Comment on "The Inhibiting Fc Receptor for IgG, Fc γRIIB, Is a Modifier of Autoimmune Susceptibility"

Divaker Choubey, Ravichandran Panchanathan and Hongzhu Liu

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cγRIIB<sub>129</sub><sup>−/−</sup> female mice produce detectable levels of anti-nuclear autoantibodies (ANAs) at the age of 4–5 mo (1). Moreover, these mice, compared with age-matched wild-type C57BL/6 mice, exhibit a reduced expression of the <i>Arm2</i> gene (a member of the <i>Ifi200</i> gene family), activation of the IFN response, and the induction of certain IFN-inducible genes at the age of ∼8 wk (much earlier than the detection of ANAs) (2). The IFN-inducible genes include the <i>If202</i> gene (encoding for the p202 protein) from the <i>If200</i> gene family (2), which is located within the <i>Nba2</i> lupus susceptibility interval (3, 4). The interval also includes the <i>Fggr2b</i> gene (4). Given that increased nuclear levels of p202 protein in B6. <i>Nba2</i>-congenic female mice are associated with the production of ANAs (3, 4), recent observations by Boross et al. (5) that Fc<sub>γRIIB</sub><sub>129</sub><sup>−/−</sup> (but not Fc<sub>γRIIB</sub><sub>B6</sub><sup>−/−</sup>) female mice at the age of 10 mo exhibit ANAs are consistent with previous observations (3, 6). However, it is intriguing that Boross et al. (5) did not examine whether Fc<sub>γRIIB</sub><sub>129</sub><sup>−/−</sup> mice exhibit the activation of a type I IFN response. Because FcγRIIB<sub>129</sub><sup>−/−</sup> mice express increased levels of p202 protein (Fig. 1) at the age of ∼8 wk, the observations by Boross et al. (5) support an interesting possibility that epistatic interactions between <i>Fggr2b</i> and <i>If202</i> family genes contribute to an increased production of type I IFN and ANAs. Therefore, further work is needed to characterize these epistatic interactions to understand their role in the development of lupus disease.

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FIGURE 1. Levels of p202 protein increase in FcγRIIB<sub>129</sub><sup>−/−</sup> mice. Splenic cells from wild-type C57BL/6 and age-matched (∼8 wk) FcγRIIB<sub>129</sub><sup>−/−</sup> male or female mice were prepared, and total cell lysates containing equal amounts of proteins were analyzed by immunoblotting, using Abs specific to the indicated proteins. The fold increases in the p202 protein levels in FcγRIIB<sub>129</sub><sup>−/−</sup> male and female mice (compared with wild-type mice) are indicated.

Response to Comment on “The Inhibiting Fc Receptor for IgG, FcγRIIB, Is a Modifier of Autoimmune Susceptibility”

In our opinion, the comment of Choubey et al. deals with two issues: 1) the direct link between FcγRIIB and Ifi202 expression and 2) the role of Ifi202 as a systemic lupus erythematosus (SLE) susceptibility gene.

The Ifi202 gene is located in the flanking region of the <i>Fggr2b</i> gene, which is of 129 origin in FcγRIIB<sub>129</sub><sup>−/−</sup> mice. As shown in the study of Jørgensen et al. (1), expression of the allelic variant of the Ifi202 gene present in the <i>Nba2</i> interval of the NZB mouse is significantly higher compared with the Ifi202 expression in C57BL/6 mice. In our opinion, the explanation for the higher Ifi202 gene expression found in FcγRIIB<sub>129</sub><sup>−/−</sup> mice is due to the <i>Sle16</i> haplotype of the 129-derived <i>Fggr2b</i> flanking region, which most likely is the same as that of the NZB-derived <i>Nba2</i> interval. On the basis of these data, we expect that in our FcγRIIB<sub>B6</sub><sup>−/−</sup> mice, the Ifi202 expression is the same as in C57BL/6 mice.

However, these data do not exclude Ifi202 as a candidate SLE susceptibility gene. The goal of our study was to define the intrinsic role of FcγRIIB in the development of autoimmunity. For that purpose, we compared two FcγRIIB knockout mouse strains independently generated in two different genetic backgrounds. We demonstrated that in a pure C57BL/6 background, FcγRIIB deficiency is not sufficient to induce autoimmunity. We concluded that epistatic interactions between one or more genes located in the 129-derived genomic region that flanks the <i>Fggr2b</i> gene and the C57BL/6 genome result in the development of autoantibodies. Subsequently, FcγRIIB deficiency enhances the

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downstream pathogenic effects of these autoantibodies. In this way, the $Fcgr2b$ knockout allele and unidentified genes in its 129-derived flanking region synergize in the development of lethal lupus in FcγRIIB$^{129-/-}$ mice. Our SLE-resistant FcγRIIBb6$^{-/-}$ KO mouse model enables individual testing of the different candidate SLE susceptibility genes within the $Fcgr2b$ flanking region, including Ifi202, by combining the expression of the 129-derived allelic variants of these genes with FcγRIIB deficiency in a C57BL/6 background.

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