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J Immunol (2004) 173 (7): 4724–4728.

<https://doi.org/10.4049/jimmunol.173.7.4724>

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A Critical Role for Fc γ RIIB in the Induction of Rheumatoid Factors¹

Thomas Moll,* Lars Nitschke,[†] Michael Carroll,[‡] Jeffrey V. Ravetch,[§] and Shozo Izui^{2*}

Rheumatoid factors (RF) are autoantibodies with specificity for the Fc portion of IgG, and IgG-containing immune complexes are likely to be the major source of RF autoantigens. Therefore, the activation of RF-producing B cells could be controlled specifically through recognition of IgG immune complexes by the low-affinity IgG FcR, Fc γ RIIB, a potent negative regulator of the BCR. To test this possibility, we determined the development of RF in C57BL/6 (B6) mice lacking Fc γ RIIB, in relation to the *H2* haplotype, complement C3, and the Y-linked autoimmune acceleration (*Yaa*) mutation. Fc γ RIIB-null B6 mice displayed substantial anti-IgG2a RF activities in their sera, in addition to anti-DNA autoantibodies. Their RF and anti-DNA responses were linked to the *H2^b* haplotype, but were suppressed almost completely by the *H2^d* haplotype. Strikingly, the absence of C3 failed to modulate RF production, but strongly inhibited anti-DNA production. Furthermore, we observed that partial Fc γ RIIB deficiency (i.e., heterozygous level of Fc γ RIIB expression) was sufficient to induce the production of RF and anti-DNA autoantibodies in the presence of the *Yaa* mutation. In contrast to Fc γ RIIB, the deficiency in another BCR negative regulator, CD22, was unable to promote RF and anti-DNA autoimmune responses in B6 mice. Our results indicate that RF autoimmune responses are critically controlled by Fc γ RIIB, together with the *H2^b* and *Yaa* gene, while C3 regulates positively and specifically anti-DNA, but not RF autoimmune responses. *The Journal of Immunology*, 2004, 173: 4724–4728.

Rheumatoid factors (RF)³ are defined as autoantibodies with specificity for the Fc portion of IgG. The presence of RF is a characteristic feature of patients with rheumatoid arthritis, and RF-containing immune complexes (IC) could contribute to several pathological manifestations, such as necrotizing arteritis and arthritis, in these patients. The development of similar lesions in lupus-prone MRL-*lpr/lpr* mice deficient in the Fas apoptosis receptor (1–3) is likely related to the fact that these mice spontaneously produce high titers of RF (4–6).

The activation of RF-specific B cells results from BCR-dependent uptake of IC, presentation of antigenic peptides derived from IC, and interaction with Ag-specific T cells. However, this process is likely to be tightly controlled, because RF activities are hardly detectable in sera from nonautoimmune mice, and the spontaneous production of RF is not a common feature of systemic lupus erythematosus. It has been shown that the only murine strains that spontaneously produce high titers of RF are deficient in Fas-mediated apoptosis (5, 6). The absence of substantial RF production in mice is likely to be related to the unique feature of the autoantigens involved in RF autoimmune responses; high-affinity RF-producing B cells, generated during the germinal center response

from low-affinity RF-specific B cells activated by IC, should be eliminated efficiently by apoptosis through interaction with excess amounts of monomeric IgG. Notably, activated B cells in the germinal center are particularly sensitive to apoptosis because of their down-regulated Bcl-2 and up-regulated Fas expression (7). This is consistent with our recent finding that autoimmune-prone mice overexpressing a *Bcl-2* transgene in B cells are able to produce substantial titers of RF (8).

In addition, the activation of RF-producing B cells can be inhibited through the interaction of RF autoantigens (i.e., IgG present in IC) with the low-affinity IgG FcR, Fc γ RIIB. Fc γ RIIB is an inhibitory receptor containing an ITIM motif and, upon its coligation to the BCR, recruits the inositol polyphosphate phosphatase. This leads to the hydrolysis of phosphatidylinositol 3,4,5-triphosphate and prevents further activation of BCR signaling (9). Thus, Fc γ RIIB sets thresholds for the IC-mediated activation of B cells. Consequently, Fc γ RIIB could efficiently down-regulate the development of RF autoimmune responses more selectively than other autoimmune responses, such as anti-DNA.

Since mice deficient in Fc γ RIIB can spontaneously develop anti-DNA autoimmune responses on a C57BL/6 (B6) background (10), in the present study we have explored whether an absent or deficient expression of Fc γ RIIB in B cells could also lead to the spontaneous production of RF. In addition, our previous study has shown that the Y-linked autoimmune acceleration (*Yaa*) mutation enhanced anti-DNA production, but failed to promote RF responses in mice overexpressing Bcl-2 in B cells (8). Therefore, the effect of the *Yaa* mutation on the induction of RF production was also investigated in mice partially deficient in Fc γ RIIB. In addition to Fc γ RIIB, the roles of C3 and another BCR negative regulator, CD22, in the induction of RF were evaluated, in comparison to anti-DNA autoantibody production. In the present study, we show that Fc γ RIIB plays a critical role in the development of RF, and that this autoimmune response is modulated by the *H2* haplotype and the *Yaa* mutation, but not by C3 and CD22.

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Received for publication May 17, 2004. Accepted for publication July 16, 2004.

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¹ This work was supported by the Swiss National Foundation for Scientific Research and the Deutsche Forschungsgemeinschaft.

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³ Abbreviations used in this paper: RF, rheumatoid factor; IC, immune complex; *Yaa*, Y-linked autoimmune acceleration; NIP, (4-hydroxy-3-iodo-5-nitrophenyl)acetyl.

Materials and Methods

Mice

B6 ($H2^b$) and B10.D2 ($H2^d$) mice were purchased from The Jackson Laboratory (Bar Harbor, ME). The production of Fc γ RIIB- and C3-deficient mice was previously described (11, 12). Fc γ RIIB- and C3-deficient mice were backcrossed for eight generations with B6 mice. B6 mice bearing the *Yaa* gene were developed by backcross procedures, and established at the 12th backcross generation as described (13). CD22 $^{-/-}$ mice with a pure B6 background were developed as described previously (14). Fc γ RIIB $^{-/-}$ B6 mice carrying the $H2^d$ haplotype or the C3 null mutation were obtained through intercross between Fc γ RIIB $^{-/-}$ and B10.D2 mice and between Fc γ RIIB $^{-/-}$ and C3 $^{-/-}$ B6 mice, respectively. Mice deficient in Fc γ RIIB and bearing the $H2^d$ haplotype were identified by flow cytometric analysis of circulating B cells using 2.4G2 anti-Fc γ R/III and anti-I-A (Y-3P anti-I-A^b and MKD6 anti-I-A^d) mAb. The C3 $^{-/-}$ genotype was determined by the absence of serum C3, as determined by ELISA (15).

Serological assays

Serum levels of anti-IgG2a RF were determined by ELISA as described previously (16). Briefly, microtiter plates were initially coated with (4-hydroxy-3-iodo-5-nitrophenyl)acetyl (NIP)-conjugated BSA, followed by an incubation with murine IgG2a^b, λ 1 (S43-10) anti-NIP mAb. Then, plates were incubated with 1/2000 diluted sera, and the assay was developed with alkaline phosphatase-conjugated rat anti-mouse κ -chain (H139.52.1). As control, serum samples were incubated with plates coated only with NIP-BSA. Results are expressed as OD₄₀₅ obtained with NIP-BSA-anti-NIP coated plates after subtracting OD values of control plates coated only with NIP-BSA. Serum levels of IgG anti-DNA autoantibodies were determined by ELISA, and results are expressed as titration units (units per milliliter), as described previously (17).

Flow cytometric analysis

Flow cytometry was performed using two-color staining of spleen cells or peripheral blood lymphocytes, and analyzed with a FACSCaliber (BD Biosciences, Mountain View, CA), as described previously. The following Abs were used: anti-Fc γ R/III (2.4G2), anti-I-A^b (Y-3P), anti-I-A^d (MKD6), and anti-B220 (RA3-6B2) mAb. To determine the interaction of LO-MM-9 and b7-6 anti-IgM mAb with Fc γ RIIB on B cells, peripheral blood B cells from B6 mice were first incubated with 10 μ g of LO-MM-9 or b7-6 mAb for 45 min at 4°C and then stained with biotinylated 2.4G2 anti-Fc γ R/III and PE-labeled anti-B220 mAb, followed by streptavidin-CyChrome.

Spleen cell culture

B cell proliferative responses were determined by incubating 2×10^5 spleen cells from B6 mice with different concentrations of rat anti-IgM (LO-MM-9 or b7-6) mAb in a total volume of 200 μ l of DMEM containing 10% FCS. Cultures were pulsed with 1 μ Ci of [³H]thymidine for the final 6 h of a 3-day culture, harvested, and counted for radioactivity.

Statistical analysis

Statistical analysis was performed with the Mann-Whitney *U* test. Probability values >5% were considered insignificant.

Results

H2 control of RF and anti-DNA autoantibody production in mice deficient in Fc γ RIIB

To assess the possible role of Fc γ RIIB in the down-regulation of RF autoimmune responses, we determined whether the lack of Fc γ RIIB expression could promote the spontaneous production of RF in B6 mice. As reported previously (10), Fc γ RIIB $^{-/-}$ B6 female mice spontaneously developed substantial titers of IgG anti-DNA autoantibodies at 6 mo of age (Fig. 1A). Serum levels of anti-IgG2a RF activities were also elevated in Fc γ RIIB $^{-/-}$ B6 mice (Fig. 1B).

It has previously been shown that BALB/c ($H2^d$) mice deficient in Fc γ RIIB failed to develop IgG anti-DNA autoantibodies, and that the lack of this response is apparently regulated by gene(s) within or closely linked to the MHC (18). Therefore, we generated Fc γ RIIB $^{-/-}$ B6 mice bearing the $H2^d$ haplotype by backcross procedure. As shown in Fig. 1, spontaneous production of RF and IgG anti-DNA autoantibodies was markedly limited in $H2^d$ mice, as compared with that in $H2^b$ mice ($p < 0.0001$ for both RF and anti-DNA). In fact, their levels were almost comparable to the baseline levels obtained in wild-type B6 mice.

Inhibition of anti-DNA, but not RF autoantibody production in Fc γ RIIB and C3 double-deficient B6 mice

We next explored the possible role of C3 in the induction of RF and anti-DNA autoantibody production in Fc γ RIIB $^{-/-}$ B6 mice, since the binding of C3 fragments to nuclear autoantigens or IgG IC could promote the activation of autoreactive B cells through amplified positive signaling via the CD21-CD19 pathway. When serum levels of RF and IgG anti-DNA autoantibodies in Fc γ RIIB and C3 double-deficient (Fc γ RIIB/C3 $^{-/-}$) B6 mice were compared with those of Fc γ RIIB $^{-/-}$ B6 mice at 6 mo of age, the absence of C3 didn't affect the spontaneous development of RF (Fig. 2). In contrast, serum levels of IgG anti-DNA autoantibodies were markedly reduced in Fc γ RIIB/C3 $^{-/-}$ B6 mice, as compared with Fc γ RIIB $^{-/-}$ mice ($p < 0.0001$).

Induction of RF and anti-DNA production in Fc γ RIIB haploinsufficient mice bearing the *Yaa* mutation

We have recently shown that the *Yaa* mutation promotes the production of IgG anti-DNA autoantibodies, but hardly that of RF in B6 mice (8). In view of a possible key role for Fc γ RIIB in RF autoimmune responses, we determined whether the *Yaa* mutation is able to promote RF production in B6 mice if their expression of Fc γ RIIB is diminished to a heterozygous level. Mature B cells in

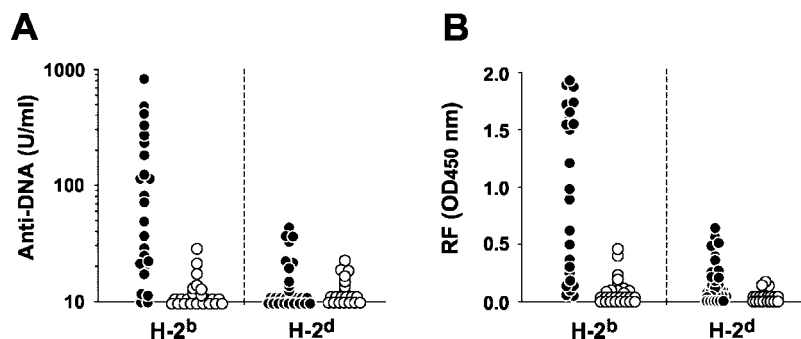


FIGURE 1. Serum levels of anti-DNA and anti-IgG2a RF in 6-mo-old Fc γ RIIB-deficient (●) or Fc γ RIIB^{+/+} control (○) B6 female mice bearing the $H2^b$ or $H2^d$ haplotype. *A*, Serum IgG anti-DNA activities were determined by incubating 1/100 diluted serum samples in microtiter plates coated with calf thymus DNA, and the assay was developed with alkaline phosphatase-conjugated goat anti-mouse IgG-specific polyclonal Ab. Results are expressed as units per milliliter. *B*, Serum anti-IgG2a RF activities were determined by incubating 1/2000 diluted serum samples in microtiter plates coated with NIP-BSA and anti-NIP (S43-10, IgG2a^b, λ 1) mAb, and the assay was developed with alkaline phosphatase-labeled anti- κ -chain mAb. Results are expressed as OD₄₀₅ after subtracting OD values obtained with control plates coated only with NIP-BSA.

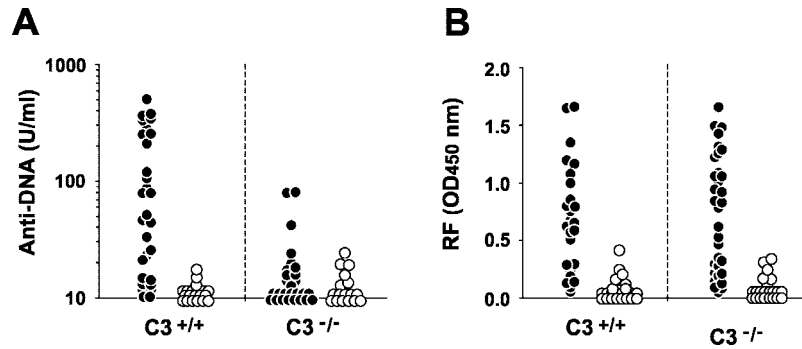


FIGURE 2. Serum levels of anti-DNA and anti-IgG2a RF in 6-mo-old Fc γ RIIB-deficient and Fc γ RIIB/C3^{-/-} B6 female mice (●) compared with Fc γ RIIB^{+/+} controls (○). *A*, Serum IgG anti-DNA activities were determined by incubating 1/100 diluted serum samples in microtiter plates coated with calf thymus DNA, and the assay was developed with alkaline phosphatase-conjugated goat anti-mouse IgG-specific polyclonal Ab. Results are expressed as units per milliliter. *B*, Serum anti-IgG2a RF activities were determined by incubating 1/2000 diluted serum samples in microtiter plates coated with NIP-BSA and anti-NIP mAb, and the assay was developed with alkaline phosphatase-labeled anti- κ -chain mAb. Results are expressed as OD₄₀₅ after subtracting OD values obtained with control plates coated only with NIP-BSA.

Fc γ RIIB^{+/-} B6 mice displayed reduced levels of Fc γ RIIB, as compared with wild-type B cells, and these expression levels were unchanged by the presence of the *Yaa* mutation (data not shown). Fc γ RIIB^{+/-} heterozygous male mice without the *Yaa* gene hardly exhibited significant anti-IgG2a RF and anti-DNA activities in their sera (Fig. 3). However, increased levels of RF as well as anti-DNA autoantibodies were observed in Fc γ RIIB^{+/-} haploinsufficient mice bearing the *Yaa* gene, as compared with Fc γ RIIB-sufficient B6 *Yaa* male mice ($p < 0.05$ and $p < 0.001$, respectively).

It has been speculated that the *Yaa* defect may decrease the threshold of BCR signaling, thereby triggering autoreactive B cells. More precisely, the *Yaa* mutation might down-modulate a negative signaling pathway triggered through coligation of BCR with Fc γ RIIB. To test this possibility, we compared the inhibitory effect of Fc γ RIIB on anti-IgM-induced proliferative responses of splenic B cells from Fc γ RIIB^{+/-} B6 mice with or without the *Yaa* mutation. We chose two different anti-IgM mAb, LO-MM-9 and b7-6, which have markedly different capacities to interact with Fc γ RIIB. This was documented by a competitive binding assay, in which the binding of 2.4G2 anti-Fc γ RII/III mAb to splenic B cells from B6 mice was substantially blocked by preincubation with LO-MM-9, but only slightly with b7-6 anti-IgM mAb (Fig. 4A). Furthermore, proliferative responses of Fc γ RIIB-sufficient B cells after stimulation with LO-MM-9 mAb were strongly inhibited, as compared with Fc γ RIIB-deficient B cells ($p < 0.05$), while stim-

ulation with b7-6 mAb induced robust responses in both types of B cells, although still statistically different ($p < 0.05$; Fig. 4B). Importantly, combined analysis with LO-MM-9 and b7-6 mAb demonstrated that the *Yaa* mutation was unable to up-regulate LO-MM-9 anti-IgM-induced proliferative responses of Fc γ RIIB^{+/-} B cells. These results suggest that the *Yaa* mutation is unlikely to be involved in the modulation of a negative signaling pathway triggered through Fc γ RIIB after its coligation with BCR by IC in RF-specific B cells.

Lack of RF and anti-DNA induction in B6 mice deficient in CD22

CD22 acts as a negative regulator of BCR signaling, through recognition of α 2,6-linked sialic acid-bearing glycans (19). Interval mapping analysis for lupus susceptibility loci suggested that the defective *Cd22^a* gene expressed in lupus-prone NZW mice is a possible candidate gene contributing to lupus susceptibility (20, 21). Therefore, we tested the development of IgG anti-DNA autoantibodies and RF in 8 mo-old CD22^{-/-} B6 female mice. In contrast to Fc γ RIIB^{-/-} mice, CD22^{-/-} B6 female mice failed to display significant anti-DNA and anti-IgG2a RF activities in their sera, as compared with wild-type B6 mice (means of anti-DNA \pm SD of 12 mice, CD22^{-/-}, 20.4 \pm 7.3 U/ml; CD22^{+/+}, 22.7 \pm 9.6 U/ml; mean OD values for RF, CD22^{-/-}, 0.031 \pm 0.033; CD22^{+/+}, 0.086 \pm 0.034). This further suggested a more specific role for Fc γ RIIB in the induction of RF autoimmune responses.

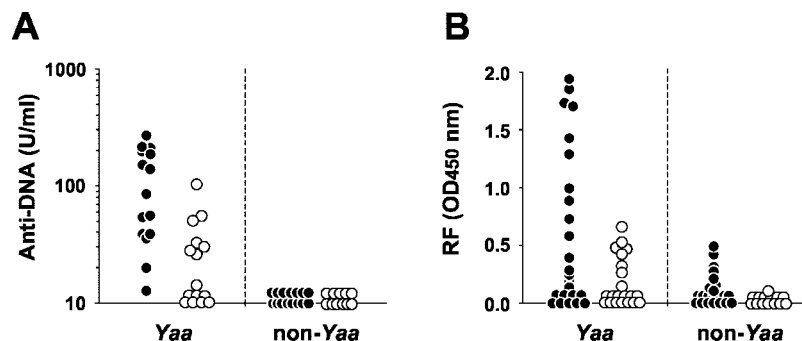


FIGURE 3. Serum levels of anti-DNA and anti-IgG2a RF in 6-mo-old Fc γ RIIB^{+/-} haploinsufficient B6 male mice with or without the *Yaa* mutation (●), compared with Fc γ RIIB^{+/+} controls (○). *A*, Serum IgG anti-DNA activities were determined by incubating 1/100 diluted serum samples in microtiter plates coated with calf thymus DNA, and the assay was developed with alkaline phosphatase-conjugated goat anti-mouse IgG-specific polyclonal antibody. Results are expressed as units per milliliter. *B*, Serum anti-IgG2a RF activities were determined by incubating 1/2000 diluted serum samples in microtiter plates coated with NIP-BSA and anti-NIP mAb, and the assay was developed with alkaline phosphatase-labeled anti- κ -chain mAb. Results are expressed as OD₄₀₅ after subtracting OD values obtained with control plates coated only with NIP-BSA.

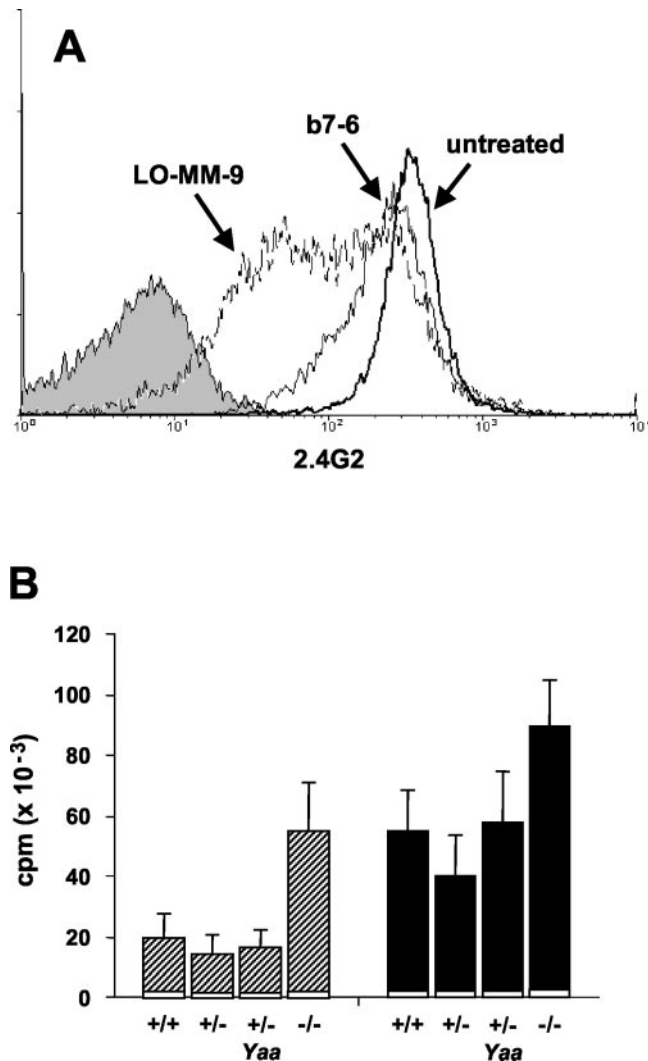


FIGURE 4. Interaction of LO-MM-9 and b7-6 anti-IgM mAb with Fc γ RIIB and splenic B cell proliferative responses after stimulation with LO-MM-9 and b7-6 mAb. *A*, Spleen B cells from B6 mice were stained with 2.4G2 anti-Fc γ RII/III mAb after preincubation with either LO-MM-9 (dotted line) or b7-6 mAb (light black line). Fluorescence intensities of 2.4G2 staining on B220⁺ B cells are shown. The shaded histogram represents the absence of 2.4G2 staining on Fc γ RIIB^{-/-} control B cells. Representative results obtained from three individual mice are shown. *B*, Splenic B cell proliferative responses following stimulation with 25 μ g/ml LO-MM-9 (\square) or b7-6 (\blacksquare) mAb in Fc γ RIIB +/+, +/-, or -/- B6 mice with or without the *Yaa* mutation. Results are expressed as cpm of [³H]thymidine incorporation (means of four to six mice per group \pm SD), and the white segments represent background proliferation without addition of mAb.

Discussion

In the present study, we explored the role of a negative regulator of BCR, Fc γ RIIB, in the production of RF. Our analysis has demonstrated spontaneous production of RF in Fc γ RIIB-deficient B6 mice and these RF responses were modulated by the gene(s) within or closely linked to the MHC and by the *Yaa* mutation, but unaffected by the absence of C3. The lack of involvement of C3 in RF autoimmune response markedly contrasted with the finding that anti-DNA autoantibody production in Fc γ RIIB^{-/-} B6 mice was strongly inhibited by the absence of C3. This further supports the notion that RF and anti-DNA autoimmune responses are differentially regulated, which is related to the different nature of the autoantigens involved in either autoimmune response.

Our demonstration that Fc γ RIIB-deficient B6 mice spontaneously produce substantial levels of RF strongly supports the hypothesis that IC are the major source of autoantigens for RF responses, and that the triggering of RF-producing B cells is specifically inhibited as a result of corecognition of IC by Fc γ RIIB and BCR. Thus, Fc γ RIIB down-regulates the excessive activation by IC of low-affinity RF-specific B cells, which cannot be efficiently eliminated by monomeric IgG, unlike high-affinity RF-specific B cells. Furthermore, Fc γ RIIB expressed on follicular dendritic cells may also contribute to the elimination of RF-specific B cells generated during the germinal center reaction, as it has been proposed that preferential interaction of IC present on follicular dendritic cells with Fc γ RIIB over BCR could result in B cell apoptosis (22). This is consistent with our recent observation that an abnormality in B cell apoptosis plays an important role in the induction of RF autoimmune responses (8).

Studies in Fc γ RIIB-deficient B6 and BALB/c mice have shown that spontaneous production of autoantibodies, such as anti-DNA, was markedly limited in BALB/c mice, as compared with B6 mice (10). The genetic analysis revealed that one of the loci that control autoantibody production in this model is linked to the MHC (18). Our analysis of Fc γ RIIB^{-/-} B6 mice bearing the *H2^d* haplotype (B6 and BALB/c mice carry *H2^b* and *H2^d*, respectively) has clearly shown that the presence of the *H2^d* haplotype provides a strong protection from the development of RF and anti-DNA autoimmune responses. These results are consistent with the previous demonstration that lupus-prone mice bearing the *H2^b* haplotype are more susceptible to the development of lupus-like autoimmune syndrome, as compared with those bearing the *H2^d* haplotype (23–26). However, it should be stressed that Fc γ RIIB^{-/-} BALB/c mice bearing the *H2^b* haplotype failed to develop significant autoimmune responses (18). This suggests that the *H2^b* haplotype by itself is not sufficient to trigger autoimmune responses in Fc γ RIIB-deficient BALB/c mice, indicating the lack of additional genetic factor(s) promoting autoimmune responses in BALB/c mice.

It is significant that the lack of C3 hardly modulated the production of RF, but markedly inhibited anti-DNA autoimmune responses in Fc γ RIIB-deficient B6 mice. This suggests that, in contrast to RF autoimmune responses, C3 deposition on nuclear autoantigens plays an important role in the amplification of anti-DNA autoantibody production through the interaction with CD21-CD19 complexes. The lack of C3 involvement in RF responses may be explained as follows: C3 deposition on nuclear autoantigens would be more intense than on IgG-containing IC, which is likely related to the fact that the early components of the classical complement pathway exhibit a strong interaction with apoptotic bodies implicated in anti-DNA autoimmune responses (27, 28). Thus, our data suggest that complement is not only involved in the elimination of potential autoantigens through the binding to apoptotic bodies, but also plays a critical role by activating autoreactive B cells through CD21-CD19 complexes. Because C3 is less efficient for the interaction and subsequent elimination of apoptotic bodies as compared with C1q, C2, and C4 (28), it appears that C3 rather acts as a positive regulator of anti-DNA autoantibody production. In contrast, C1q, C2, and C4 are protective against the development of anti-DNA autoantibody responses; this is consistent with the findings that C1q- or C4-deficiency promotes the spontaneous production of anti-DNA autoantibodies in mice (27, 29, 30). All these results are in agreement with the strong association of systemic lupus erythematosus with C1q, C2, and C4 deficiency, but not with C3 deficiency (31).

We have recently shown a synergistic interaction between the *Yaa* mutation and Bcl-2 overexpression on IgG anti-DNA production, but not on RF production (8). We interpreted these results as

follows: unlike anti-DNA-specific B cells, the activation of RF-specific B cells is negatively regulated through corecognition of IC by Fc γ RIIB, and the *Yaa* mutation may be unable to counteract the potent negative signal triggered by Fc γ RIIB engagement in B cells expressing normal levels of Fc γ RIIB. Nevertheless, our present study has shown that the *Yaa* mutation is able to promote RF responses in Fc γ RIIB^{+/-} haploinsufficient mice, indicating that the *Yaa* mutation can counteract Fc γ RIIB-mediated negative signaling, if the latter is partially deficient. However, we observed that the presence of the *Yaa* mutation is unable to up-modulate B cell proliferative responses in the presence of LO-MM-9 anti-IgM mAb, which interacts efficiently with Fc γ RIIB, thereby down-regulating B cell proliferation. This strongly suggests that, even if *Yaa* acts as a positive regulator of BCR signaling, it may not directly impede the negative signaling pathway triggered by Fc γ RIIB upon coligation with BCR.

Another B cell coreceptor that is potentially involved in the inhibition of autoantibody production is CD22, which—like Fc γ RIIB—acts as a negative regulator of BCR signaling (32). It has been suggested that recognition of α 2,6-linked sialic acid-bearing glycans on autoantigens by CD22 on B cells may be a mechanism to prevent activation of potentially autoreactive B cells (33). However, despite the development of IgG anti-DNA autoantibodies reported in CD22^{-/-} mice bearing a mixed genetic background of 129 and B6 strains (34, 35), the CD22^{-/-} mice with a pure B6 background used in the present study failed to develop RF as well as anti-DNA autoantibodies. Differences in the genetic background of CD22-deficient mice likely account for this discrepancy. Nevertheless, the lack of RF autoimmune responses in CD22^{-/-} B6 mice further indicates a more specific role for Fc γ RIIB in the control of RF autoimmune responses.

Our previous and current studies have demonstrated that an abnormality in B cell apoptosis and Fc γ RIIB is critical for the induction of RF autoimmune responses. This is likely related to the unique feature of the autoantigens involved in these responses. The abundance of monomeric IgG in the circulating blood efficiently induces peripheral tolerance of high-affinity RF-specific B cells, which can potentially be generated in the germinal centers during the course of immune responses against self and foreign Ags. In addition, corecognition of RF autoantigens (i.e., IC) by BCR and Fc γ RIIB inhibits the priming and maturation of low-affinity RF-specific B cells. In this regard, it would be of interest to determine whether the development of RF in patients with rheumatoid arthritis is associated with unique genetic abnormalities, such as functional defects in B cell apoptosis and/or Fc γ RIIB.

Acknowledgments

We thank A. Heiter, G. Celetta, and G. Brighthouse for their excellent technical assistance.

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