Human Rheumatoid Factor Production Is Dependent on CD40 Signaling and Autoantigen

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High-affinity pathologic rheumatoid factor (RF) B cells occur in autoimmune diseases such as rheumatoid arthritis, but are deleted in healthy individuals. The reasons for the survival and differentiation of these autoreactive B cells in rheumatoid arthritis are not known. Previous studies in mice transgenic for a human IgM RF have shown that peripheral encounter with soluble human IgG leads to deletion of high-affinity RF B cells; however, deletion can be prevented when concomitant T cell help is provided. This study aimed to further discern the minimal factors necessary not only for the in vivo survival of RF B cells, but also for their differentiation into Ab-secreting cells. The combination of MHC class II-reactive T cells and Ag induced the production of RF in human IgM RF transgenic mice, while either stimulus alone was ineffective. Neutralizing Abs against CD40 ligand (CD40L), but not against IL-4 or IL-15, abrogated IgM-RF production. Moreover, blockade of CD40L-CD40 allowed IgG to delete the RF precursor cells. Most importantly, activating Abs to CD40 could substitute entirely for T cell help in promoting the survival of RF precursors and in stimulating RF synthesis in T cell deficient animals. The data indicate that CD40 signaling alone can prevent deletion of RF B cells by Ag and in the presence of IgG is sufficient to trigger RF synthesis. The results suggest that selective induction of apoptosis in high-affinity RF B cells may be achieved by blockade of CD40L-CD40 interaction. The Journal of Immunology, 1999, 163: 3116–3122.

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toantibodies specific for the Fc portion of IgG are known as rheumatoid factors (RFs) because of their common occurrence in patients with rheumatoid arthritis (RA). RFs also can be detected in up to 30% of normal individuals, but these RFs are of low affinity and low titer and do not have any pathological significance. In contrast, high-affinity RFs found in RA patients can form immune complexes, activate complement, and augment local inflammatory reactions (1, 2).

Most autoreactive B cells are deleted or rendered anergic at the immature stage in the bone marrow, as has been demonstrated conclusively in studies of transgenic mice (3–7). The autoreactive B cells that escape tolerization in the bone marrow are eliminated in the periphery (8–10). Nevertheless, high-affinity RF B cells in RA accumulate in the joints. The RFs expressed by these B cells show signs of somatic mutation, affinity maturation, and class switching, indicating a local failure of peripheral tolerance mechanisms (11–14).

Our previous studies in mice transgenic for a human IgM RF have shown that peripheral encounter with soluble IgG leads to tolerance induction in high-affinity RF B cells via deletion (15, 16). However, when T cell help is provided either simultaneously or within a few days before deletion, binding of human IgG (hIgG) to the B cell receptor leads instead to activation and secretion of the higher-affinity RF (17).

The effect of surface Ig cross-linking has been studied extensively in vitro using B cell lymphomas (18). Death of those cells can be induced by anti-Ig treatment (19–25). Similarly, hypercross-linking of the B cell receptor in mature B cells results in apoptosis in vitro (26) and in vivo after administration of anti-IgD Abs (27). Comparable to our findings in the RF transgenic mice, activation-induced cell death of B cells can be prevented by Th cells (28). Depending on the system, the T cell help can be mediated by the interaction of CD40 ligand (CD40L; CD154) with CD40 and/or by secreted ILs, especially IL-4 (24–26, 28–30).

There is no evidence in RA for the existence of IgG-specific T cells that prevent apoptosis and promote RF synthesis. However, the rheumatoid synovium provides an environment rich in both pro- and antiinflammatory cytokines (31). Furthermore, recent studies have demonstrated that nurse-like cells obtained from bone marrow and synovium of patients with RA can promote survival of human B cells in culture by direct cell contact involving adhesion molecules like CD106 and CD157 (32). Hence, it is important to determine what Ag nonspecific factors can substitute for T cell help and foster the survival and differentiation of high-affinity RF B cells in vivo.

In the present experiments, we have examined the requirements for the survival and differentiation of B cells with human RF activity. The data indicate that the combination of MHC class II-reactive T cells and soluble Ig is sufficient to induce RF synthesis. Dissection of potential T cell-derived signals responsible for aborting B cell death has shown that, although IL-4 and IL-15 extend RF B cell viability in vitro, they do not decisively influence either the survival of RF B cells in vivo or the secretion of RF. In contrast, interference with CD40 signaling allows the deletion of RF B cells by IgG, even in the presence of MHC class II-reactive T
cells providing Th factors. Furthermore, an activating anti-CD40 Ab can entirely substitute for T cell help and is sufficient to facilitate the survival of IgG-stimulated RF B cells and to promote RF secretion in the complete absence of T cells. Because CD40L is constitutively expressed by synovial fluid T cells in RA, and also may be detected on activated platelets and endothelial cells (33–35), the data provide an explanation for the survival and matura-
tion of pathogenic RF B cells in inflamed joints and suggest that CD40L blockade may facilitate the deletion of newly emerging RF B cells by Ag.

Materials and Methods

Mice

All mice were housed in the animal facility of the University of California at San Diego and were free of parasitic infectious agents as assessed by sentinel screening. C57BL/6, C57BL/6 bm12, and B6 RAG1−/− mice were purchased from Jackson Laboratories (Bar Harbor, ME). The AB29 trans-
genic mice expressing the rearranged Ig H and L chain genes encoding the mutated, pathogenic human Les RF have been previously described (36). The line R29 was generated by repeated backcrossing of AB29 mice to T and B lymphocyte-deficient B6 RAG1−/− mice (16). Positive progeny of transgenic matings were identified by measuring the level of human IgM RF in the serum of 4- to 5-wk-old mice by ELISA as previously described (36).

Ag

Normal hlgG (Miles Laboratories, Elkart, IN) was purified using a protein A-Sepharose column. Before in vivo injection, aggregates were removed by ultracentrifugation as described previously (15). All preparations of hlgG were tested for endotoxin by the Limulus amebocyte assay (Associ-
ates of Cape Cod, Woods Hole, MA) and were shown to have levels of <0.01 U/mg. Deletion of RF B cells was induced by i.p. injection of 2 mg hlgG, as described previously (15).

Abs

Surface staining of spleen cells was performed using the following Abs: rabbit anti-human IgM-FITC or -biotin (Jackson ImmunoResearch, West Groove, PA), mouse anti-human κ-PE, goat anti-mouse κ-FITC, goat anti-
mouse IgM-PE, rat anti-mouse Thy-1-FITC, and rat anti-mouse B220-PE (PharMingen, San Diego, CA). Samples were analyzed on a FACScalcium flow cytometer, and data were processed using CellQuest (Becton Dick-
inson, San Jose, CA) and FlowJo (Treestar, Stanford, CA) analysis pro-
grams. The following purified Abs were used for in vivo injections: the activating anti-CD40 Ab 3/23 (PharMingen) and the anti-CD154 Ab MR1 (PharMingen), all at 200 μg per i.p. injection. Neutralizing anti-IL-15 (R&D Systems, Minneapolis, MN) and anti-IL-4 Ab (PharMingen) were injected i.p. at 250 μg/mouse.

In vitro IL treatment and detection of apoptosis

Spleen cells of AB29 and R29 RF transgenic mice, treated in vivo as indicated, were incubated for 48 h in vitro at 107 cells/ml in RPMI 1640 medium supplemented with 10% FBS, penicillin and streptomycin, 2 mM l-glutamine, and 5 × 10−3 M 2-ME (complete medium), in some cases supplemented with recombinant mouse IL-4 (10 ng/ml; R&D Systems), recombinant human IL-15 (20 ng/ml; Sigma, St. Louis, MO), and recom-
inant mouse IL-13 (30 ng/ml; R&D Systems). Apoptosis was assessed using the dye DiOC6 as previously reported (37). Briefly, spleen cells were harvested and stained with a biotinylated anti-human IgM Ab followed by streptavidin-allophycocyanin (PharMingen). Cells were then incubated with propidium iodide (PI, 50 μg/ml) and DiOC6 (10ng/ml) and analyzed by flow cytometry. The percentages of hlgM-positive cells staining high with DiOC6 and negative for PI reflected the viable RF B cell population. Absolute numbers of viable RF B cells were determined by counting in vitro cultured spleen cells with trypan blue and adjusting the numbers according to the percentages of hlgM-positive cells as assessed by flow cytometry of the same cultures.

In vivo IL treatment and injection of alloreactive spleen cells

Recombinant mouse IL-4 (PharMingen) and recombinant human IL-15 (Sigma) were used for in vivo i.p. injections. Three i.p. injections of 200 ng of each cytokine were administered on days 0, 1, and 3 after injection of hlgG. C57BL/6 bm12 spleen cells were used as a source of T cell help, as previously described (17). Then, 2 × 107 bm12 spleen cells were injected i.v. on the same day as injection of hlgG.

In vivo RF suppression is dependent on Ag. AB29 mice were left untreated (control) or injected with either hlgG, C57BL/6 bm12 spleen cells (bm12 spleen), or both. After 7 days, the mice were sacrificed and percentages of RF B cells, expressing hlgM, compared with total spleen cells were determined by flow cytometry (A). Levels of IgM RF in the serum of the same mice on day 7 after the various treatments were deter-

![FIGURE 1.](http://www.jimmunol.org/2007/04/3017/fig1.png)

FIGURE 1. In vivo RF synthesis is dependent on Ag. AB29 mice were left untreated (control) or injected with either hlgG, C57BL/6 bm12 spleen cells (bm12 spleen), or both. After 7 days, the mice were sacrificed and percentages of RF B cells, expressing hlgM, compared with total spleen cells were determined by flow cytometry (A). Levels of IgM RF in the serum of the same mice on day 7 after the various treatments were determined by ELISA and compared with a standard containing a known amount of IgM RF, as described in Materials and Methods (B). Mean values ±SD are shown for three mice per group. Asterisks indicate sig-

ificant differences to the mice injected with hlgG alone (p < 0.01 by Student’s two-tailed t test). One representative experiment of four is shown.

Collection of immune cells

Spleens were teased into single-cell suspensions in complete medium. Ly-
sis of erythrocytes was performed by incubation in ammonium chloride buffer (ACK lysis buffer).

ELISA

IgM RF levels were determined by ELISA as described (36). Briefly, 96-
well ELISA plates were coated overnight with hlgG (Cappell, Durham, NC) and blocked with 1% BSA in PBS. IgM RF levels in serum samples were detected with biotinylated anti-hlgM Abs (Accurate Chemicals & Scientific, Westbury, NY) followed by streptavidin-HRP (Zymed, San Fran-
cisco, CA) and peroxidase substrate (Kirkegaard & Perry Laboratories, Gaithersburg, MD). Absorbance was measured at 450 nm and compared with a standard curve of binding by purified Les IgM RF.

Results

In vivo RF synthesis requires autantigen

Exposure of RF B cells to soluble IgG in vivo leads to their de-

letion (15). However, concomitant transfer of MHC class II-reac-
tive T cells, provided by injecting C57BL/6 bm12 T lymphocytes, mediated survival of RF B cells (Fig. 1A) and was able to stimulate RF secretion (17). Unmanipulated AB29 transgenic mice had very low levels of circulating IgM RF (<20 μg/ml), although 30–40% of the B cells expressed the transgene. MHC class II-reactive T lymphocytes have been shown to induce autoantibody production in the absence of additional stimuli (38, 39). However, transfer of C57BL/6 bm12 T lymphocytes to AB29 mice did not increase RF
levels unless the animals were coinjected with hIgG. In the latter case, serum RF levels rose significantly within 7 days (Fig. 1B).

The injection of 2 mg hIgG alone did not augment RF levels, but instead led to the deletion of the RF B cells by 7 days, as previously reported (15).

**IL-4, IL-15, and anti-CD40 signaling increase survival of hIgG-exposed RF B cells in vitro**

Activating anti-CD40 Abs and IL-4 have been shown to inhibit apoptosis of murine and human B lymphoma cells induced by surface IgM receptor cross-linking (24, 26, 28–30). To assess the effect of these factors on the survival of RF B cells taken from IgG-injected AB29 mice, we cultured splenocytes with activating anti-CD40 Ab (3/23) or with IL-4, IL-13, or IL-15. Staining with DiOC6 was used to determine the amount of apoptotic cells. DiOC6 accumulation inside cells has been demonstrated to depend on the mitochondrial membrane potential and correlates with apoptosis (37). Viable cells stained highly positive for DiOC6, and percentages of viable RF B cells were determined by cell-surface staining with anti-hIgM Ab (Fig. 2). Both anti-CD40 Ab and IL-4 promoted RF B cell survival, compared with cultures with medium alone. The percentages of viable cells determined at 48 h after the initiation of the cultures (Fig. 3A), as well as the corresponding absolute numbers of surviving cells (Fig. 3B), were significantly increased by the addition of IL-4 or anti-CD40 Ab. IL-15, which in contrast to IL-4 has been detected in the synovial fluids of RA patients (31, 40–42), also increased the survival of RF B cells to some extent, although not reaching statistically significant differences in cell numbers after 48 h in vitro culture. IL-13, which has also been demonstrated to be present in synovial fluid of RA patients (43), had no effect on survival of RF B cells.

**Rescue of RF B cells by MHC class II-reactive T cells can be abrogated by anti-CD40L blockade in vivo**

To assess the importance of soluble factors on the in vivo survival of IgG exposed RF B cells, we injected 200 ng IL-4 or IL-15 on days 0, 1, and 3, after hIgG administration, and measured percentages of RF B cells in the spleens of the treated mice on day 5. Intraperitoneal injections of 50 ng of IL-4 have been reported to protect mice from autoimmune encephalomyelitis and if given repeatedly over a prolonged period of time to prevent autoimmune diabetes in nonobese diabetic mice (44, 45). However, these treatments did not inhibit the deletion of RF B cells. Neutralizing Abs against IL-4 and IL-15 also had no significant influence on the number of RF B cells in the spleens of AB29 mice injected with C57BL/6 bm12 splenic cells, in contrast to the survival-promoting effects of the two cytokines in vitro (data not shown). However, the administration of an anti-CD40L Ab together with hIgG and C57BL/6 bm12 splenic cells completely blocked the rescue of RF B cells from apoptosis (Fig. 4A). The percentages of nontransgenic mouse κ-bearing B cells did not differ significantly between treatment groups, indicating a specific effect on the transgenic RF B cells.
cells (Fig. 4B). Anti-CD40L treatment correspondingly inhibited IgM RF secretion. Serum levels of IgM RF in anti-CD40L-treated mice were indistinguishable from untreated control mice, whereas injection with Ag and C57BL/6 bm12 spleen cells resulted in an increase of serum levels up to 100-fold (Fig. 4C).

The fact that the Ab was able to block the rescue of RF B cells, despite an ongoing MHC class II alloresponse, demonstrates a crucial role for CD40 signaling for the in vivo rescue of RF B cells from deletion induced by IgG.

Activating anti-CD40 Ab can substitute for T cell help to induce RF synthesis in vivo

Stimulation of CD40 either by anti-CD40 Abs or soluble CD40L in vitro has been reported to induce B cell proliferation (46, 47) and Ig secretion (48–51) and prevent surface Ig-mediated apoptosis (24–26, 28). To determine whether CD40 signaling is the paramount costimulatory signal necessary to prevent deletion of RF B cells after encounter with Ag, and to induce RF synthesis, we used T cell-deficient AB29 mice generated by repeatedly backcrossing AB29 mice generated by repeatedly backcrossing AB29 mice onto a RAG-deficient background (R29 strain) (16). In R29 mice, we were able to study the influence of a monoclonal activating anti-CD40 Ab on hIgG-induced deletion in the absence of T cells. R29 mice were injected with hIgG in the presence or absence of anti-CD40 Ab, and the percentages of RF B cells were assessed 6 days later by FACS. As reported previously, IgG induced equivalent deletion of RF B cells in the R29 and AB29 strains (16). However, the deletion could be blocked completely by anti-CD40 Ab (Fig. 5A), which instead stimulated RF synthesis (Fig. 5B). Significantly, serum IgM RF levels rose in mice injected with Ag and anti-CD40 Abs, but not in mice injected with anti-CD40 alone.

**FIGURE 4.** Rescue of RF B cells in vivo from Ag-induced cell death can be blocked by anti-CD40L Abs. AB29 mice were either injected with hlgG or combinations of hlgG and C57BL/6 bm12 spleen cells or hlgG, C57BL/6 bm12 spleen cells, and anti-CD40L Ab. Untreated animals served as controls. Seven days later, the mice were sacrificed, and percentages of RF B cells compared with total spleen cells were determined by flow cytometry (A). Percentages of nontransgenic mκ-expressing B cells are shown (B). IgM RF levels in the serum of the same mice were determined on day 7 after treatment by ELISA (C). The data represent mean values of three mice per group. Asterisks indicate a significant difference to mice that were injected with hlgG, C57BL/6 bm12 spleen cells, and anti-CD40L Ab (p < 0.004 by Student’s two-tailed t test). One representative experiment of three is shown.

**FIGURE 5.** CD40 signaling can rescue RF B cells from Ag-induced cell death. R29 mice were treated as indicated; uninjected mice served as controls. Six days later, the mice were sacrificed, and percentages of RF B cells in respect to total spleen cells were determined by flow cytometry (A). Levels of IgM RF in the serum of the same animals on day 6 were assessed by ELISA (B). One representative experiment with three mice per group is shown; the experiment was repeated twice with similar results. Asterisks indicate a significant difference to mice injected with hlgG only (p < 0.01 by Student’s two-tailed t test).
Use of the RAG-deficient background allowed interference by Th factors, produced nonspecifically by mouse T cells, to be ruled out. Therefore, the data demonstrate that signaling through CD40 alone can substitute for T cell help in preventing deletion of RF B cells by IgG and in inducing RF synthesis.

Discussion

RF B cells are specific for the Fc part of IgG. The healthy immune system usually rids itself of high-affinity autoreactive B cells. In normal individuals, nonpathogenic, low-affinity RF B cells are abundant in lymph nodes, but high-affinity RFs are not detectable. However, in RA patients, high-affinity pathogenic RF B cells, including IgG RF-secreting cells, accumulate within the inflamed synovium. There they may contribute to the pathogenesis of joint inflammation by the formation of immune complexes and complement fixation (2). The reasons why these cells persist in RA patients, but not in normal people, are still not known.

Studies of B cell tolerance in B cell transgenic mice revealed that autoreactive B cells are silenced by either clonal deletion or induction of anergy, depending on the nature of the autoantigen. This silencing occurs similarly in B cells specific for hen egg lysozyme (HEL), H-2 molecules, DNA, erythrocytes, and mouse IgG (3–7, 10). In contrast to these transgenic mouse models, the human RF transgenic B cells in our mice do not react with endogenous mouse Ags because they are specific for hIgG. However, these high-affinity RF B cells are deleted following injection with soluble hIgG (15). Concomitant provision of T cell help in the form of allosereactive cells interfered with deletion of RF B cells and instead lead to activation and RF secretion (17), comparable to the findings in the HEL/anti-HEL transgenic system (52). Although the RF B cells are not autoreactive in our transgenic mice, nevertheless they allow one to study the factors involved in activation vs tolerization of these B cells in the periphery. Because RF B cells found in patients are not anergic but rather activated and producing high-affinity RF, it is conceivable that their phenotype is comparable to the transgenic RF B cells after in vivo injection of hIgG in the presence of costimulation.

Our present studies aimed to dissect the specific signals responsible for interference with tolerance induction in RF transgenic mice, to gain insights into the potential mechanisms for RF B cell persistence and activation in RA, and to identify the minimal stimuli required for RF synthesis.

Factors that inhibit B cell apoptosis, induced by surface IgM cross-linking, include IL-4 and CD40/CD40L interaction (24, 26, 28–30). Activated T cells can deliver both signals. Several studies have demonstrated B cell proliferation (46, 47), Ig secretion (48–51), and prevention of apoptosis (24–26, 28) by stimulation of CD40 using anti-CD40 Abs or soluble CD40L in vitro. CD40 signaling in conjunction with IL-4 and IL-5 has also been shown to stimulate proliferation of tolerant autoreactive B cells and IgM production (53). In the non tolerant HEL-reactive B cells, survival and clonal proliferation is controlled by a combination of signals from CD40L and Fls ligand (54). Our model system differs in that CD40 and IL-4 or anti-CD40L Ab can substitute for T cell help in preventing deletion of RF B cells by IgG and in inducing RF synthesis.

The survival of RF B cells in vitro was extended by coculture with IL-4 or anti-CD40 Ab (Fig. 3). Whereas among the cytokines tested, IL-4 was the most potent survival factor, IL-15 also had a positive effect. This in vitro finding was intriguing, because high levels of IL-15 have been found in synovial fluids of RA patients, and a role for this cytokine in the pathogenesis of RA has been proposed (40–42). However, in contrast to the in vitro studies, injection of these ILs in vivo did not prevent IgG-induced RF B cell deletion, although this was potentially due to the short half-life of the cytokines in the animal. To rule out this possibility, the effects of anti-IL Abs also were tested. The administration of anti-IL-4 or anti-IL-15 Abs did not substantially inhibit the RF production induced by the combination of MHC class II-reactive T cells and IgG (data not shown). Under the same conditions, injection of a blocking anti-CD40L Ab abrogated T cell help (Fig. 4). These results indicate that the signal delivered by interaction of CD40L on activated T cells with CD40 on RF B cells is decisive not only for the survival of the cells after interaction with IgG but also for the synthesis of RF.

The crucial role of CD40 signaling for RF production, independent of specific T cell help, was confirmed by using RAG-deficient IgM RF transgenic mice (R29), which lack mature T and B cells, with the exception of the B cells expressing the rearranged human RF. In these mice, deletion of RF B cells by hIgG exposure could be completely blocked by an anti-CD40 Ab (Fig. 5). Moreover, anti-CD40 Ab was as effective as T cells in stimulating RF synthesis. Therefore, in the transgenic system, CD40 signaling is apparently all that is required to prevent deletion of RF B cells after IgG exposure and represents the critical costimulatory signal required for RF synthesis. This is to our knowledge the first report showing B cell activation and Ig secretion in vivo by CD40 stimulation in the complete absence of T cells.

The fact that serum RF levels did not change in R29 mice injected solely with anti-CD40 Abs, nor in AB29 mice injected with MHC class II-reactive T cells alone, demonstrated that Ag is required for differentiation of RF B cells into Ab-secreting cells. Provision of strong T cell help alone is not sufficient to drive RF production. Thus, the selectivity of autoantibody production during graft vs host reactions may depend upon the availability of free extracellular autoantigen at sites of T-B interaction (38, 39). Although high-affinity RF B cells are exposed to IgG both in the circulation and in the synovium, the concentration of IgG aggregates is higher within the joints. However, it is the provision of costimulatory signals that is the critical factor in determining whether the encounter with IgG leads to deletion or expansion of RF B cells.

Previous studies from several laboratories have shown that the RF genes in the inflamed synovium of RA patients have multiple replacement mutations and have undergone affinity maturation (1, 11, 12, 14). The data are consistent with an Ag and T cell driven activation-mutation-selection mechanism. However, IgG-reactive T cells have never been found in the synovium, and T cell derived cytokines (IL-2 and IL-4) are barely detectable. Our data indicate that CD40 cross-linking is a sufficient second signal to induce RF synthesis in vivo, even in T cell-deficient mice. CD40L is detectable on T cells from the rheumatoid synovium (33), and also may be expressed by activated platelets (35), endothelial cells (34), and even by some B cells (55–57). In this regard, mixed synovocytes have been reported to support terminal differentiation of B cells into plasma cells, but whether or not they can express CD40L is not clear (58). Collectively, the data suggest that the rheumatoid
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The concept that autoantibody production can be reduced by blockade of CD40L-CD40 signaling is additionally supported by studies in lupus-prone mice demonstrating reduced IgG autoantibody levels after anti-CD40L Ab treatment (60). If our results can be extrapolated to the human, one would predict that high-dose CD40L blocking Ab would promote the deletion of newly emerging autoreactive B cells that are concomitantly exposed to high-dose Ag. Moreover, the kinetics of disappearance of RF B cells might be a surrogate marker for the deletion of other autoantibody-producing cells that contribute to joint inflammation.

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References


