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Cutting Edge: Both Activating and Inhibitory Fc Receptors Expressed on Mast Cells Regulate Experimental Allergic Encephalomyelitis Disease Severity¹

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Mast cell-deficient mice (W/W^v) exhibit significantly reduced severity of experimental allergic encephalomyelitis (EAE), a murine model of multiple sclerosis. In this study, the contribution of FcR-mediated mast cell activation to disease was examined. W/W^v mice were reconstituted i.v. with bone marrow-derived mast cells (BMMCs) from wild-type mice or those lacking functional FcRs. Eight weeks later, EAE was induced by immunization with the myelin oligodendrocyte glycoprotein 35–55 peptide. Disease scores were analyzed in reconstituted mice and compared with age-matched W/W^v mice and wild-type littermates. Mice reconstituted with FcγR^{-/-} BMMCs or FcγRIII^{-/-} BMMCs exhibited less severe clinical symptoms similar to W/W^v controls, while reconstitution with FcRIIB^{-/-} BMMCs resulted in disease significantly more severe than wild-type controls. Notably, mice reconstituted with FcγRIII^{-/-} BMMC exhibit a relapsing-remitting course of disease. These data demonstrate that both activating and inhibitory FcRs expressed on mast cells influence the course of EAE. The Journal of Immunology, 2003, 170: 1630–1634.

Experimental allergic encephalomyelitis (EAE)³ is the prototypic rodent model of multiple sclerosis (MS), a debilitating disease of the CNS, and shares many of its clinical features. MS and EAE are CD4⁺ T cell-mediated autoimmune diseases characterized by localized myelin destruction and perivascular inflammation culminating in clinical paralysis and/or impaired motor function (for review, see Ref. 1). Unlike MS, EAE does not occur spontaneously, but must be experimentally induced by immunization with myelin components. Although many studies have focused on the contribution of autoreactive T cells, other cell types also play significant roles in the inflammation and nerve damage associated with this disease syndrome. Mast cells, members of the myeloid lineage of hemopoietic cells, are among these. Best known for their role in

allergic disease, mast cells exhibit a widespread tissue distribution (2). They are located throughout connective tissues beneath epithelial surfaces, in the respiratory system, along the mucosa of the gastrointestinal and genitourinary tracts and adjacent to blood vessels, lymphatic vessels, and near peripheral nerves. Mast cells are also present in the CNS where they are found predominately in the leptomeninges, thalamus, hypothalamus, and around intraparenchymal vessels (for review, see Ref. 3). These cells produce a number of immunological mediators, many of which may contribute to the inflammatory processes associated with MS and EAE disease.

There is a wealth of indirect data consistent with the idea that mast cells are involved in the disease process. Mast cells can be detected within MS and EAE lesions in the brain and spinal cord (for review, see Ref. 3). Inhibitors of mast cell degranulation and mast cell mediator activity, including theophylline, proximil, and cyproheptadine, can decrease or suppress EAE or MS (3, 4). In addition, neuropeptides can trigger mast cell degranulation (5), and supernatants from activated mast cells can degrade myelin in vitro (3). Gene microarray analysis revealed that transcripts encoding tryptase and receptors for IgE, IgG, and histamine, which are all expressed by mast cells, are up-regulated in CNS plaques from patients with chronic MS (6).

We recently demonstrated a definitive in vivo role for mast cells during the acute phase of myelin oligodendrocyte glycoprotein (MOG)-induced EAE (7). Mast cell-deficient WBB6/F₁-Kit^{W/Kit^{Wv}} (W/W^v) mice exhibit significantly reduced incidence and disease severity when compared with wild-type littermate controls. The selective reconstitution of mast cells in W/W^v mice restores severe disease confirming their role in EAE. The mast cell mediators that influence disease pathology, the sites of mast cell influence, and the mechanism(s) of mast cell activation in this model of MS are not yet defined.

Although mast cells are responsive to a variety of stimuli including microbial products (via Toll-like receptor (TLR) signaling pathways), complement, and neuropeptides (2, 5, 8, 9),

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³ Abbreviations used in this paper: EAE, experimental allergic encephalomyelitis; MS, multiple sclerosis; MOG, myelin oligodendrocyte glycoprotein; TLR, Toll-like receptor; BMMC, bone marrow-derived mast cell; Hct, hematocrit; WT, WBB6/F₁-Kit^{W/Kit^{Wv}}.

aggregation of Fc Ab receptors on the mast cell surface is perhaps one of the best understood mechanisms of mast cell activation and degranulation. Both human and murine mast cells express Fc γ RIII, a low affinity activating receptor that preferentially binds complexed IgG; Fc ϵ RI, the high affinity IgE receptor; and Fc γ RIIB, an inhibitory receptor (10, 11). Fc γ RIIB has been shown to down-regulate both Fc γ RIII- and Fc ϵ RI-induced mast cell mediator release (12). The recent development of FcR-deficient mice has made it possible to document a link between FcR signaling and autoimmune disease (for review, see Ref. 13). For example, lack of FcRIIB expression in C57BL/6 mice renders them susceptible to autoimmune disease in an induced model of arthritis or Goodpasture syndrome. In addition, these mice spontaneously develop lupus in a strain-specific manner. In a murine model of EAE, Fc γ -deficient mice (which lack functional Fc γ RI, Fc γ RIII, and Fc ϵ RI) exhibit significantly attenuated disease, and FcRIIB-deficient mice develop more severe disease than wild-type controls (6, 14).

Many studies have documented that myelin-reactive Abs are produced in MS. Elevated IgG Ab titers to several myelin Ags, as well as increased numbers of autoreactive B cells specific for oligodendryl and myelin Ags, are present in the cerebral spinal fluid of MS patients (15). Although MOG comprises only 0.05% of the myelin sheath, a major IgG Ab response directed against this protein can be detected and has been correlated with disease severity and demyelination (16–18). Stimulation by autoreactive Abs binding FcRs on resident NK cells, macrophages, or mast cells in the CNS may trigger the release of inflammatory mediators and initiate or exacerbate the myelin destruction characteristic of this disease syndrome.

The inability to induce significant clinical disease in Fc γ R-deficient mice as well as the implied role of Abs suggests this is a major pathway for inflammatory cell activation in this disease. However, because cells derived from multiple lineages express these receptors, the relative contribution of Fc-mediated signaling in individual cell types has not been assessed. In this study, we have used FcR-deficient bone marrow-derived mast cells (BMMCs) to reconstitute mast cell-deficient WBB6/F₁-Kit^W/Kit^{Wv} (W/W^v) mice to examine the specific contribution of mast cell FcRs in EAE. We demonstrate that both activating and inhibitory receptors regulate mast cell activity in this disease.

Materials and Methods

Animals

Five- to 6-wk-old WBB6/F₁-Kit^W/Kit^{Wv} (W/W^v; H2^b_{xi}) female mice and their congenic littermates, WBB6/F₁-Kit⁺/Kit⁺ (WT), were purchased from The Jackson Laboratory (Bar Harbor, ME). Fc γ R^{-/-} (H2^b) and FcRIIB^{-/-} (H2^b) were purchased from Taconic Farms (Germantown, NY). Fc γ RIII^{-/-} (H2^b) mice were obtained from J. Ravetch (Rockefeller University, New York, NY).

Bone marrow mast cell differentiation and reconstitution

Bone marrow was harvested from the femurs of 5- to 6-wk-old female mice (WT, FcRIIB^{-/-}, Fc γ R^{-/-}, or Fc γ RIII^{-/-}) and differentiated as previously described (7). BMMCs were transferred i.v. and EAE was induced 8 wk later. Before disease induction, hematocrits (Hct) were determined to assess the selectivity of the reconstitution as described (7).

Histology

To verify mast cell reconstitution of W/W^v mice, spleens and small intestines were harvested from each group of mice at the end point of each experiment (days 36–42 post-EAE disease induction). The organs were fixed in 4% para-

formaldehyde for 6 h, quick-frozen in OCT (Tissue Tek, Torrance, CA) before sectioning (12 micron), and stained with toluidine blue. Tissue sections were randomly selected and the number of mast cells was counted. The area of the tissue sections was determined using NIH Image software (Bethesda, MD).

EAE disease induction and evaluation

Disease was induced as previously described (7). MOG_{35–55} peptide (MEVG WYRSPFSRVVHLY-RNGK) was synthesized by the Emory University Microchemical facility (Atlanta, GA). Mice were scored in a blinded fashion daily for clinical signs of paralysis: 0, no physical sign of disease; 1, tail flaccidity; 2, hind limb weakness; 3, hind limb paralysis; 4, fore limb paralysis and/or the inability to right from supine.

MOG-specific Ab ELISA

MOG_{35–55} ELISAs were performed as previously described using 1/100 sera dilutions (7).

Statistical analysis

Statistical analyses were performed using GraphPad Prism (San Diego, CA). Data were considered significant if $p < 0.05$. To assess differences in EAE disease course among three or more groups of mice, repeated measured ANOVA, followed by the Dunnett's multiple comparison post test, were performed. Differences in group mean day of onset or group mean high score were evaluated using one-way ANOVA followed by Dunnett's multiple comparison post test. χ^2 contingency tables were used to compare disease incidence (number of sick mice/total number of mice). ELISA data were analyzed by unpaired Student's t test.

Results and Discussion

FcR-deficient bone marrow cells can generate mast cell precursors *in vitro* that reconstitute mast cell populations in W/W^v mice *in vivo*

Before *in vivo* reconstitution, we examined the ability of FcR-deficient bone marrow stem cells to give rise to mast cells *in vitro*. Fc γ R^{-/-} mice contain a targeted disruption of the common γ -chain gene that encodes a receptor component shared by multiple activating FcRs, and therefore, lack expression of Fc γ RI, Fc γ RIII, and Fc ϵ RI. Bone marrow cells from wild-type (WT) mice and those lacking expression of either the common Fc γ R chain (Fc γ R^{-/-}), Fc γ RIII (Fc γ RIII^{-/-}), or FcRIIB (FcRIIB^{-/-}) were cultured with IL-3 and stem cell factor as previously described (7). After 6 wk in culture, all cells expressed high levels of *c-kit* as determined by flow cytometric analysis (>96% purity) and demonstrated characteristic toluidine blue staining of mast cell granules comparable to wild-type cells differentiated under the same conditions (data not shown).

Disease was induced 8 wk after transfer of BMMCs, W/W^v mice were euthanized 4–6 wk postdisease induction, and selected tissues were analyzed for establishment of mast cell populations. Intravenous injection of wild-type H-2^b BMMCs restores mucosal and connective tissue mast cells including those in the spleen and intestine in W/W^v mice by 8- to 10-wk post-transfer (M. B. Tanzola and M. Robbie-Ryan, unpublished observations). Although there were comparable numbers of intestinal mast cells in all groups, there were notable increases in the numbers of spleen cells observed in the Fc γ R^{-/-} and Fc γ RIII^{-/-} reconstituted mice (see Fig. 1).

W/W^v mice also exhibit severe macrocytic anemia that is not corrected by transfer of BMMCs (19). Hct values for the reconstituted mice were determined and compared with W/W^v mice ($n = 9$, Hct $39.5 \pm 2.2\%$) and WT littermate controls ($n = 9$, Hct $57.7 \pm 3.0\%$). The mice reconstituted with WT BMMCs

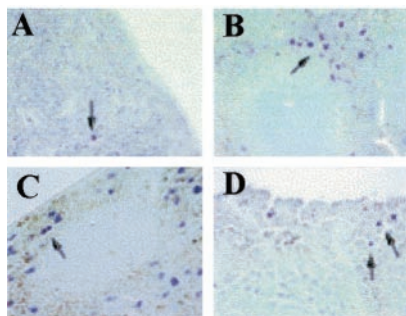


FIGURE 1. FcR^{-/-} BMMCs can reconstitute mast cell populations in W/W^v mice. Wild-type and FcR-deficient mast cells were transferred i.v. to W/W^v mice. After 8 wk, EAE was induced. Spleens were harvested on days 36–42 postdisease induction, and sections were stained with toluidine blue to detect mast cells (magnification, $\times 20$). *A*, W/W^v + WT BMMCs (0.52 ± 0.29 mast cells/mm², score 3). *B*, W/W^v + FcR $\gamma^{-/-}$ BMMCs (5.0 ± 0.8 mast cells/mm², score 2). *C*, W/W^v + Fc γ RIII^{-/-} BMMCs (23.7 ± 6.1 mast cells/mm², score 0). *D*, W/W^v + FcRIIB^{-/-} BMMCs (0.07 ± 0.05 mast cells/mm², score 4) (magnification, $\times 20$). In the representative tissue sections shown, splenic mast cells were distributed in the red pulp of the spleen in all groups. With the exception of the FcRIIB^{-/-} mice, the density of splenic mast cells in reconstituted mice is higher than that of wild-type, unmanipulated animals (0.02 ± 0.03 mast cells/mm²).

(Hct $42.0 \pm 1.7\%$), FcR $\gamma^{-/-}$ BMMCs (Hct $39.2 \pm 3.4\%$), Fc γ RIII^{-/-} BMMCs (Hct $27.1 \pm 5.4\%$), and FcRIIB^{-/-} BMMCs (Hct $37.2 \pm 3.5\%$) remained anemic, confirming that the BMMC reconstitution is selective for mast cells only.

Activating FcRs on mast cells regulate EAE severity

EAE was induced in WT, W/W^v, and W/W^v mice reconstituted with either FcR $\gamma^{-/-}$ or WT BMMCs. WT ($n = 9$) and W/W^v mice reconstituted with WT BMMC ($n = 9$) have significantly more severe disease as measured by mean clinical score ($p < 0.001$), mean high score ($p < 0.05$), and disease incidence ($p = 0.058$) as compared with W/W^v controls ($n = 9$) (Fig. 2 and Table I) consistent with previous results (7). In contrast, FcR $\gamma^{-/-}$ BMMC-reconstituted mice exhibit a decrease in disease incidence ($p = 0.058$) and a lower mean clinical score ($p < 0.001$) when compared with the WT controls, demonstrating that either Fc γ RIII or Fc ϵ RI contribute to the mast cell-mediated effects on disease observed in the acute phase of EAE. The W/W^v plus FcR $\gamma^{-/-}$ BMMC mice also exhibited a significant delay in disease onset relative to all groups studied ($p < 0.05$), including the W/W^v control, suggesting a

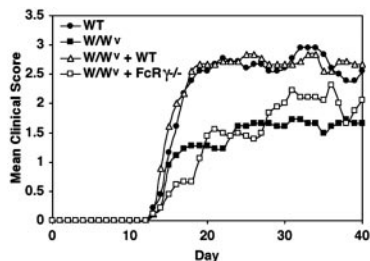


FIGURE 2. The expression of activating FcRs on mast cells is required for full disease manifestation. W/W^v mice ($n = 9$ all groups) were reconstituted with 3×10^6 in vitro-differentiated FcR $\gamma^{-/-}$ BMMCs and 8 wk later disease was induced as described above. Clinical scores were recorded daily and the mean daily clinical score for three independent experiments is shown. Scores of the FcR $\gamma^{-/-}$ BMMC-reconstituted mice were statistically different from the WT control group as determined by repeated measures of ANOVA followed by Dunnett's multiple comparison test ($p < 0.001$).

protective role for mast cells in the absence of FcR activation in the early stages of EAE.

Reconstitution of W/W^v mice with Fc γ RIII deficient BMMCs results in a reduced disease severity

Mast cells express both Fc ϵ RI and the low affinity Fc γ RIII. The same reconstitution protocol was used to determine the effect of a Fc γ RIII deficiency in mast cells. Fc γ RIII^{-/-} BMMC-reconstituted mice exhibit a significant reduction in disease severity compared with those reconstituted with WT BMMC ($p < 0.001$) (Fig. 3). This inability of Fc γ RIII-deficient mast cells to restore disease occurs despite the higher levels of reconstitution (as assessed by spleen mast cell numbers) in these animals when compared with wild-type and FcRIIB^{-/-} BMMC recipients (Fig. 1). This observation may reflect a role for these receptors in mast cell turnover and/or site of homing of the mast cell population in vivo. The decrease in disease is intermediary when compared with the disease scores of W/W^v mice suggesting that the Fc ϵ RI may also play a role. Because Fc ϵ RI-deficient mice are not available, we were unable to directly examine the contribution of this specific receptor. Mice reconstituted with Fc γ RIII^{-/-} BMMC also exhibit a remission in disease between days 36 and 43 (Fig. 3 and Table I). This is in contrast to the disease profile of the FcR $\gamma^{-/-}$ BMMC-reconstituted group which, by day 40, exhibit clinical disease comparable to WT-reconstituted mice (Fig. 1 and Table I), suggesting that mast cell activation through different FcRs may have distinct effects on the disease profile.

Table I. Summary of EAE disease parameters from BMMC reconstitution experiments^a

Group	Mean Day of Onset	Mean High Score Days 0–40	Mean High Score Days 36–43	Incidence
WT	14.9 ± 0.4	3.28 ± 0.18	2.72 ± 0.25	9/9
W/W ^v	15.7 ± 1.3	$1.83 \pm 0.46^*$	1.78 ± 0.48	6/9 [†]
W/W ^v + WT BMMC	15.0 ± 0.5	3.28 ± 0.19	2.83 ± 0.29	9/9
W/W ^v + FcR $\gamma^{-/-}$ BMMC	$19.9 \pm 2.2^*$	$2.00 \pm 0.39^\ddagger$	2.00 ± 0.37	6/9 [†]
W/W ^v + FcRIIB ^{-/-} BMMC	14.7 ± 0.5	3.72 ± 0.21	3.39 ± 0.23	9/9
W/W ^v + Fc γ RIII ^{-/-} BMMC	17.2 ± 0.8	2.56 ± 0.51	$0.86 \pm 0.45^*$	7/9

^a Results are expressed as mean \pm SEM.

^{*}, $p < 0.05$, compared to WT as assessed by ANOVA followed by Dunnett's multiple comparison post test.

[†], $p = 0.058$ as calculated by χ^2 contingency table for group incidence.

[‡], $p < 0.1$, compared to WT as assessed by ANOVA followed by Dunnett's multiple comparison post test.

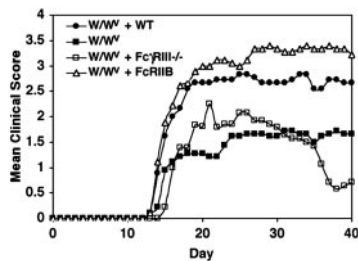


FIGURE 3. Fc γ RIII and FcRIIB play contributory roles in regulating mast cell activation state during EAE. Fc γ RIII^{-/-} or FcRIIB^{-/-} BMMCs (3×10^6) were injected i.v. into W/W^v mice ($n = 9$) and EAE was induced 8 wk later. Clinical scores were recorded daily and the mean daily clinical score for three independent experiments is shown. Scores from all groups were statistically different from the WT control group as determined by repeated measures of ANOVA followed by Dunnett's multiple comparison test ($p < 0.001$).

Reconstitution with mast cells lacking the Fc inhibitory receptor, FcRIIB, results in enhanced disease

FcRIIB is a low affinity IgG receptor that contains an immunoreceptor tyrosine-based inhibition motif. When coligated with an immunoreceptor tyrosine-based activation motif-containing receptor such as Fc γ RIII, inhibition of calcium signaling occurs (for review, see Ref. 13). Mast cells from FcRIIB^{-/-} mice show exaggerated sensitivity to IgG-mediated degranulation and an enhanced passive cutaneous anaphylactic response (13). FcRIIB has also been implicated as a disease-modifying gene in MS patients (20). W/W^v mice reconstituted with mast cells lacking FcRIIB demonstrate significantly enhanced disease scores over the entire course of acute disease compared with mice reconstituted with WT BMMCs ($p < 0.001$, Fig. 3). Thus, engagement of multiple FcRs on mast cells, both activating and inhibitory, contributes to mast cell activation and can modulate disease severity.

MOG-specific Ab production in mast cell-reconstituted mice

We examined both IgG and IgE levels in mice from all groups on day 36–42 postdisease induction. With the exception of the mice reconstituted with Fc γ RIII^{-/-} BMMC, all experimental groups expressed levels of MOG-specific IgG and IgE comparable to immunized WT and W/W^v mice (Fig. 4). Notably, the lower IgG Ab levels observed in all W/W^v mice reconstituted with Fc γ RIII^{-/-} BMMCs correlate with the remission in disease that occurs around day 36 (Fig. 3) in these mice. There were no differences in total IgE production detected in any group of mice (data not shown).

The characterization of FcR-deficient mice has revealed the importance of both activating and inhibitory IgRs in a variety of immune responses and demonstrated their critical role in the pathogenesis of several diseases including autoimmunity (6, 13, 14). Our results confirm that a lack of FcR signaling in the mast cell population alone greatly affects clinical disease. These observations are consistent with the defined role that anti-MOG Abs play in both the human disease and the MOG-induced EAE model.

There are a variety of ways that mast cell FcRs may influence disease course. FcRIIB may act to regulate the levels of IgG through catabolism and reduce the levels of myelin-specific IgG that enter the CNS causing direct damage to the myelin sheath through complement-dependent mechanisms (13). Abdul-Majid et al. (14) speculate that the inability to induce EAE in Fc γ RIII^{-/-} mice is due to inefficient uptake of Ag-Ab complexes leading to deficient Ag processing or presentation during induction of secondary immune responses in the CNS. Whether mast cells can participate in Ag presentation in vivo is still unclear. Most likely, cross-linking of cell-associated FcRs stimulates local FcR⁺ cells,

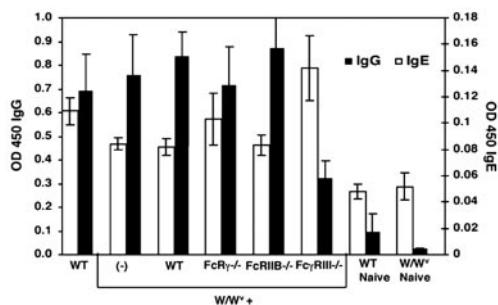


FIGURE 4. Determination of MOG-specific IgG and IgE levels in reconstituted mice. Serum was collected from WT, W/W^v, W/W^v + WT BMMC, W/W^v + Fc γ R γ ^{-/-} BMMC, W/W^v + FcRIIB^{-/-} BMMC, and W/W^v + Fc γ RIII^{-/-} BMMC ($n = 7$) on days 36–42 postdisease induction and WT and W/W^v naive controls ($n = 3$). MOG-specific IgG (■, background 0.035) and MOG-specific IgE (□, background 0.033) were assessed by ELISA. Results are expressed as mean OD₄₅₀ minus background \pm SE of the mean and are the results of duplicate measurements from mice in three independent experiments. W/W^v + Fc γ RIII^{-/-} BMMC MOG-specific IgG titers are statistically different from all groups analyzed except WT naive control ($p < 0.05$). One Fc γ RIII^{-/-} BMMC-reconstituted mouse exhibited elevated MOG-specific IgE (OD = 0.28) that may function to skew the combined data for the group and may not reflect a true elevation in Ab titers.

including mast cells, to release proinflammatory mediators. This may occur both in the CNS as well as in the periphery where the generation of T and B responses and trafficking can be affected.

The activation of mast cells through FcRs occurs only after the autoimmune B cell Ab response is well-established. It is likely that other Ig-independent mechanisms of mast cell activation are also operating in this disease model at the earliest stages of disease induction. Infection-associated inflammation is thought to contribute to the initiation and progression of some autoimmune diseases (21). Activation of mast cells through TLRs may operate in such instances. We speculate that the lack of local activation of mast cells through TLRs during EAE disease induction, a protocol that requires immunization with complete Freund's adjuvant, contributes to the reduced disease severity observed in the W/W^v mice. Current studies are underway to address these issues as well as the questions concerning the location of the activated mast cells and the specific mediators released by these cells that can affect disease pathogenesis and progression.

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