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Christine M. Grimaldi; ... et. al

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BRIEF REVIEWS

B Cell Selection and Susceptibility to Autoimmunity

Christine M. Grimaldi, Ruthmarie Hicks,‡ and Betty Diamond[1] *†*

***Autoreactive B cells arise routinely as part of the naive B cell repertoire. The immune system employs several mechanisms in an attempt to silence these autoreactive cells before they achieve immunocompetence. The BCR plays a central role in B cell development, activation, survival, and apoptosis, and thus is a critical component of the regulation of both protective and autoreactive B cells. The strength of signal mediated by the BCR is determined by numerous factors, both B cell intrinsic and B cell extrinsic. Perturbations in the molecules that regulate the BCR signal strength or that activate pathways that engage in cross talk with the BCR-mediated signaling pathways can lead to the aberrant survival and activation of autoreactive B cells. In this review, we will discuss the some newly identified genetic loci and factors that modulate the BCR signal transduction pathway and, therefore, the regulation of autoreactive B cells. We will also provide evidence for a model of autoreactivity in which a reduction in the strength of the BCR signal allows the survival and the modulation of a naive B cell repertoire replete with autoreactivity. The Journal of Immunology,* 2005, 174: 1775–1781.**

The stochastic nature of Ig gene rearrangement gives rise to a diverse repertoire of as many as 10^{11} different specificities (1), thus, ensuring reactivity to a wide array of Ags. However, a major disadvantage of such great diversity is, of course, the potential to generate autoantibodies. Central to the regulation of these potentially pathogenic B cells is the BCR. Signal transduction events mediated by the BCR regulate B cell maturation and activation, as well as the elimination of self-reactive B cells. The outcome of BCR engagement is influenced by a composite of factors, which include valency and concentration of the Ag, the affinity of the BCR for Ag, and a cohort of coreceptors, intracellular enzymes, and adapter molecules, which modulate the signaling strength of the BCR.

In B cell-mediated autoimmune diseases, such as systemic lupus erythematosus (SLE),[1] there is emerging evidence that a complex array of genetic abnormalities contribute to aberrant negative selection and activation of autoreactive B cells. Some of the candidate genes associated with disease progression and pathogenesis encode molecules that are known to modulate the strength of the BCR signal (2). Genetically manipulated mice have provided an understanding of how changes in BCR signaling strength affect B cell fate. There are also nongenetic influences on BCR signaling strength. This has been demonstrated in the clinic by the alterations in B cell repertoire and the induction of autoantibodies caused by therapies that affect cytokine-mediated pathways in a subset of patients (3, 4). In this review, we will summarize the data that demonstrate how alterations in the molecules that regulate the strength of BCR signaling impact autoreactive B cells. In addition, we provide evidence for a link between sex hormones and B cell autoreactivity through the regulation of molecules that reduce the strength of BCR signaling or through the activation of pathways that synergize with the BCR signaling pathway.

BCR signaling

The BCR is comprised of surface Ig, which confers antigenic specificity, and the accessory molecules, Igα and Igβ, which initiate the intracellular signaling cascade. Cross-linking of the BCR triggers a complex series of molecular events that ultimately determine whether a B cell will undergo maturation, proliferation, or apoptosis. How the B cell interprets the BCR signal to accomplish these seemingly disparate outcomes is an area of intense investigation and is critical to the understanding how autoreactive B cells evade negative selection.

The strength of the BCR signal is determined by accessory molecules that either augment or attenuate the potency of signal. A detailed description of cell surface molecules, adapter proteins, and intracellular enzymes that modulate the strength of the BCR signal is beyond the scope of this review and is well described in recent review articles (5–7). A rather simplistic, but well-accepted model of BCR signaling is that a composite of both positive and negative regulators of the BCR is required for B cell homeostasis. Positive regulators include the transmembrane phosphatase CD45 (8) and the CD19/CD21 coreceptor complex (9). Negative regulators include CD22, CD72, paired Ig-like receptor B, FcRγIIb, and programmed death 1 (PD-1) (10, 11). As will be discussed in further detail, perturbations in the molecules that either positively or negatively regulate the

Departments of *Medicine and †Microbiology, Columbia University, New York, NY 10032; and ‡Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461

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[1] Address correspondence and reprint requests to Dr. Betty Diamond, Department of Medicine, Columbia University, 1130 St. Nicholas Avenue, Audobon III Building, 9th Floor, Room 924, New York, NY 10032. E-mail address: bd2137@columbia.edu

[2] Abbreviations used in this paper: SLE, systemic lupus erythematosus; PD-1, programmed death 1; T1, transitional type 1; BAFF, B cell-activating factor belonging to the TNF family; SHP-1, Src homology region 2 domain-containing phosphatase 1; E2, 17β-estradiol; Tg, transgenic.

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BCR can favor the inappropriate survival and activation of autoreactive B cells.

The role of Ag and the BCR

Ag also plays a role in the regulation of BCR signals. The relative abundance of Ag, valency of the antigenic epitopes, anatomical site of Ag encounter, the stage of the B cell at the time of Ag encounter, and the ability of Ag to activate the complement cascade all help establish the degree of BCR cross-linking. Extensive cross-linking of BCRs with polyvalent Ag transmits a stronger signal than does suboptimal cross-linking. Strong BCR signals can result in either activation and differentiation or apoptosis, depending on the context of the signaling event. This perhaps accounts for the induction of SLE in models with impaired clearance of apoptotic debris (12).

Weak interactions with Ag are believed to play a role in survival of B cells. This is well illustrated in mice in which B cell maturation is blocked at the pre-B cell stage in surface IgM-deficient mice (13) and at the immature B cell stage in Igβ-deficient mice (14). Although it has become generally accepted that these weak tonic BCR signals play a role in B cell repertoire selection and survival, controversy exists as to whether these signals are Ag dependent or Ag independent.

Role of the BCR in establishing the naive repertoire

Expression of surface IgM marks the first stage at which developing B cells express a functional BCR, and are, thus, subject to selection events mediated by the BCR. Selection at this stage is evident because there is substantial loss in B cell numbers (15), with a preferential loss of autoreactive cells (16). Immature B cells that survive the selection process in the bone marrow undergo several transitional stages of development before giving rise to mature B cell subsets. Immature B cells become transitional type 1 (T1) B cells before exiting the bone marrow (17). They home to the spleen where they localize to the periarteriolar lymphoid sheath (18). T1 B cells give rise to T2 B cells, and then, perhaps, to T3 B cells (19) before differentiation into the mature conventional B cell subsets. Similar to the immature B cell stage, there is a substantial loss of cells through the transitional B cell stages (19). This loss is believed to reflect BCR-mediated negative selection that shapes the mature B cell repertoire. As will be discussed, positive selection events mediated by the BCR may also influence development of the preimmune repertoire.

Determining the mature B cell phenotype

It is generally accepted that the conventional mature follicular and marginal zone B cell subsets derive from the transitional B cell pool. There is some evidence for a branch point at the late transitional stage toward prefollicular and premarginal zone B cells (20); however, the presence of such precursors requires further investigation. Studies in which the expression of specific molecules of the BCR signaling cascade is altered have clearly shown that the strength of the BCR signal helps determine the fate of B cell maturation (7). Manipulation of the BCR to produce very strong signals, as seen in CD22-deficient mice, favors the development of the nonconventional B1 B cell population (which arises through mechanisms distinct from the conventional B cell subsets) (21). A modest decrease in signaling strength, as observed in PKCβ-deficient mice, favors the development of follicular B cells (22). Finally, a strongly diminished BCR signal, which can be achieved by a deficiency in Btk (23), favors the development of marginal zone B cells. Thus, a general paradigm has emerged in which a strong BCR signal favors B1 B cells, a strong-to-intermediate signal favors follicular B cells, and a weak signal favors marginal zone B cells. However, there are some exceptions to this model. For example, mice deficient in the phosphatase and tensin homolog PTEN, which downregulates CD19-mediated activation of phosphoinositide 3-kinase, exhibit an expansion of both marginal zone and B1 B cells (24).

There is experimental evidence that the surface density of the BCR itself can skew the development of B cell subsets (25–27). Also, the specificity of the BCR may skew the development of mature subsets. For example, the B cells from transgenic mice that express an anti-phosphorylcholine Ab preferentially develop into marginal zone and B1 B cells (28, 29). However, it can be argued that the degree of BCR cross-linking, and not Ag specificity per se, is responsible for skewing of the naive repertoire to distinct B cell subsets (30).

However, it is important to recognize that BCR-mediated pathways are not the only ones to regulate B cell differentiation. For instance, non-BCR-related molecules such as Pyk-2 (31), Lsc (32), and Dock2 (33) are required for marginal zone B cell development.

The BCR and negative selection

Studies using mice transgenic for an autoreactive BCR have demonstrated that, in the presence of self-Ag, autoreactive B cells are barred from entry into the mature, immunocompetent B cell repertoire. This is accomplished by three distinct mechanisms of tolerance induction: receptor editing, deletion, or anergy induction. BCR engagement of immature B cells can result in the reactivation of the recombinase machinery to generate a new, presumably non-autoreactive, specificity (34, 35). B cells that successfully undergo receptor editing may be spared elimination (36). However, when the autoreactive specificity is not extinguished, immature B cells will be deleted from the repertoire by apoptosis (37–40). Autoreactive B cells with less extensive BCR cross-linking are rendered anergic (41, 42). These cells do not undergo rapid cell death, but are no longer responsive to BCR engagement. The precise mechanisms by which the BCR determines the mode of negative selection have yet to be clearly established.

It remains to be determined how BCR ligation can induce negative selection of immature B cells and also activation of mature B cells. Comparison of anti-IgM-treated immature and mature B cells in vitro has revealed no major differences in the molecules of the BCR signal transduction pathway. However, subtle differences, such as increased calcium immobilization, an increase in the breakdown of inositol 1,4,5-triphosphate, and enhanced phosphorylation of regulatory tyrosine residues (43, 44) have been reported and may be responsible for determining whether an apoptotic or activation program is initiated. In addition, the BCR of mature B cells enter into lipid rafts following Ag engagement, whereas the BCR of immature B cells is excluded (45, 46). Other differences between immature and mature B cells that may affect the outcome of BCR signaling include decreased levels of the negative regulator CD22 (47) and increased levels of the positive regulators B cell linker protein, Btk, and phospholipase Cγ (43) in immature B cells.

There are several reports demonstrating T1 B cells, similar to immature B cells, are sensitive in vitro to BCR-induced apoptosis, whereas T2 B cells are resistant (48, 49). Other studies suggest that both T1 and T2 B cells are sensitive to BCR-mediated apoptosis, but only T2 B cells can be rescued by T cell help (CD40 and IL-4) (50). The ability of T3 B cells to undergo BCR-mediated apoptosis remains to be determined. There is now increasing in vivo evidence that transitional B cells of the spleen are also the target of negative selection (50–52).

Not all autoreactive B cells are eliminated from the preimmune repertoire. Cells with minimal interaction with self-Ag are ignored either because of the low affinity of the BCR or the low concentration of accessible Ag at the immature and transitional B cell stages (53). These remain viable in the periphery. However, when activated, these low-affinity B cells can be converted to high-affinity B cells by the process of somatic mutation and affinity maturation. During a germinal center response, these newly arising high-affinity autoreactive B cells are subject to elimination. This has been demonstrated by their rescue by increased expression of endogenous or exogenous Bcl-2 (54, 55). It is not yet clear how their elimination occurs, although it can be postulated that it requires Ag engagement of the BCR in the absence of cognate T cell help (56–58). The Abs believed to mediate pathogenesis in lupus display somatic mutations and have undergone isotype class switching (59, 60). In autoimmune prone hosts, therefore, it would appear that the BCR-mediated selection events that block the emergence of autoreactive B cell at the germinal center stage are impaired. This defect in tolerance may occur concomitant with a defect in tolerance induction in the naive B cell repertoire, as in the autoimmune-prone NZB/NZW F_1 and MRL/*lpr* mice (61). Whether there can be a defect in germinal center selection without a defect in selection of immature cells is not known, because the mechanisms of germinal center selection are poorly understood.

The BCR and positive selection

It is generally accepted that positive selection events also shape the immunocompetent repertoire. As described above, the specificity of the BCR may influence B cell selection into the B1, marginal zone, and follicular compartments. In addition, constitutive signals mediated by the BCR are critical for maintenance of the mature B cell pool (62). It has been proposed that these weak signals are generated by BCR engagement with self-Ag. A skewing of the BCR repertoire between the preimmune and the mature populations has been reported. Studies by Gu et al. (63) demonstrated a preferential usage of a restricted set of J558 V_H genes in mature B cells, suggesting that ligand selection influences the makeup of the mature repertoire. In addition, Shlomchik, Janeway, and coworkers (64) demonstrated a skewing of the V_L repertoire between the transitional and mature B cell pools in H chain transgenic mice. It is important to note that some of the observed differences in the preimmune and mature repertoires may be the result of negative selection of high-affinity autoreactive BCRs. However, because these studies attempt to study development of a diverse repertoire with no apparent bias for autoreactive specificities, the presumption is that positive selection must also shape the mature repertoire.

Additional factors influence positive selection. The B cell-activating factor belonging to the TNF family (BAFF; also known as BlyS) influences the survival of transitional B cells and promotes their development into mature B cells (65, 66). It has been suggested that coligation of the innate immune receptor TLR9 and BCRs with microbial components influences the selection of certain specificities into the marginal zone B cell population (67). Thus, the BCR clonotype and the ability to compete for a limiting supply of self-Ag and survival factors are critical factors for final selection into the mature B cell pool. Although it is clear that defects in negative selection lead to the escape of deleterious specificities, the role of positive selection in the expansion and activation of autoreactive B cells has yet to be fully elucidated. However, in the case of BAFF, there is evidence that overexpression associates with loss of tolerance (68).

BCR signaling strength and predisposition to autoimmunity

Genetically engineered mice that are deficient in or overexpress molecules that modulate the strength of the BCR signal have provided information on the regulation of autoreactive B cells. In many of these mouse models, a partial SLE has been observed. Mice transgenic for the positive regulator CD19 exhibit an expansion and activation of autoreactive B cells, including those that secrete anti-DNA Abs (69). Similarly, loss of the negative regulators FcRγIIb (70) and PD-1 (71) result in a lupus-like phenotype characterized by the production of anti-DNA Abs and immune complex-mediated glomerulonephritis. Deficiency in CD22 (21, 72) or Src homology region 2 domain-containing phosphatase 1 (SHP-1) (73) has also been reported to result in the escape and activation of anti-DNA B cells. In CD19-overexpressing mice and CD22- and SHP-1-deficient mice, the source of IgM autoantibodies appears to be B1 B cells, and the Abs, presumably, have little to no somatic mutations. Thus, although alterations in the levels of key BCR regulatory molecules can result in impaired tolerance induction of autoreactive B cells, the aberrant expression of a single BCR accessory molecule is not sufficient to mimic the complex array of genetic defects that contribute to SLE.

It is interesting to note that several studies have demonstrated genetic alterations in the BCR signaling pathway in patients with SLE. Polymorphisms have been identified in the genes that encode *pd-1* (74), *fcrgIIb* (75), and *cd22* (76), which may associate with disease. Alterations in the levels of CD19 (77), FcRγIIb (78), CD45 (79), SHP-1 (79), and Lyn (79) have been observed in patients with B cell-mediated autoimmune diseases. In addition, a trend of an augmented calcium influx and enhanced tyrosine phosphorylation in response to BCR engagement has been reported in SLE patients (80).

Identification of genetic loci that regulate the BCR

We have developed a peptide-induced model of lupus. BALB/c mice immunized with a peptide mimetope for dsDNA produces a cross-reactive Ab response to the eliciting peptide and to dsDNA (81–83). Similar to lupus-prone mice, the IgG anti-DNA Abs form immune complexes in the kidney of peptide-immunized mice. Immunization of the DBA/2 mouse strain, which shares the same $H\text{-}2^d$ haplotype, elicits a low-titered anti-peptide response and no detectable anti-DNA response (84). Thus, the BALB/c genetic background confers susceptibility to a loss of B cell tolerance, whereas the DBA/2 genetic background maintains tolerance, in this model. Both strains mount a T cell response to Ag and demonstrate that the presence or absence of an anti-DNA response is determined by the B cell population (84). In addition, B cells of DBA/2 mice are more

susceptible to BCR-mediated apoptosis and exhibit a stronger BCR-mediated calcium influx than B cells of BALB/c mice (84). Consistent with this observation, the naive, unmanipulated B cell repertoire of DBA/2 mice contains a lower frequency of DNA-reactive B cells than that of BALB/c mice (84). Taken together, these data demonstrate that the stronger BCR signal transduced in DBA/2 maintains tolerance more effectively, eliminating a broader population of autoreactive B cells, whereas a weaker BCR signal present in BALB/c mice fails to effectively eliminate some autoreactive B cells from entry into the immunocompetent repertoire.

To identify the genes that confer susceptibility to peptide-induced lupus, we completed a backcross analysis of BALB/c mice onto DBA/2 mice (R. Hicks, V. Jeganathan, and B. Diamond, manuscript in preparation). The backcross analysis revealed three susceptibility loci: two with significant linkage on chromosomes 7 and 9 and one with suggested linkage on chromosome 4. Because the locus on chromosome 9 revealed the most significant linkage, we produced a speed congenic mouse designated BC-9. These mice exhibit similar BCR-mediated apoptosis and calcium influx as BALB/c mice (Fig. 1*A*). Thus, at least some of the gene products responsible for the signaling strength differences between the BALB/c and DBA/2 strains reside within the chromosome 9 locus. Because this locus does not contain genes that have been previously established to play a role in BCR signaling, further dissection of this region will provide novel information about the molecules that regulate the BCR signal. This model is also restrictive in that neither parental strain, nor the congenic strain, displays spontaneous autoimmunity. Thus, alterations in BCR strength that shape the naive repertoire can lead to induction of Abs cross-reactive with autoantigens following exposure to a particular Ag. Although these autoantibodies may result in autoimmune disease, in the absence of the necessary Ag exposure, they may never be produced.

Role of estrogen in modulating the strength of the BCR

SLE affects females 10 times more frequently than males and strikes predominantly during the reproductive years. More than 20 years ago, it was documented that the female lupus-prone NZB/NZW F_1 mice display an earlier onset of disease and a shortened life span compared with males (85). Administration of 17β-estradiol (E2), a highly active metabolite of estrogen, into NZB/NZW F_1 mice accelerates disease onset in females, whereas administration of testosterone ameliorates disease progression (85, 86). These studies provided compelling evidence that an alteration in sex hormones levels is one of the factors that might contribute to the female predominance in SLE

To study the role of E2 in lupus, we studied the regulation of anti-DNA B cells using an Ig transgenic (Tg) mouse model generated in our laboratory that expresses the IgG2b H chain of an anti-DNA Ab (87). Normally, R4A Tg BALB/c mice maintain tolerance through the deletion of the DNA-reactive B cells that arise in the immature repertoire (53, 61, 87). E2 administration is sufficient to break tolerance of Tg high-affinity DNA-reactive B cells. E2-treated mice display a lupus phenotype characterized by a rise in serum anti-DNA titers, glomerular immune complex deposition, and in vivo expansion and activation of Tg DNA-reactive B cells (88). Examination of the B cell subsets in E2-treated mice revealed several interesting findings. First, we observed a reduction in the number of transitional B cells. This was in agreement with earlier studies by Kincade et al. (89) that demonstrated that B cell lymphopoiesis is reduced in both pregnant mice and in E2-treated mice. Despite this reduction, there is an alteration in the ratio of transitional T1:T2 B cells due to a relative expansion of T2 cells in E2-treated mice (90). In addition, BCR-mediated apoptosis is reduced in the transitional B cell population (91). These data are suggestive of impaired negative selection occurring at the transitional B cell stage. Analysis

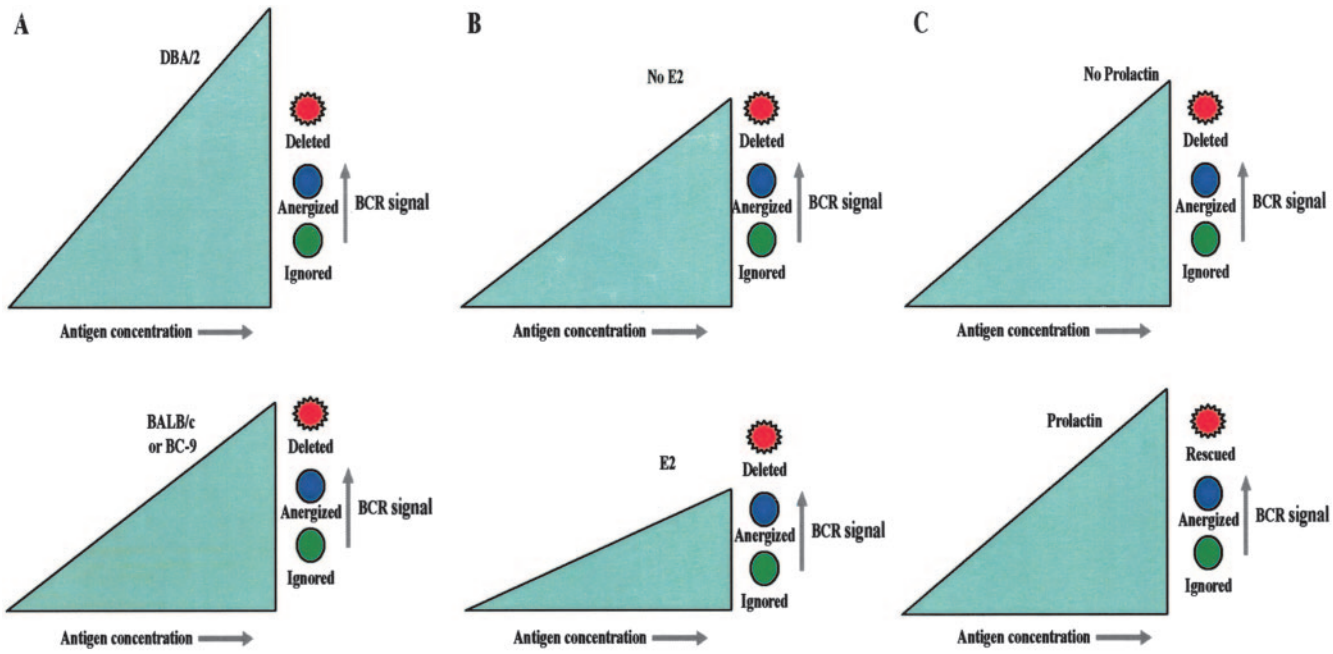

FIGURE 1. The strength of the BCR signal determines susceptibility to autoreactivity. *A*, Genetic determinants contribute to the differences in BCR signaling strength observed in DBA/2 and BALB/c or BC-9 mice. DNA-reactive B cells, which arise routinely as part of the naive repertoire, are more efficiently eliminated by a stronger BCR signal (DBA/2) than by a weaker signal (BALB/c and BC-9). *B*, Treatment of anti-DNA Ig Tg BALB/c mice with E2 results reduces the BCR signaling strength to a level that is insufficient to delete potentially pathogenic, high-affinity DNA-reactive B cells. *C*, Treatment of anti-DNA Ig Tg mice with prolactin results in the rescue of high-affinity DNA-reactive B cells without alterations in the signaling strength of the BCR.

of B cells isolated from E2-treated mice demonstrates that a population of DNA-reactive marginal zone B cells, but not the follicular B cells, is spontaneously activated in vivo (90). Thus, these results suggest that marginal zone B cells are capable of secreting high-affinity anti-DNA Ab, which can lead to immune complex deposition. Although our data suggest that marginal zone B cells secrete potentially pathogenic Abs, a clear role for autoreactive marginal zone B cells in human SLE has yet to be established.

Because we have previously identified L chains that form high- and low-affinity anti-DNA Abs in association with the R4A H chain (53, 61, 88), we performed single-cell PCR to analyze the repertoires of transitional and mature B cells .[3] From these studies, we determined that high-affinity anti-DNA B cells are routinely eliminated at the both the immature and transitional B cell stages in normal mice. However, in E2-treated-mice, high-affinity DNA-reactive B cells are rescued from negative selection, and mature to immunocompetence. In addition, the high-affinity anti-DNA B cells outcompete the low-affinity anti-DNA B cells for entry into the mature B cell pool. We propose from these studies that an elevation in estrogen alters the strength of BCR signaling such that there is diminished negative selection of potentially pathogenic B cells.

We have shown that both estrogen receptors, ERα and ERβ, are expressed in B cells, demonstrating that the B cell is, in fact, a target for the action of estrogen. These receptors act as transcription factors to regulate the expression of numerous target genes. To begin to unravel the molecular effects of estrogen on B cells, we performed microarray analysis and subtractive hybridization (91). Of particular interest was the identification of *bcl-2*, *cd22*, and *shp-1* as estrogen-responsive genes, which we confirmed by protein levels (91). The *bcl-2* gene is known to be directly E2 responsive (92), and its increased expression in B cells has been shown to perturb negative selection of autoreactive B cells, although in most mouse strains, increased Bcl-2 expression alone is not sufficient to induce a fulminant autoimmune phenotype.

The increase of CD22 and SHP-1 in E2-treated mice was an intriguing finding because the conclusions drawn from studies of CD22- and SHP-1-deficient mice suggest that reduced expression of these molecules leads to the activation of autoreactive B cells. We propose that a weakened BCR signal resulting from increased CD22 and/or SHP-1 levels would favor the escape of autoreactive B cells from negative selection. BCR ligation of CD22 and SHP-1 transfected surface IgM^{pos} K46 cells with anti-IgM results in a markedly reduced calcium influx (91). Consistent with data generated from mouse models of BCR signaling, the weaker BCR signal created by overexpression of CD22 or SHP-1 may be responsible for the diminished susceptibility to BCR-mediated apoptosis of transitional cells and for the expansion of marginal zone B cells that we observe in vivo (Fig. 1*B*). We are in the process of generating transgenic mice that overexpress CD22 or SHP-1 to determine whether increased expression of these molecules alone alters negative selection of autoreactive B cells.

Interestingly, we have recent data showing that B cells of C57BL/6 mice are not responsive to E2 treatment. Thus, we have an opportunity to study the genetic basis for the B cell response to estrogen.

Non-BCR-mediated alterations in B cell repertoire selection

From our studies of hormonal modifications of B cell development, we determined that prolactin also rescues autoreactive B cells from deletion (93). Prolactin treatment does not alter BCR signaling strength (Fig. 1*C*). We postulated that B cells from prolactin-treated mice are rescued from negative selection without altering signaling strength. Factors known to rescue B cells from BCR-mediated apoptosis include IL-4, IL-10, and CD40 ligation. We demonstrated up-regulation of CD40 on B cells of prolactin-treated mice (93). We hypothesize that the rescue of autoreactive B cells from apoptosis in prolactin-treated mice is mediated by CD40 ligation. It is undoubtedly the case that both genetic and nongenetic factors routinely alter the susceptibility of immature B cells to BCR-mediated apoptosis without, in fact, altering the BCR signaling strength. Susceptibility to prolactin-mediated changes in the B cell repertoire does not occur in C57BL/6 mice (93) and, similar to E2-mediated changes, is also genetically determined.

Conclusion

The studies of many laboratories as well as our own provide compelling data to suggest that each individual sets a unique threshold for the elimination or survival or autoreactive B cells; hence the naive B cell repertoire of each individual includes a different spectrum of autoreactive specificities. Signaling through the BCR is central to B cell differentiation and activation and to setting the threshold for negative selection. The analysis of two nonspontaneous mouse models of lupus described above demonstrates that a reduction in the strength of BCR signaling favors the escape of autoreactive B cells that arise in the naive repertoire (Fig. 1, *A* and *B*). It is clear that the strength of the BCR signal is regulated by a complex array of molecules, some of which remain to be determined. It is also clear that cross talk with non-BCR-mediated pathways can influence the outcome of BCR ligation (Fig. 1*C*). Furthermore, exposure to environmental factors affects the BCR repertoire and alters the degree of autoreactivity. It is clear from clinical experience and from our own studies described here that these factors affect individuals differently and their effect may be dependent on genetic background. A better understanding of the factors that regulate the function of the BCR may lead to the development of compounds that manipulate the BCR signaling strength and cross talk with the BCR signaling pathway and, thus, may have therapeutic potential to modify the immune response to eliminate or reduce autoreactivity while maintaining immunocompetence.

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