere with viral replication, it is now clear that IFN- α and IFN- β have pleiotropic effects on the modulation of both innate and adaptive immune responses. Soon after viral infection, the type I IFNs induce dendritic cell (DC) and macrophage maturation and activation,¹ and then at later stages, promote T- and B-cell survival, activation and differentiation.^{2–4} Analysis of B cells from mice that lack the type I IFN receptor (IFN α R) has shown that type I IFNs induce the expression of activation antigens involved in lymphocyte migration (CD69), co-stimulation (CD86) and cytokine responses (CD25, heparan sulfate).⁵ Recent studies have also documented direct B-cell induction of the same activation antigens in the context of a viral infection.^{6,7} Moreover, following viral infection of mixed (wild-type and IFN α R-

deficient) bone marrow chimeras, type I IFNs directly induce IFN α -sufficient B cells to undergo isotype switching to IgG2c and differentiate into antibody-producing cells.⁸

SYSTEMIC AUTOIMMUNITY MIMICS VIRAL INFECTION

Systemic autoimmune diseases such as systemic lupus erythematosus (SLE) can be characterized as pathologic, over-exuberant, anti-viral responses that target self-components instead of virally infected cells. Consistent with the ‘viral phenotype’, SLE is often characterized by the increased production of type I IFNs, as indicated by: (1) detection of IFN- α directly in sera from a limited number of SLE patients;^{9,10} (2) induction of IFN-inducible genes in WISH reporter cells by at least 30% of SLE patient sera;¹¹ and (3) expression of a type I IFN-dependent signature in 40–75% of SLE patient peripheral blood mononuclear cells.^{12–14} In most cases, this IFN signature is associated with more severe clinical disease, as well as higher titers of autoantibodies, especially those reactive with RNA binding proteins.^{11,14} The correlation between IFN signature and autoantibody titers most likely reflects both direct and indirect effects of type I IFNs on B-cell survival and function. In both viral infection and SLE, type I IFN production is triggered by nucleic acid activation of pattern recognition receptors. The endosomal/lysosomal Toll-like receptors (TLRs), TLR7(8) for RNA and TLR9 for DNA, are most relevant for B-cell and plasmacytoid DC activation in SLE, and also contribute to immune activation in patients afflicted with Sjögren’s syndrome and dermatomyositis.¹⁵ Recent studies have also implicated members of the IFN-inducible *PYHIN* gene family. For example, the cytosolic receptors, Aim2 and IFI16, can detect microbial DNA and may contribute to autoantibody production and renal disease in SLE.^{16–18}

Although it is relatively straightforward to envision how viral DNA gains access to the appropriate TLR7/9 compartments, or even the cytosol, the mechanisms responsible for the targeting of self-constituents to nucleic acid receptors are less clear. In the case of B cells, the B-cell receptor (BCR) plays an indispensable role. B cells bind DNA, RNA or autoantigens associated with DNA or RNA through their BCR, and the BCR then transports these ‘autoadjuvants’ to the appropriate TLR-associated compartment.^{19,20} This BCR/TLR activation pathway then triggers the production of autoantibody specificities commonly associated with SLE. Uptake of similar autoantigens, or autoantigen-associated immune complexes (ICs), by DCs or other antigen-presenting cells, is facilitated by Fc γ Rs^{21,22} or anti-microbial peptides such as LL37.²³ The subsequent engagement of TLR9 and TLR7 can then drive the abundant production of pro-inflammatory cytokines and type I IFNs. Plasmacytoid DCs are considered the major source of IFN- α in both viral infections and SLE,²⁴ but other cell types also contribute to the IFN profile of this disease.

However, SLE is a multifaceted heterogeneous disease and many genes are regulated by type I IFNs. In the following review, we will briefly summarize the clinical and genetic data linking type I IFNs to SLE. We will then go on to discuss both extrinsic and intrinsic mechanisms that can promote the type I IFN-driven activation, differentiation and function of autoreactive B cells.

THERAPEUTIC AND GENETIC ASSOCIATIONS BETWEEN TYPE I IFNs, SLE AND AUTOANTIBODY PRODUCTION

Type I IFN therapy can promote autoantibody production

The connection between type I IFN and the activation of autoreactive B cells was initially revealed by the analysis of patients undergoing IFN- α therapy for hepatitis C infection or various malignancies.²⁵ These patients often developed *de novo* autoantibodies or showed increased titers of pre-existing autoantibodies.²⁶ Depending on the study and patient group,

between 18 and 72% of the patients were reported to exhibit elevated anti-nuclear antibody titers.^{26–29} A somewhat lower frequency (4–19%) developed more outright symptoms of autoimmune disease, with SLE diagnosed in approximately 1%.^{26–28,30}

The human observations have been paralleled by investigations in mouse models. Early studies in experimental SLE showed that administration of exogenous type I IFNs accelerated disease progression and severity in NZB and NZB/W mice.^{31,32} More recently, *in vivo* delivery of IFN- α -producing viral vectors has been shown to drive sustained B-cell proliferation, short-lived plasma cell production and rapid germinal center (GC) formation.^{33,34} These findings strengthen the common view that type I IFNs play an important role in the clinical manifestations of SLE and influence the selection, survival, activation and differentiation of autoreactive B cells.

Genome-wide association studies link SLE risk factors to the activation of autoreactive B cells

Genome-wide association studies have identified several type I IFN-associated risk alleles. The strongest association is with gain-of-function mutations in IRF5.³⁵ IRF5 expression is relatively restricted to DCs and B cells, where it serves as a transcriptional activator of IFN- α and additional proinflammatory cytokines downstream of TLR7 and TLR9.³⁶ Ectopic expression of IRF5 promotes type I IFN expression in response to TLR7 ligands, making it an important mediator of the TLR7 response pathway.³⁷ IRF5-deficient mice have an impaired immune response to DNA and RNA viruses, and fibroblasts from these mice were resistant to apoptosis.³⁸ Not surprisingly, IRF5 risk alleles correlate with high IFN- α serum levels,³⁹ and specific IRF5 risk haplotypes are associated with patient subsets defined on the basis of autoantibody reactivities.³⁵

However, IRF5 has IFN-independent effects on B cells. IRF5^{-/-} B cells do not undergo isotype switching to IgG2a after CpG activation, and this process is not rescued by the addition of exogenous IFN- α .⁴⁰ Moreover, CpG-activated IRF5^{-/-} B cells produce lower levels of interleukin (IL)-6 compared with the control group, despite displaying normal proliferative responses.⁴¹ Importantly, IRF5 deficiency, or even heterozygosity, dramatically reduces autoantibody titers and clinical disease in autoimmune-prone mice, presumably through IFN-dependent and -independent pathways.⁴²

Additional SLE risk alleles have been associated with increased responsiveness to IFN- α . For example, Tyk2, a signaling molecule downstream of IFNAR-1, is important for proper signal transduction via the Jak-1/STAT1 pathway.⁴³ Mice deficient in Tyk2 showed decreased responses to type I IFN stimulation and are resistant to collagen-induced arthritis.^{44,45} STAT4 is a transcription factor also downstream of IFNAR, and a risk allele of STAT4 correlates with increased sensitivity to IFN- α .⁴⁶ Loss of function mutations in the cytosolic exonuclease Trex1, another SLE risk allele, result in excessive levels of IFN- β through a mechanism that most likely involves activation of a cytosolic DNA sensor by retroviral elements, or other sources of DNA, normally degraded by Trex1.⁴⁷ Trex1-deficient mice develop a myocarditis associated with the production of heart-specific autoantibodies, and autoantibody production is entirely type I IFN dependent.⁴⁸

Other polymorphisms, identified in murine SLE models, also link type I IFNs to lupus. For example, the NZB allele of the Nba2 locus encodes the IFN-inducible protein Ifi202, a member of the PYHIN (pyrin/HIN-200 domains) protein family of DNA sensors. Ifi202 expression in B cells and other non-T spleen cells is increased in mice expressing the Nba2 risk allele.⁴⁹ Ifi202 is a transcriptional regulator that, among other activities, renders cells resistant to p53-mediated apoptosis and suppresses expression of the Fc γ R2 inhibitory

receptor.⁵⁰ Intriguingly, expression levels of *Ifi202* are reduced in *IRF5*^{-/-} mice,⁵¹ but upregulated by IL-6 and estrogen.⁵²

IFNaR deficiency and murine models of SLE

To further explore the role of type I IFNs in SLE, the gene-targeted IFNaR-deficient haplotype has been backcrossed onto multiple murine models of SLE (Table 1). Considering the pleiotropic effects of IFN- α , and the many potential immunoregulatory defects contributing to the loss of tolerance and ensuing clinical features of SLE, it is not surprising that IFNaR deficiency resulted in discordant outcomes in the various models. Of all the murine models analyzed to date, mice injected with 2,6,10,14-tetramethylpentadecane, commonly known as pristane, have the strongest IFN signature. At 4–8 months after pristane injection (depending on strain), these mice develop SLE-like symptoms, including renal disease, through a mechanism that is highly TLR7-dependent.⁵³ Clinical disease was associated with elevated IFN- β levels in the peritoneal lavage, increased expression of IFN-stimulated genes (ISG) like *Mx1*, *IP-10* and *IRF7*, as well as anti-double-stranded DNA antibodies and/or high titers of autoantibodies against the common SLE-associated RNA binding proteins.^{54,55} Therefore, as might be predicted, pristane-injected IFNaR-deficient mice had a markedly improved disease profile. Despite elevated IgG titers and IC deposition in the kidneys, there was a complete loss of double-stranded DNA and RNA binding protein autoantibodies, and markedly improved proteinuria.⁵⁵

NZB mice develop an autoimmune hemolytic anemia associated with red blood cells and double-stranded DNA autoantibody production, as well as IC deposition in the kidneys. B-cell activation, autoantibody titers and IC deposition were all greatly decreased in NZB IFNaR-deficient mice.⁵⁶ NZB $\times$ NZW (BW F1) mice, and various recombinant inbred strains derived from this cross, have proven to be more useful spontaneous models of human SLE. For example, NZM2328 mice develop anti-nuclear antibodies, chronic glomerulonephritis and have a female sex bias.⁵⁷ Extensive backcrossing of IFNaR deficiency to NZM2328 dramatically reduced autoantibody titers, proteinuria and early mortality.⁵⁸

IFNaR deficiency has been further analyzed in the BW F1-related strains B6.Nba and in B6.Nba $\times$ NZW BC mice. As mentioned above, the NZB-derived Nba2 interval includes members of the IFN-inducible PYHIN protein family, and therefore would be predicted to be an IFN-driven disease model. Nba2 (B6.Nba2) retained most of the pathogenicity of the BW F1 strain with similar autoantibody titers and extent of renal disease.^{49,59} Although autoantibody titers appear to have been only modestly reduced in B6.Nba2 IFNaR-deficient mice, and IC deposition was essentially unchanged, the B6.Nba.2 $\times$ NZW mice had markedly improved proteinuria.⁵⁹ Whether the discrepancy reflects the impact of local type I IFN production⁶⁰ or a switch in autoantibody isotype remains to be determined.

By contrast, IFNaR deficiency had only a very modest effect in B6 Fc γ RII^{-/-} Yaa mice. These mice lack both the inhibitory Fc γ R and have an extra copy of TLR7. IFNaR deficiency did not result in either lower serum IgG or lower autoantibody titers.⁴² The only change detected in renal pathology was a decrease in the number of glomerular crescents and a slight improvement in survival.⁴² As described elsewhere in this review, effects of type I IFN and IFN-inducible genes include increased expression of TLR7 and decreased expression Fc γ RII. Thus, the lost requirement for type I IFN in this model may reflect the pre-existing 'IFN-like' properties in the B6 Fc γ RII^{-/-} Yaa model.

Perhaps more surprisingly, type I IFNs appear to protect autoimmune-prone Fas-deficient and -sufficient MRL mice. In these strains, IFNaR deficiency conferred more high-titered autoantibody levels and more severe renal disease.⁶¹ Moreover, injection of IFN- β into MRL/lpr mice exhibiting early kidney disease significantly decreased kidney pathology

compared with the control group.⁶² However, in the closely related B6-lpr model, IFN α R deficiency led to a decrease in B-cell activation and therefore lower numbers of autoantibody-secreting cells, and a less severe disease phenotype.⁶³ Exactly how the MRL background negates the effects of type I IFNs warrants further investigation; however, the activity of type I IFNs may be superseded by increased expression of IFN γ , as a loss of the IFN γ receptor, IFN-RII, partially protected MRL/lpr mice from end-organ disease.⁶¹ Nevertheless, overall, the general impact of IFN α R deficiency is reduced B-cell activation and autoantibody production, reduced renal disease and improved survival.

EXTRINSIC EFFECTS OF TYPE I IFN ON B CELLS

IFN-induced B lymphocyte stimulator expression promotes B-cell survival

Mature B cells rely on the cytokines B lymphocyte stimulator (BLyS, also known as BAFF) and A proliferation-inducing ligand (APRIL) for their survival in the periphery. These two cytokines bind with varying affinity to the three known BLyS receptors: BLyS receptor 3, trans-membrane activator and cyclophilin ligand interactor, and B-cell maturation antigen. Several groups reported that the availability of BLyS in the periphery is a major limiting factor for B-cell survival and selection,^{64–66} and an anti-BLyS monoclonal antibody has recently been found effective for the treatment of SLE.⁶⁷ BLyS also plays a key role in the appropriate establishment of the mature B-cell repertoire through its effects on transitional B-cell selection. Autoreactive B cells that survive negative selection in the bone marrow move into the transitional B-cell compartments of the spleen. These cells are still subject to deletion upon encounter of self-antigens; however, this BCR-mediated negative selection step is less stringent than bone marrow selection, and relies in part on competition between B-cell clones for essential growth factors.⁶⁸ Autoreactive cells require higher levels of BLyS for survival than their non-autoreactive counterparts, and under physiologically normal selection conditions, autoreactive cells are at a competitive disadvantage and fail to move into the mature B-cell pool. However, elevated levels of BLyS can rescue autoreactive B cells that would otherwise be subject to deletion at the transitional stage.^{64–66} Elevated BLyS levels have also been associated with enhanced GC formation.⁶⁹ Predictably, mice prone to develop SLE-like disease have elevated levels of serum BLyS.⁷⁰ Elevated BLyS levels have also been found in cohorts of patients suffering from systemic autoimmune diseases, including rheumatoid arthritis, Sjögren's syndrome and SLE.^{71–74} Moreover, the constitutively elevated titers of BLyS present in BLyS transgenic mice cause an SLE-like autoimmune disease associated with increased anti-nuclear antibody titers, IC formation and kidney pathology.^{69,75,76}

Importantly, clinical and experimental studies have shown that type I IFNs, produced during the course of viral infections, induce DCs and macrophages to produce BLyS and APRIL, allowing for increased survival of anti-viral B cells.⁷⁷ In the context of autoimmune disease, similar increases in BLyS and APRIL production most likely promote the survival of autoreactive B cells. Furthermore, type I IFN-induced BLyS can promote isotype switching to IgG and IgA.³ Therefore, it is tempting to speculate that the elevated type I IFN levels observed in SLE may directly induce DCs and macrophages to produce excess amounts of BLyS. Consistent with this suggestion, exogenously delivered IFN- β increased BLyS levels dramatically in mouse models of multiple sclerosis. Moreover, this increase was dependent on the type I IFN system, as mice deficient in IFN α R had no increase in BLyS serum levels.^{78,79}

Apoptosis/availability of debris

The majority of autoantigens targeted by autoantibodies in SLE and other systemic diseases are intracellular components presumably made available to the immune system through cell

death. In fact, numerous defects in molecules involved in the clearance of apoptotic debris can result in anti-nuclear antibody production and clinical features of SLE.⁸⁰ The induction of cell death by type I IFN is well established and likely contributes to the efficacy of IFN therapy in the treatment of certain cancers. Potential mechanisms include cell cycle arrest, induction of pro-apoptotic molecules such as TRAIL, Fas and caspase 8, or activation of cytotoxic effector cells (reviewed in Chawla-Sarkar *et al.*⁸¹). Failure to appropriately remove cell debris results in prolonged availability of potential autoantigens that can both stimulate B cells directly and also be taken up by other kinds of antigen-presenting cells. These APCs in turn can activate cytotoxic as well as helper T-cell populations that either produce more cell debris or promote B-cell differentiation. In fact, IFN-primed DCs have been found to be particularly efficient activators of potent CD8 killer cells.⁸² Moreover, *in vitro* treatment of peripheral blood mononuclear cells with IFN- α induced the differentiation of DCs capable of capturing and presenting antigens from apoptotic cells.⁸³

DIRECT EFFECTS OF TYPE I IFN ON B CELLS

TLR7 expression

Type I IFNs markedly enhance B-cell responses to TLR7 ligands, and TLR7 expression in naïve B cells is highly dependent on prior type I IFN exposure. B cells inherently express very low levels of TLR7, but this level increases almost fivefold following a 4 h incubation with IFN- α .⁸⁴ Basal levels of TLR7 are even two- to threefold lower in IFN α -deficient B cells compared with IFN α -sufficient B cells. As a result, IFN α -deficient B cells proliferate very poorly in response to small-molecule TLR7 ligands such as R848 or CL097, despite essentially normal proliferative responses to TLR2, TLR4 and TLR9 ligands. Moreover, even IFN α -sufficient B cells require low levels of type I IFN (either provided from an exogenous source or by the B cells themselves) for an optimal response to TLR7 ligands.⁸⁴ A similar requirement for type I IFN has been reported for human B-cell responses to TLR7 ligands.⁸⁵ Type I IFN also enhances the response to endogenous, and therefore more physiologically relevant, TLR7 ligands and promotes responses to RNA-associated autoantigens. B cells expressing a transgene-encoded BCR AM14, essentially a rheumatoid factor specific for IgG2a, can be activated by ICs that incorporate RNA through a mechanism dependent on TLR7. These RNA IC responses are also greatly increased by the addition of type I IFNs.¹⁹

BCR signaling threshold

Studies using F(ab')₂ anti-IgM as a BCR crosslinking agent indicate that type I IFNs lower the BCR signaling threshold. B cells previously treated with type I IFN exhibit a stronger Ca²⁺ flux and proliferate more extensively following anti-IgM stimulation.^{5,19,86} Similar effects were observed following DNA IC activation of AM14 BCR Tg cells, described above. AM14 B cells normally proliferate robustly when stimulated with IC that incorporate CpG-rich, but not CpG-poor, mammalian DNA. However, prior treatment with IFN- α enhanced the response to CpG-rich ICs and also promoted responses to CpG-poor DNA ICs; both responses remained TLR9-dependent.^{19,86} In contrast to TLR7, IFN- α had minimal effects on the level of TLR9 expression, and therefore these data are consistent with the premise that a reduced BCR signaling threshold enhances BCR/TLR9-dependent responses to autoantigens that incorporate suboptimal TLR9 ligands. Although the shift in BCR signaling threshold may contribute to the adjuvant effects of type I IFNs,⁸⁷ such decreased signaling threshold could lead to activation of otherwise autoantigen-refractory B cells. Presumably, type I IFN partially activates components of the BCR signaling cascade, but the exact mechanism(s) warrants further investigation.

Cell surface molecules that promote antigen presentation

Type I IFN can also induce the upregulation of a number of cell surface molecules that influence B-cell function and survival. These include CD69, CD86 and MHC class II molecules.⁵ CD69 can form a complex with SIP¹ and negatively regulate its activity, leading to the retention of circulating B cells in lymphoid tissues.⁸⁸ CD86 is a coreceptor that enhances B-cell interactions with T cells. Type I IFN also leads to accelerated BCR internalization.⁵ Taken together with increased self-peptide expression (due to increased levels of MHC class II), these molecules could promote the capacity of autoreactive B cells to present self-peptides to T cells and thereby receive T-cell help and drive GC formation.

Survival and differentiation

Type I IFNs have been reported to directly improve B-cell survival *in vitro*⁵ and to reduce sensitivity to FasL-mediated apoptosis through a mechanism involving phosphorylation of AKT and the upregulation of the prosurvival molecules Bcl-2 and Bcl-x_L.⁸⁹

Type I IFN exposure also affects the B-cell response to IL-6, a cytokine involved both in B-cell survival and differentiation. In a series of elegant co-culture experiments involving human plasmacytoid DCs and peripheral blood B cells, type I IFN was shown to drive CD40Lprimed B cells to differentiate into non-Ig-secreting plasmablasts. IL-6 could then drive these plasmablasts to become actively antibodysecreting plasma cells.² The mechanism responsible for IFN/IL-6 synergy was subsequently explored using mouse embryo fibroblasts. Here, type I IFNs were shown to promote crosstalk between the IFN α R and the gp130 subunit of the IL-6 receptor. IL-6 induced the phosphorylation of STAT1 and STAT3, and type I IFNs induced phosphorylation of IFN α R-1. P-IFN α R then provided a docking site for the P-STATs, thereby promoting dimerization and full-scale activation.⁹⁰ Taken as a whole, in the context of SLE, type I IFN/IL-6 activation of B cells could play a major role in the differentiation and survival of autoantibody-producing plasma cells.

Subsequent studies, involving human peripheral blood B cells stimulated with TLR7/8 ligands, further showed that plasmacytoid DC-produced type I IFN promoted the extended proliferation of both naïve and memory B cells. In addition, IFN- α has been reported to upregulate the transcription factors BLIMP and XBP in memory B cells, and thereby promote class-switched antibody production.⁹¹ Importantly, the presence of type I IFN during the GC reaction seems to favor class-switch recombination to IgG2a, the isotype mainly associated with immunopathology in SLE.^{8,92}

The transcription factor T-bet plays an important role in class-switch recombination in B cells and is known to promote IgG2a production.^{93,94} Not unexpectedly, type I IFN treatment of human blood B cells was shown to upregulate T-bet.^{95–97} T-bet-deficient B cells are impaired in class-switch recombination to IgG2a, IgG2b and IgG3. Loss of T-bet in autoimmune Fas^{lpr/lpr} mice leads to decreased autoantibody production and less severe IC-mediated renal disease.⁹³

Type I IFNs also induce naïve B cells to express heparin sulfate on the cell surface. Heparin sulfate is a glycoaminoglycan that is known to bind a variety of cytokines including IL-6. Moreover, heparin sulfate is essential for the B-cell response to APRIL; as mentioned above, APRIL is a cytokine involved in B-cell survival and also class-switch recombination.⁹⁸

Trafficking of B cells to GCs

In order for B cells to respond effectively to antigen *in vivo*, they need to accumulate in a supportive microenvironment. Early studies of B-cell trafficking showed that IFN- α is required to upregulate the homing receptor L-selectin (CD62L). CD62L recognizes

GlyCam-1 on high endothelial venules and is necessary for B and T cells to egress from the blood to secondary lymphoid organs like the spleen or lymph nodes. Culturing human B cells and B-cell lines in the presence of IFN- α increased the expression of CD62L on the cell surface.⁹⁹

The splenic marginal zone (MZ) contains specialized B cells, which are the first defense against blood-borne antigens. Several studies have shown that MZ B cells mainly form IgM-producing short-lived plasma cells.¹⁰⁰ It is now clear that many B cells in the MZ are self-reactive and produce antibodies critical for clearance of cell debris.¹⁰⁰ Sequestration of these autoreactive cells in the MZ prevents their subsequent involvement in GC responses and avoids the potential generation of high-affinity IgG autoantibodies. Interestingly, recent studies have shown that during an immune response, type I IFN-producing DCs traffic to the marginal sinus and activate MZ B cells to downregulate S1P₁. This allows the MZ B cells to carry antigens to the GCs for the proper activation of follicular (FO) B cells and T cells.¹⁰¹ Deregulation of this system by the excessive levels of type I IFN associated with SLE could cause prolonged shuttling of self-antigen bearing MZ B cells to the GCs. This may explain the formation of spontaneous GCs characteristic of autoimmune diseases.

Cytokine production by B cells

Although the pathogenicity of autoreactive B cells is normally associated with autoantibody production, B cells can also secrete relatively high levels of cytokines, which in turn regulate T-cell responses.¹⁰² Depending on the context of their initial activation, B cells can differentiate into discrete subsets designated Be1 and Be2.^{92,93} Be1 cells produce IFN- γ and IL-12 and therefore promote Th1-dependent inflammatory processes. Importantly, IFN- α promotes the development of Be1 cells from naïve human B cells. B cells treated with IFN- α activated STAT4 and, as mentioned above, upregulated the transcription factor T-bet. Combined effects of P-STAT4 and T-bet result in IFN- γ production. Activation of B cells with *Staphylococcus aureus* in combination with IFN- α lead to a 10-fold increase in IFN- γ -producing B cells over IFN- α treatment alone.⁹⁵ Activation of AM14 B cells by stimulatory ICs also induced T-bet transcription through a TLR9- dependent mechanism, but IFN- γ production was not examined in that study.⁸⁶

CONCLUSION/OUTLOOK

Clinical trials are proving B cells to be an essential component in the development of autoimmune diseases ranging from SLE to multiple sclerosis.^{103–105} Abundant clinical and experimental studies point to the various aspects of B-cell function regulated by type I IFNs. B-cell antigen presentation is essential for GC formation. B-cell cytokine production promotes inflammation, and B-cell-derived autoantibodies can deposit in kidneys, vessels and joints, resulting in tissue injury. All these activities can be enhanced by type I IFNs. However, factors other than type I IFNs activate B cells, and type I IFNs impact a wide range of cell types beyond B cells. Ongoing clinical trials will be needed to determine the efficacy and specific effects of type I IFN-targeted therapies for the spectrum of clinical symptoms that contribute to systemic autoimmunity.⁶⁰

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Table 1

Effect of loss of the type I IFN pathway on disease manifestation in experimental SLE models

IFNaR ^{-/-} strain	Serum IgG/IgG autoAbs	B-cell number/activated B cells	IC deposition/renal disease	Mortality	Reference
129/Sv TMPD	ND ↓chromatin ^a , RBP	ND	NS IC deposition ↓ proteinuria	ND	55
NZM 2328	ND	↓	ND	↓↓	58
>BC6	↓↓ chromatin	↓	↓↓proteinuria		
NZB	NS	↓↓	↓ IC deposition	↓	56
>BC6	↓↓ RBC, dsDNA	↓↓Elispot	ND		
B6 NBA/2 or	↓ ↓ chromatin	ND	NS IC deposition	ND	59
B6 NBA/2×NZW	ND	ND	NS IC deposition		59
BC3	↓ chromatin		↓ proteinuria		
B6×129Sv/lpr F3	↓ ND	↓ ↓	↓ IgG/C3 deposit ↓ nephritis	ND	63
B6 R2KO Yaa	NS NS	ND	NS ↓ glomerular crescents	↓	42
MRL/lpr	↑ IgG2b; NSIgG2a	ND	↑ IC deposition	↑	61
MRL/+	↑ dsDNA; RF		↑proteinuria		

Abbreviations: Abs, antibodies; dsDNA, double-stranded DNA; IC, immune complex; IFN, interferon; IFNaR, IFN receptor; IgG, immunoglobulin G; NS, no significant difference; ND, not determined; RBC, red blood cells; RBP, RNA binding proteins; RF, rheumatoid factor; SLE, systemic lupus erythematosus.

^aShift from nuclear to cytoplasmic strain.