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Fcγ Receptor IIB on Follicular Dendritic Cells Regulates the B Cell Recall Response

Dahui Qin,* Jiuhua Wu,* Kalpit A. Vora,† Jeffrey V. Ravetch,‡ Andras K. Szakal,§ Tim Manser,† and John G. Tew2*

Generation of the B cell recall response appears to involve interaction of Ag, in the form of an immune complex (IC) trapped on follicular dendritic cells (FDCs), with germinal center (GC) B cells. Thus, the expression of receptors on FDC and B cells that interact with ICs could be critical to the induction of an optimal recall response. FDCs in GCs, but not in primary follicles, express high levels of the IgG Fc receptor FcγRIIB. This regulated expression of FcγRIIB on FDC and its relation to recall Ab responses were examined both in vitro and in vivo. Trapping of IC in spleen and lymph nodes of FcγRII−/− mice was significantly reduced compared with that in wild-type controls. Addition of ICs to cultures of Ag-specific T and B cells elicited pronounced Ab responses only in the presence of FDCs. However, FDCs derived from FcγRIIB−/− mice supported only low level Ab production in this situation. Similarly, when FcγRIIIB−/− mice were transplanted with wild-type Ag-specific T and B cells and challenged with specific Ag, the recall responses were significantly depressed compared with those of controls with wild-type FDC. These results substantiate the hypothesis that FcγRIIB expression on FDCs in GCs is important for FDCs to retain ICs and to mediate the conversion of ICs to a highly immunogenic form and for the generation of strong recall responses. The Journal of Immunology, 2000, 164: 6268–6275.

Memory is an intrinsic feature of the adaptive immune response, enabling the animal to mount a rapid and efficient recall response upon re-exposure to Ag. The generation of memory B cells has been proposed to be dependent on the ability of Ag to be trapped as immune complexes (ICs)3 in secondary follicles bearing germinal centers (GCs) (1–5). ICs form almost instantaneously in primed animals upon Ag challenge, and the vast majority is cleared by phagocytic cells (6, 7). However, some ICs are bound by a group of Ag transport cells that carry ICs into follicles where GCs develop. Follicular dendritic cells (FDCs) retain ICs on their surface, and convert some into IC-coated bodies (icososomes) (8, 9), which can be endocytosed by GC B cells. The iccosomal Ag undergoes processing and presentation to T cells, which provide the help necessary for growth and differentiation (10, 11).

Dissection of this pathway in vitro yielded the finding that ICs are poorly immunogenic when added to Ag-specific B and T cell cultures, presumably due to the inhibitory role of FcγRIIB expression on B cells (12–16). This prompted the speculation that one function of the FDC is to convert the poorly immunogenic ICs to a form capable of stimulating potent B cell responses (17). Complement and complement receptors appear to be important for trapping of ICs by FDC (18–20), and several studies have suggested that Fc receptors for IgG are also involved (21–23).

Mice express three FcRs for IgG: FcγRI, FcγRII, and FcγRIII. FcγRI and FcγRIII are associated with the common FcR γ-chain and trigger cellular activation responses upon cross-linking, while FcγRI is a monomeric inhibitory receptor, modulating activation responses when coligated to an immunoreceptor tyrosine-based activation motif (ITAM)-containing receptor such as the B cell receptor (BCR) complex. Myeloid cells express the low affinity FcγRII and FcγRII constitutively and may express the high affinity FcγRI upon activation. B cells exclusively express the low affinity inhibitory FcγRIIB receptor (24).

To begin testing the hypothesis that a major FDC accessory function is to trap and convert ICs into a highly immunogenic form through FcRs, we characterized the expression of these receptors on FDCs. The consequence of this expression was investigated to determine whether the presence of specific FcRs on FDCs is important for generating a B cell recall response in vitro and in vivo. Of the three FcγRs, we found that FcγRIIB is highly expressed on FDCs in secondary follicle GCs. Because this expression pattern of FcγRIIB correlated with the appearance of the secondary response, we studied the functional consequences of this expression. Addition of FDCs derived from wild-type mice to cultures containing Ag-primed T and B cells and Ag-containing ICs resulted in potent Ag-specific IgG responses. In contrast, analogous cultures containing FDCs lacking FcγRIIB (derived from FcγRIIIB−/− mice) or in which the anti-FcγRIIB mAb 2.4G2 was present were markedly depressed in their ability to augment Ag-specific IgG production. The importance of FcγRIIB expression on FDCs was evident in vivo as well. ICs stimulated potent recall responses in vivo only when FcγRIIB was expressed on FDCs; reconstitution of FcγRIIIB−/− mice with Ag-primed T and B cells from wild-type...
mice resulted in animals that responded poorly to IC stimulation. These results suggest that FcyRIIB expression on FDCs is important for an optimal B cell recall response and provides an explanation for why ICs, despite their ability to mediate feedback regulation of B cell activity, are potent stimulators of the recall response in vivo.

**Materials and Methods**

### Animals

Female C57BL or BALB/cByJ mice, 6–8 wk of age, were purchased from The Jackson Laboratory (Bar Harbor, ME). FcγRIIB knockout mice (25) were housed in standard plastic shoebox cages with filter tops. Food and water were supplied ad libitum, and the mice were used between 8–20 wk of age.

### Ag and immunization

Common FcγRII chain −/−, FcγRIIB −/−, and +/+ mice (8–10 wk old, maintained on a mixed C57BL/6 × 129 background) were immunized i.p. (100 μg/mouse) with NP-(4-hydroxy-3-nitrophenyl) acetyl)-chicken γ-globulin (CGG) precipitated in alum for induction of primary responses.

For passive deposition of ICs, groups of mice were injected with rabbit anti-HRP (Sigma, St. Louis, MO) antiserum containing 8 mg of Ig or the same amount of normal rabbit serum. One day later, the mice were injected with 11 μg of purified HRP (Sigma) i.p. in saline. The mice were killed 1 day later, and their spleens were frozen and sectioned as described below.

When OVA was used, wild-type C57 mice were primed by injecting 100–200 μg of OVA (Sigma catalogue no. A5053) precipitated with aluminum potassium sulfate (A7167, Sigma) in the nape of the neck as previously described (17, 26). Secondary immunizations were performed 2 wk later by injection into the front legs, hind feet, and i.p. (20 μg alum Ag/site).

### Spleen sectioning and immunohistochemistry

Spleens were removed at various times after immunization and embedded in Tissue-Tek OCT compound (Fisher Scientific, Bridgewater, NJ) by flash-freezing in a 2-methylbutane bath cooled with liquid N2. Frozen spleens were stored at −80°C until sectioned. Six-micron-thick sections were cut on a cryostat microtome and thaw-mounted onto 0.05% poly-L-spleens were stored at

### FACS analysis

FDCs were isolated from immunized C57 mice as described above. The FDC preparation was split into two aliquots and incubated with FITC-conjugated 2.4G2 Ab (PharMingen) for 30 min in the cold. The aliquots of FDCs were then incubated with biotinylated FDC-M1 or biotinylated iso-

type control IgG for 2 hi nt h e cold. After washing twice, the cells were incubated with streptavidin-conjugated PE for 30 min in the cold. The labeled cells were observed using FACScan. Data for 10,000 cells from each aliquot were collected and analyzed.

### Lymphocyte preparation

Memory lymphocytes were obtained from draining lymph nodes of OVA-immunized mice 1 mo or more after the final OVA challenge. The lymph nodes were bathed in complete DMEM with 10% FBS and ground between two sterile slides. This harsh treatment of the lymph nodes disrupts Ag-bearing FDCs and plasma cells (29). Consequently, very little Ab is produced when these cells are cultured in the absence of added Ag. After disrupting the lymph node and releasing the cells with the slides, the cell suspensions were filtered through nylon mesh to remove stromal tissue.

### Cell cultures

Enriched FDC preparations (1 × 10^6 cells) were added to 3 × 10^5 B and T memory cells in 96-well tissue culture plates (catalogue no. 3595, Costar, Cambridge, MA) containing 200 μl of complete culture medium/well.

The culture medium used in all studies consisted of DMEM supplemented with 10% FCS, 20 mM HEPES, 2 mM glutamine, 50 μg/ml gentamicin, and MEM-nonessential amino acids. The culture cells were incubated at 37°C in a 5% CO2 incubator for 14 days, and medium was harvested on days 7 and 14.

### Ab assay

Culture medium was collected from the lymphocyte cultures every 6–7 days and anti-OVA-specific IgG was measured by means of a solid phase ELISA as described previously (30). Murine IgG specifically bound to OVA was detected using biotinylated goat anti-mouse IgG (Southern Bio-
technology Associates) and AP-labeled streptavidin (Kirkegaard & Perry, Gaithersburg, MD). The levels of anti-OVA in the cultures were determined from standard curves prepared using a standard serum in each well. Using quantitative precipitin analysis (31).

### In vivo IC trapping

The mice used in these studies were given water containing KI (50 μg/ml) for 1 wk to saturate iodine in the thyroid gland. The serum used to from IC was obtained from hyperimmunized mice (primed and boosted twice) containing 1.5 mg/ml anti-OVA IgG. The iodinated HSA-anti-HSA IC was injected s.c. into the feet on the right site (2.5 μg/site). Fourteen days later spleen and draining and nondraining popliteal lymph nodes were harvested. Macrophages trapped, but rapidly degraded, IC made of [125I]HSA-anti-

HSA (t1/2 = 30 min), and the radiolabel was rapidly released in the urine. Autoradiography revealed that after only a few days macrophages in the draining lymphoid tissue had cleared the IC, and persisting radioactivity was exclusively associated with intact HSA on FDCs (21, 32). The amount of IC trapped and retained on FDCs for 2 wk after challenge was determined by radioactivity retained in lymph nodes using a gamma counter. A
small amount of the iodinated HSA was saved and counted at the same time as the lymph nodes and spleens to convert the counts to picograms of retained Ag (21, 32).

**Results**

**FcγRIIB expression on FDCs and up-regulation in secondary follicles**

To determine which of the Fcγ receptors is expressed on FDCs, mice lacking expression of FcγRI and FcγRIII due to the absence of the common FcR γ-chain were exploited. In sections FDCs appear as integral members of a sponge-like network known as the follicular reticulum or FDC-reticulum. These FDC-reticula are formed by interdigitating dendrites from a number of FDCs. Values within this spongework of FDCs are filled with B cells and some T cells. This microenvironment, located in the light zone of secondary follicles, brings together Ag, FDCs, B cells, and Th cells. Spleen sections obtained from nonimmunized γ−/− mice (that lack FcγRI and FcγRIII due to the absence of the common FcR γ-chain) were labeled with anti-CR1 mAb 8C12 or the mAb 2.4G2, which detects both FcγRI and FcγRII. As shown in Fig. 1, the follicular reticulum was easily visualized by anti-CR1 (A) as previously reported (33). In reactive follicles containing GCs (C, arrows) FDCs could be visualized using the mAbs FDC-M2 (B) and FDC-M1 (C). These same regions of the reactive follicles labeled strongly with 2.4G2 (D), which in the γ−/− background only detected FcγRIIB. Importantly, identical labeling results were obtained when using immunized wild-type mice (data not shown).

To confirm that FDC-M1 and 2.4G2 were labeling the same cells, we used a two-color histological analysis of FDC-reticula (Fig. 2). Adjacent parallel sections were labeled using 2.4G2 (Fig. 2A, red labeling), FDC-M1 (Fig. 2B, green labeling), and then both labels on the same section (Fig. 2C). The overlapping of the green and red gave the yellow FDC-reticulum shown in Fig. 2C. The double labeling was further established by testing FDC in a single-cell suspension (confirmed by microscopy) using immunized mice as donors and staining using FDC-M1 and 2.4G2. Nearly 30% of the cells in the FDC-enriched preparation labeled with FDC-M1 and FACS analysis revealed that almost all these cells also labeled with 2.4G2.

In contrast with Fig. 1, Fig. 3 presents representative results from a similar histological analysis of the spleens of mice with a targeted inactivation of the FcγRIIB gene. While the A panels show that the primary follicular reticulum as defined by 8C12 labeling is well developed in FcγRIIB−/− spleen, 2.4G2 labeling of the follicular reticulum (C panels) is absent in GCs (arrows), and FDC-M1 labeling (B panels) is reduced. Collectively, these data define the FcγR on FDCs in GCs as FcγRIIB, consistent with previous suggestions (23, 34), and indicate that the level of expression of this receptor is highly induced on FDCs in this microenvironment.

To further substantiate the latter point, an identical histological analysis was performed on spleens obtained from young unimmunized wild-type mice housed in specific pathogen-free conditions. The spleens of such mice contained mainly primary follicles lacking GCs. Fig. 4 presents representative data from this experiment. The primary follicular reticulum is easily visualized with 8C12 labeling (A), but reticular labeling in the primary follicle is not observed using FDC-M1 or 2.4G2.

**Absence of FcγRIIB reduces immune complex trapping in the follicle**

While passively formed ICs strongly label the splenic follicular reticulum in wild-type mice (Fig. 5A), these same ICs give rise to reduced labeling of this reticulum in FcγRIIB−/− mice (Fig. 5B). A semiquantitative analysis of IC deposition in these splenic sections indicated that IC trapping was reduced severalfold in the FcγRIIB−/− mice. These results were confirmed and extended using radiolabeled ICs to quantify the amount of IC trapping in both splenic and lymph node (LN) follicles (Table I). Retained IC persisted in the spleen and draining LNs, in contrast to nondraining LNs. The amount of Ag retained in FcγRIIB−/− mice was reduced to about 25% of normal in the spleen, which is compatible with the histochemistry, and to 50% of normal in the draining LNs.

**FcγRIIB in the conversion of IC into potent immunogens**

To directly test the hypothesis that FDCs are able to convert a poorly immunogenic IC into a highly immunogenic form, OVA-containing ICs were added to OVA-primed T and B cells derived
from normal mice, and the level of secretion of OVA-specific IgG Ab was measured. In the absence of FDCs only picogram levels of anti-OVA were induced at any dose of IC used (Fig. 6A). In contrast, addition of FDCs from normal mice to these cultures elicited substantial levels of OVA-specific IgG over a wide dose range of IC.

Because the FDC preparation used in Fig. 6 was enriched but not pure, depletion studies were conducted to exclude the possibility that the adjuvant-like activity was mediated by other cells. The FDC-specific Ab FDC-M1 was used to generate an FDC-depleted fraction. As shown in Fig. 7B, depletion of most FDCs resulted in a 90% reduction of the stimulatory response observed, confirming that FDCs in the in vitro culture of memory T and B cells were responsible for the stimulatory effect of IC. Because the data presented above show that expression of the FDC-M1 epitope and FcγRIIB on FDCs is highly correlated, FDCs expressing high levels of FcγRIIB would have been preferentially depleted in this experiment.

In vivo, FDCs may engage ICs through FcγRIIB, CR1/2, or a combination of these receptors. To determine whether the FcγRIIB on FDCs has the ability to convert the IC into a potent immunogen in vitro, FDCs were prepared from FcγRIIB<sup>−/−</sup> or FcγRIIB<sup>+/−</sup> mice and added to cultures of OVA-primed T and B cells. Deficiency of FcγRIIB on the FDCs dramatically reduced the stimulatory effect of these cells on IgG Ab production (Fig. 7A), establishing that this receptor is important for enabling the FDCs to convert the IC into a potent immunogen in vitro. However, the addition of FDC from the FcγRIIB<sup>−/−</sup> mice to the memory cells plus OVA-anti-OVA increased anti-OVA production from <10
ng/ml to >500 ng/ml, indicating that some adjuvant activity persisted in the absence of FcγRIIB. Because the development or regulation of FDC activity may be perturbed in FcγRIIB−/− mice (see below), analogous experiments were performed by blocking FcγRIIB (with soluble 2.4G2) in cultures containing FDCs derived from wild-type mice. Results similar to those achieved with FDCs isolated from FcγRIIB-deficient mice were obtained (Fig. 7B).

These in vitro results suggested that FcγRIIB mediate a specific function on FDCs by enabling ICs to stimulate a B cell recall response in vivo. To dissect the in vivo role of FcγRIIB on FDCs, LN lymphocytes were obtained from OVA-immune mice and were injected into irradiated wild-type and FcγRIIB−/− mice. Two weeks later, serum Ab levels were determined and compared. The specific anti-OVA levels in wild-type mice increased to 6272 mg/ml (a robust response), while the response in FcγRIIB−/− mice remained low (<10% of that level; p < 0.01). These in vivo results support the in vitro studies presented above and suggest that FcγRIIB functions specifically to enable the retained IC to stimulate B cells in the secondary follicular reaction.

Discussion
Ag in the form of ICs has been proposed to be essential to the formation of the GC (2, 5) and the generation of the secondary response (2, 17). Two classes of molecules expressed in the follicle have the capacity to bind ICs: the complement receptors for C3d
Nevertheless, transfer of CR1/2-expressing B cells into a study when wild-type B memory cells bearing FcγRIIB, but trapping of Ag by FDCs was substantially reduced in the presence of OVA-anti-OVA IC (no FDCs); all produced <10 ng of anti-OVA IgG/ml. B, FDCs were obtained from wild-type mice, and then a portion was cultured with 2.4G2 (10 μg/ml) to block FcγRII on FDCs. Note that blocking with 2.4G2 markedly inhibited the ability of FDCs to convert IC into an effective immunogen. The differences between the 2.4G2-treated and control groups were statistically significant (p < 0.05).

FIGURE 6. Ability of FDCs to convert poorly immunogenic IC into an effective immunogen for secondary responses in vitro. A, Memory T and B lymphocytes (Ly) were cultured with various amounts of OVA-anti-OVA IC formed near equivalence in the presence or the absence of FDCs from normal mice (5 × 10^5 Ly/well with or without 1 × 10^6 FDC). B, FDCs from the LN of normal mice or the same number of the cells contaminating the FDC preparation (after depleting FDC) were added to memory T and B cells taken from OVA-immune mice. Ten nanograms of OVA in an OVA-anti-OVA IC near equivalence was used as the immunogen. Cultures were washed on day 7 to remove any free IC, and anti-OVA was measured on day 14. Controls included normal memory T and B lymphocytes plus IC, and FDCs alone, and all produced <10 ng of anti-OVA/ml (data not shown). These data are typical of three experiments of this type.

FIGURE 7. FDC-FcγRIIB is important for FDCs to convert IC into an effective immunogen. FDCs were cultured with memory T and B cells taken from OVA-immune mice in the presence of OVA-anti-OVA IC and compared for their ability to convert the IC into an effective immunogen. The IC (50 ng of OVA) was formed near equivalence. Cultures were washed on day 7 to remove any soluble IC, and anti-OVA IgG was measured on day 14. A, FDCs were obtained from FcγRIIB−/− and wild-type mice. In one replicate of this study, FDCs were enumerated using the CR1,2-positive and B220-negative population. The FcγRIIB−/− FDCs identified in this fashion also failed to stimulate a significant Ab response even when FDC number was doubled. Controls included normal memory T and B lymphocytes cultured alone, FDCs alone (FCγRIIB−/− and FcγRIIB+/-/−), and memory T and B cells plus OVA-anti-OVA IC (no FDCs); all produced <10 ng of anti-OVA IgG/ml. B, FDCs were obtained from wild-type mice, and then a portion was cultured with 2.4G2 (10 μg/ml) to block FcγRII on FDCs. Note that blocking with 2.4G2 markedly inhibited the ability of FDCs to convert IC into an effective immunogen. The differences between the 2.4G2-treated and control groups were statistically significant (p < 0.05).

and C4b (CR1/2) (18–20) and the Fc receptors for IgG ICs (FcγRII) (22, 23, 35). These receptors are expressed on both B cells and FDCs; however, given our results and those of others, their function on each cell type is apparently quite different. Expression of CR1/2 on B cells is essential for their stimulation as well as sur-

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* Mice were injected with HSA-anti-HSA immune complexes (2.5 μg 125I-labeled HSA and 5 μg anti-HSA) in right hind foot. Right popliteal lymph nodes were draining lymph nodes (draining PLN) and left popliteal lymph nodes (PLN) were nondraining LN (nondraining PLN). Fourteen days after injecting IC, the spleens and lymph nodes were collected and 125I-labeled IC trapped on FDC were counted. The spleens and LN were weighed and picograms of HSA per milligram of tissue were calculated.

Data are presented as mean ± SE from seven FcγRII−/− mice and five FcγRII−/− mice.

immune response and leads to the generation of memory cells (36, 37, 42).

FcγRIIB expression on B cells can result in the generation of an inhibitory signal, triggered by its coligation to the BCR by ICs (12–16). Given the general inhibitory function of FcγRIIB on hematopoietic cells (12–16), it was unexpected that the capacity of the FDCs to convert ICs into a form capable of stimulating B cell activation was dramatically enhanced by FcγRIIB expression on FDC. Strikingly, our results indicate that FcγRIIB functions as a positive regulator of the adjuvant property of FDCs. Interestingly, a balanced effect was obtained in FcγRIIB−/− mice, where B cell activation and proliferation would not be down-regulated by FcγRIIB, but trapping of Ag by FDCs was substantially reduced (Fig. 5 and Table I). The net outcome of the opposing effects was minimal, as the immune response in the FcγRIIB−/− mice was essentially normal (25). This normal response stands in marked contrast with the subnormal recall response obtained in the present study when wild-type B memory cells bearing FcγRIIB were used in combination with FDC from FcγRIIB knockout mice (Figs. 7A and 8). These observations suggest that FcγRIIB-bearing FDC are critical for recall responses derived from wild-type FcγRIIB-bearing B cells, and this concept is consistent with results from models where the lack of FDC is associated with a lack of germinal centers and the recall Igs IgG and IgA (43–45). FDC deficiencies occur in animals lacking lymphotoxin or TNF, or receptors for these cytokines (33, 43).
In this regard, and in contrast to its function on B cells, FcγRIIB expressed on FDCs may play a role, allowing more efficient trapping and retention of IgG containing ICs in follicles than could be achieved with CRs alone. Indeed, Fig. 5 and Table I show that IC trapping in follicles is reduced in FcγRIIB−/− mice. Although additional experiments will be required to test this idea, several of our observations argue against this simple interpretation. First, histological analysis of the splenic follicular reticulum in FcγRIIB-deficient mice showed that FDC-M1 expression was significantly reduced (Fig. 3), indicating that the absence of FcγRIIB precludes as yet undefined steps in either FDC maturation or activation. Second, the in vitro adjuvant effect of purified FDCs from normal mice on T cell-dependent B cell activation by ICs is readily blocked by soluble 2.4G2, a treatment that represses the inhibitory function of FcγRIIB on B cells (14–16). Finally, FDCs from FcγRIIB-deficient mice are unable to augment potent IC-mediated B cell recall responses in vitro in a complement-deficient system, whereas FcγRIIB expression on FDCs influences whether an IC is stimulatory or inhibitory to a B cell.

References


