Secreted IgM Enhances B Cell Receptor Signaling and Promotes Splenic but Impairs Peritoneal B Cell Survival

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B cell survival has a central role in maintaining immune responses to foreign organisms while curbing autoimmunity. In this study, we show that mature B cell survival is impaired and B cell turnover is accelerated in the spleen of mice lacking secreted IgM. Although in vitro responses to BCR cross-linking were normal, there was a marked reduction in basal ERK and global tyrosine phosphorylation in splenic B cells from serum IgM-deficient mice, suggesting diminished interaction with cognate Ag in vivo. The provision of BAFF either in vitro or in vivo reversed the increase in B cell apoptosis, demonstrating that other survival signals can compensate for the loss of secreted IgM in the spleen. In striking contrast to the splenic compartment, peritoneal B cell survival was enhanced in secreted IgM-deficient mice, despite a similar reduction in basal BCR signaling compared with wild type mice. These results suggest that secreted IgM acts as an adjuvant, boosting BCR signals to maintain survival and maintenance of mature splenic B cells while increasing B cell apoptosis in the peritoneum. BAFF administration mitigated the consequences of secreted IgM deficiency on B cell survival in the spleen but not in the peritoneum. This work provides new insight into the regulation of B cell signaling and homeostasis in different peripheral compartments by secreted IgM. The Journal of Immunology, 2010, 184: 3386–3393.

Peripheral B cell development and survival are dynamic, interactive processes that occur in different microenvironments and provide the platform for rapid and robust B cell responses to infections as well as pathologic autoimmunity. They are orchestrated through signals received by the BCR as well as B cell-activating factor of the TNF family (BAFF) (1–5). Although there is evidence for constitutive BCR signaling in B cell development, self-ligand interactions play a key role in orchestrating the B cell repertoire through the modulation of BCR signals (6–8). The majority of this evidence arises from studies using mice with a monoclonal BCR, but there are also some indirect data from polyclonal mice through analysis of BCR repertoires to support Ag-driven selection (9). In addition to this putative positive selection of B cells by autoantigen into different compartments, B cells bearing strongly self-reactive BCRs are tolerated through a number of mechanisms to avoid production of pathogenic autoantibodies (10). The critical role of B cell survival and maintenance in the defense against pathogens and tolerance to self-Ags underscores the importance of understanding these mechanisms.

Mature B cells in the spleen can be divided into two main subsets. Follicular (FO) B cells are the predominant precursors of germinal center reactions and form the bulk of mature B cells, whereas marginal zone (MZ) B cells are poised to respond rapidly to Ags filtered from the blood stream (11, 12). Low-affinity interactions with self-Ag are considered important for the selection of B cells into these different compartments. Alterations in several molecules that positively or negatively regulate BCR signaling result in alterations in the number of MZ and/or FO B cells (13, 14). Within a permissible range, weaker signals promote MZ B cell formation, whereas stronger BCR signals favor an FO B cell fate. However, using a monoclonal BCR transgenic mouse, MZ B cells were shown to form preferentially in the context of low-affinity Ag interaction, suggesting that FO B cells are a default pathway in which B cells have not encountered Ag (8). B1 cells make up a substantial proportion of B cells present in peritoneal and pleural cavities and display an Ab repertoire skewed toward reactivity to self-Ags (15–17). High BCR signal strength seems to favor a peritoneal B1 phenotype (5).

We previously showed that mice lacking serum IgM (Sμ−) have increased numbers of MZ B cells and reduced FO B cells, abnormalities that are completely reversed by the exogenous administration of IgM over a 2-wk period (18). These changes could be due to altered BCR signaling as a consequence of differences in autoantigen encounter. IgM was shown to have an important role in clearing apoptotic cells through its interaction with C1q (19, 20). Therefore, the effect of secreted IgM could be to reduce self-Ag availability for cognate B cell interaction by promoting clearance. In this scenario, BCR signals would be reduced by natural IgM, thereby reducing Ag load. Indeed, the failure to adequately remove apoptotic cells could account for the increased tendency of mice deficient in serum IgM to develop autoimmunity (21, 22). An alternative, essentially opposing, scenario is that natural IgM potentiates BCR signals by acting as an adjuvant to boost the immunogenicity of soluble Ag. IgM immune complexes are known to be highly immunogenic in the response to foreign Ags (23).

In this paper, we demonstrate that splenic B cell survival is impaired in the absence of natural IgM, associated with a diminution in basal BCR signaling. In the peritoneum, where basal BCR signals are significantly greater than in the spleen of wild type (WT) mice, B cell survival is enhanced by the loss of serum IgM. These data led us to propose that in the splenic microenvironment, IgM boosts BCR signaling, thereby promoting B cell survival. In contrast, in the peritoneum, where self-Ag is more abundant, secreted IgM drives BCR signaling to levels that increase B cell apoptosis. These ob-

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Abbreviations used in this paper: 7-AAD, 7-aminoactinomycin D; BAFF, B cell-activating factor of the TNF family; BCMA, B cell maturation Ag; BR3, BAFF-R3; FO, follicular; MZ, marginal zone; nil, no stimulation; pERK, phosphorylated ERK; Sμ−, serum IgM deficient; TACI, transmembrane activating and calcium modulator and cyclophilin ligand interactor; WT, wild type.

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peritoneal cells in medium with or without 10 μg/ml anti-IgM (Fab’2), BAFF (2 μg/ml; Chemicon International, Temecula, CA) was added to some cultures. The cells were pulsed with 1 μCi [3H]thymidine (GE Healthcare) for the final 12 h of culture to assess proliferation or stained with 7-AAD and Ki-67 to assess cell death and proliferation. Purities of splenic B cells were >90% as assessed by flow cytometry.

BAFF administration in vivo and BAFF quantification by ELISA

Mice

Sµ− mice (24) on a C57BL/6 background were bred and maintained in specific pathogen-free facilities under Home Office (U.K.) guidelines. Litter-matched controls were used for all experiments. Mice were used between 8 and 14 wk of age. All animal studies were conducted in accordance with protocols approved by the Home Office.

Flow cytometry

FO and MZ splenic B cell subsets were identified using anti–B220-APC or B220-PerCy7; anti–CD23-PE; anti–CD21-FITC, or anti–CD23-biotin and anti–CD21-PE. Peritoneal B1 and B2 cells were identified using B220-PerCy7, CD23-PE, and CD5-FITC or CD5-biotin. All Abs were purchased from BD Biosciences (San Jose, CA), unless otherwise stated. Cells stained with biotinylated Abs were incubated for 20 min with streptavidin-APC or streptavidin-Cy7, CD23-PE, and CD5-FITC or CD5-biotin. All Abs were purchased from BD Biosciences (San Jose, CA), unless otherwise stated. Cells stained with biotinylated Abs were incubated for 20 min with streptavidin-APC or streptavidin-Cy7. Cell staining was analyzed using the BD LSR and FlowJo software. Binding of BAFF to the surface of B cells was determined using anti–BAFF-PE (R&D Systems, Minneapolis, MN). The expression of BAFF receptors on splenic and peritoneal B cells was determined using anti-mouse B cell maturation Ag (BCMA) (R&D Systems), anti-CD21 transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) (eBioscience, San Diego, CA), and anti–mouse BAFF-R3 (BR3) (eBioscience). 7-aminoactinomycin D (7-AAD) (Molecular Probes, Eugene, OR) staining was performed following the manufacturer’s instructions after surface staining on unfixed cells and read within 1 h of staining. Cell proliferation was determined by staining for intracellular Ki-67 (BD Biosciences), using eBioscience fixation and permeabilization staining buffers.

Phosphoflow staining was performed by incubating 0.5 × 10^6 splenic or peritoneal cells in medium with or without 10 μg/ml anti-IgM F(ab’2); (Jackson ImmunoResearch Laboratories, West Grove, PA) for 10 min at 37°C. Cells were then fixed in PhosFlow Fix Buffer I (BD Biosciences) for 10 min at 37°C and surface stained with anti–CD19-PECy7 (BD Biosciences) in PhosFlow Perm/Wash Buffer I (BD Biosciences). Cells were incubated for 10 min at room temperature, pelleted, and incubated with anti-phosphorylated ERK (pY204; Santa Cruz Biotechnology, Santa Cruz, CA), anti-phosphorylated Syk-PE (pY348; BD Biosciences), anti–Lck-PE (Santa Cruz Biotechnology), anti–Syk-FITC (BD Biosciences), or anti–ERK-488 (Santa Cruz Biotechnology) for 30 min in the dark at room temperature. Cells were washed and analyzed on the LSR using FlowJo software. Mean fluorescence intensity after stimulation was divided by the mean fluorescence intensity without stimulation to calculate the fold induction.

B cell isolation and cell culture

B cells were isolated from the spleens of mice by negative selection using CD43 microbeads (Miltenyi Biotec, Auburn, CA). B cells were left untreated or were stimulated for 72 h with 10 μg/ml anti-IgM (Fab’2), BAFF (2 μg/ml; Chemicon International, Temecula, CA) was added to some cultures. The cells were pulsed with 1 μCi [3H]thymidine (GE Healthcare) for the final 12 h of culture to assess proliferation or stained with 7-AAD and Ki-67 to assess cell death and proliferation. Purities of splenic B cells were >90% as assessed by flow cytometry.

Immunoblots

Sµ− mice were treated daily with 5 μg BAFF (Chemicon International) i.v. for 5 d. Control WT and Sµ− mice were injected with PBS. All mice were culled on day 6, and splenic and peritoneal B cells were isolated. BAFF levels in the serum from WT and Sµ− mice were quantified by ELISA (R&D Systems), following the manufacturer’s instructions.

Replacement of IgM

Sµ− mice were injected i.p. on six occasions at regular intervals over a 2-wk period with 200 μg/mouse polyclonal murine IgM (Rockland, Gilbertsville, PA).

Immunoblots

Spleen B cells were taken ex vivo or treated with medium or 10 μg/ml anti-IgM (Fab’2) for 5 and 30 min at 37°C. Cells were then pelleted and treated with lysis buffer containing 1% Triton X-100, 150 mM NaCl, 10 mM Tris-HCl, 1 mM EDTA, 1 mM EGTA, 0.5% Igepal, H2O, and phosphatase and protease inhibitors (Pierce, Rockford, IL). Protein concentration was calculated using a bichinchoninic acid kit (Pierce Chemical, Rockford, IL); 10 μg each sample was mixed with 4× reducing buffer and boiled for 5 min. Proteins were separated by SDS-PAGE (10%), transferred to nitrocellulose membranes, and visualized with specific Abs using the ECL detection system (GE Healthcare, Piscataway, NJ); anti-GAPDH (Millipore, Bedford, MA)
MA), anti-phosphorylated ERK (pERK) and -ERK (Santa Cruz Biotechnology), anti-phosphotyrosine (Upstate Biotechnology, Lake Placid, NY), and anti-Bim (BD Pharmingen).

Statistics
Where appropriate, a one-way ANOVA or the Student t test was performed. Where statistical significance was found, p values are included.

Results
Secreted IgM promotes splenic but reduces peritoneal B cell survival
We previously showed alterations in splenic and peritoneal B cell subsets in the absence of secreted IgM (18). To explore the underlying mechanisms that link secreted IgM to B cell homeostasis, B cell survival was assessed in the spleen and peritoneal cavity of Sm−/− mice. Although the lack of secreted IgM did not alter the total number of splenic B cells (WT: 3.5 × 10^7 ± 0.35; Sm−/−: 3.1 × 10^7 ± 0.18), there was significantly more apoptosis in FO and MZ splenic B cell subsets in Sm−/− mice as assessed by 7-AAD (Fig. 1A). These changes were not observed in all splenic B cell subsets because the percentage of newly formed (T1) B cells undergoing apoptosis was similar in WT and Sm−/− mice. An increase in the expression of proapoptotic survival factor Bim in splenic B cells accompanied the reduction in B cell survival in Sm−/− mice (Fig. 1B). In striking contrast, peritoneal B cell survival was enhanced in the B1 and B2 subsets in the absence of secreted IgM (Fig. 1C). The relative reduction in B1a cell death was most marked (68%) compared with B1b (38%) and B2 (54.9%) cells. I.v. administration of a polyclonal anti-IgM 14-d period completely reversed the changes in B cell death found in the spleen and partially reversed the changes in B cell death in the peritoneum of Sm−/− mice (Fig. 1D, 1E).

Because BAFF is critical to B cell survival, we determined its presence on B cells but found no differences between WT and Sm−/− mice (Fig. 2A). In addition, serum levels of BAFF were similar in WT and Sm−/− mice (Fig. 2B). However, bound BAFF was substantially greater in B cells from the peritoneal compartment compared with the spleen (p = 0.0001; Fig. 2A). The increased binding of BAFF to peritoneal B cells compared with their splenic counterparts could be explained by differences in expression of one or more of the three BAFF receptors, BR3 and BCMA expression was comparable in B cells from the spleen and peritoneum of WT and Sm−/− mice, although BCMA expression was generally low (Fig. 2C, 2D). However, there was significantly more TACI expression on peritoneal B cells compared with splenic B cells (Fig. 2E), as previously reported (25, 26), which could account for the increased BAFF binding in that compartment.

Increased proliferation of splenic but not peritoneal B cells from Sm−/− mice
Because the lack of secreted IgM resulted in an increased rate of B cell death in the spleen but no reduction in B cell numbers, we next investigated alterations in B cell turnover. Ki-67 revealed greater splenic, but not peritoneal, B cell proliferation in the absence of secreted IgM (Fig. 3A, 3B). Note, increased cell proliferation was restricted to the B cell population within the spleen; there was no significant difference in Ki-67 staining in the B220 population (Fig. 3A). In a similar fashion to the preservation of T1 B cell survival, the rapid proliferation of T1 B cells was unaffected in Sm−/− mice. WT and Sm−/− mice were fed BrdU over a 14-d period, and the percentage of BrdU+ splenic B cells was determined by flow cytometry. BrdU incorporation revealed increased turnover in splenic B cells from Sm−/− mice compared with WT mice (Fig. 3C). Furthermore, an increase in BrdU incorporation was observed in the FO and MZ B cell subsets (Fig. 3C). These changes in BrdU incorporation in Sm−/− mice, although significant and in agreement with the Ki-67 proliferation data, were not as marked as that seen for Ki-67. In agreement with the Ki-67 staining, there was no significant difference in the low levels of BrdU incorporation in the peritoneum in mice lacking secreted IgM (Fig. 3C). The transfer of murine polyclonal IgM into Sm−/− mice completely restored splenic B cell proliferation to the level observed in WT mice (Fig. 3D). As expected, the transfer of IgM had little effect on the low B cell proliferation in the peritoneum of Sm−/− mice (Fig. 3E).

Secreted IgM enhances BCR signaling in the spleen and peritoneum
B cell survival and proliferation are governed, in part, by signals received through the BCR. Therefore, we determined basal BCR signaling and in vitro responses to anti-IgM (ab′)2 in Sm−/− mice.

FIGURE 2. Differential binding of BAFF to splenic and peritoneal B cells. A. Percentage of splenic and peritoneal B cells binding BAFF in WT and Sm−/− mice. B. BAFF concentration in serum from WT and Sm−/− mice. Expression of BR3 (C), BCMA (D), and TACI (E) on splenic and peritoneal B cells from WT (black bars) and Sm−/− mice (white bars); mean ± SEM are shown. Dashed line represents the level of isotype control. Representative curves illustrating expression on WT splenic B cells (dotted line) and WT peritoneal B cells (solid line); shaded curve represents isotype control.
Global basal tyrosine phosphorylation of splenic B cells was diminished in the absence of secreted IgM, although tyrosine phosphorylation increased normally in response to BCR cross-linking (Fig. 4A). Similarly, a reduction in basal ERK phosphorylation in Sm2m mice, but a normal pERK response to BCR stimulation, was found by Western blotting and flow cytometry (Fig. 4B). Basal Syk phosphorylation in splenic B cells was below the level of detection of the flow cytometry-based assay, but equivalent induction of pSyk in response to BCR cross-linking was found in Sm2m and WT mice (Fig. 4B). Collectively, these results suggest diminished BCR engagement in the absence of secreted IgM in vivo, despite the fact that B cells from Sm2m mice are capable of mounting a normal BCR-triggered response in vitro.

It was reported that peritoneal B cells have higher basal levels of tyrosine phosphorylation and Lck expression, which are thought to be linked to increased Ag engagement in that compartment (27). In WT mice, phosphoflow analysis confirmed increased pERK, Lck, and pSyk in peritoneal B cells compared with B cells from the spleen (Fig. 4C, 4D), with comparable levels of total ERK and Syk (Fig. 4E). However, in mice lacking secreted IgM, peritoneal B cells had significantly diminished basal levels of Lck, pSyk, and pERK compared with peritoneal B cells from WT mice (Fig. 4D), suggesting that, similar to the splenic microenvironment, secreted IgM boosts BCR signals in the peritoneum. There was no difference in total ERK or Syk between WT and Sm2m mice (Fig. 4E).

**BAFF rescues splenic B cells from apoptosis in the absence of secreted IgM**

WT and Sm2m splenic B cells proliferated in vitro after stimulation with anti-IgM F(ab')2 (Fig. 5A). However, 7-AAD staining revealed impaired survival of B cells from Sm2m mice compared with WT mice after a 72-h culture, with or without BCR stimulation (Fig. 5A). Because BAFF is known to be an important survival factor for mature splenic B cells, we investigated whether it could reverse the increase in cell death in Sm2m mice. The addition of BAFF to B cells from Sm2m mice reduced B cell death to similar levels observed in B cells from WT mice and enhanced the proliferative response of B cells, such that B cells from WT and Sm2m mice responded equally after stimulation with anti-IgM F(ab')2 (Fig. 5B). This rescue of B cell death was also observed following daily BAFF administered i.v. to Sm2m mice (Fig. 5C). Moreover, splenic B cell proliferation was reduced in Sm2m mice following BAFF treatment (Fig. 5C). The restoration of B cell survival induced by BAFF was accompanied by a shift in the ratio of MZ to FO B cells toward that seen in WT mice (Fig. 5D). BAFF treatments led to a modest increase in the number of splenic B cells (3.3 × 10^7 ± 1.1 in Sm2m mice compared with 4.1 × 10^7 ± 0.6 in BAFF-treated Sm2m mice). Although BAFF had a substantial effect on splenic B cell homeostasis in Sm2m mice, there did not seem to be any changes in peritoneal B cell survival or proliferation (data not shown). Given that the percentage of B cells that bound BAFF in the peritoneum was >90% (Fig. 2A), it was not unexpected that BAFF injections did not influence B cell apoptosis in this compartment.
compartment. Collectively, these findings demonstrate that BAFF can partly compensate for the loss of secreted IgM in the spleen.

**Discussion**

In this study, we showed that secreted IgM enhances mature splenic B cell survival associated with a reduction in B cell proliferation. In addition, we demonstrated that BCR signals are enhanced by secreted IgM, which presumably reflects the formation and binding of IgM–Ag immune complexes. Although IgM is known to be important in the clearance of apoptotic cells, which would lead to a reduction in available Ag and, therefore, diminished BCR engagement, our data suggest that this property of IgM is not relevant in B cell survival and homeostasis. Indeed, the opposite seems to be true (i.e., secreted IgM boosts BCR signals). Although the lack of secreted IgM led to a similar reduction in basal BCR signaling in the spleen and peritoneum, in the latter compartment, the absence of IgM led to enhanced, rather than diminished, B cell survival. The alterations in both compartments were reversed by the exogenous administration of serum IgM over a 2-wk period, although only B cell homeostasis in the splenic compartment was completely restored to normal. It is possible that a longer period of administration of serum IgM would be required to increase B cell apoptosis to normal levels in the peritoneum because of the low rate of B cell turnover.

The increased basal BCR signaling in peritoneal B cells could account for the contrasting fate of B cells in the two niches in the absence of secreted IgM. The differing Ag environment in the spleen and peritoneum modulates B cell phenotype and function (27). The reduced survival of WT B cells in the peritoneum compared with spleen has been attributed to their anergic phenotype secondary to increased Ag engagement (28). Our observations support a model (Fig. 6) in which peritoneal B cells are susceptible to apoptosis due to high BCR signaling, whereas splenic BCR signals are close to the minimum required for survival. Moreover, the BCR signaling
threshold necessary for splenic B cell survival can be reduced by BAFF (29). This model fits our observations that the reduction in BCR signaling due to a lack of secreted IgM would enhance peritoneal, but reduce splenic, B cell survival (Fig. 6). Syk and ERK can also be activated through BCR-independent signals, raising the possibility that non-BCR signals could be modified in the absence of secreted IgM.

We propose that the ability of secreted IgM to enhance BCR signals is due to the increased immunogenicity of IgM–Ag complexes compared with soluble Ag. It has long been established that IgM can promote immune responses to soluble Ag and that mice deficient in secreted IgM have an impaired immune response (24, 30, 31). This property of IgM is likely to be linked to its capacity to trigger complement activation (32). Moreover, the delivery of Ag to lymphoid follicles is dependent upon complement, and B cells can capture cognate Ag through complement receptors and their BCR (33). MZ B cells seem to be particularly adept at transporting IgM immune complexes into follicles, a process that relies on the presence of complement (23, 34). All of these studies examined the immune response to a single exogenous Ag, which is more easily defined than the role of autoantigens in the development and maintenance of the naive B cell pool. Notwithstanding this limitation, and extrapolating from these observations on immunized mice, our data suggest that IgM immune complexes, which would include complement components, could have a similar role in the maintenance of mature B cells in Ag-naive mice, perhaps by directing autoantigens into primary follicles.

The impairment of survival in Sμ− mice was confined to the mature B cell subsets; the rapidly proliferating newly formed splenic T1 B cells were unaffected. This is consistent with the notion that the requirement for ligand in the generation of signals promoting B cell positive selection only applies to the maintenance of the mature B cell pool and not to newly formed B cells (35, 36). There is persuasive evidence that ligand-independent BCR signaling is sufficient to drive B cell development through to the mature B cell pool (6). However, a BCR engineered so that it is unable to bind to Ag can support B cell development through the CD23+ stage, but these mature B cells have impaired survival (37). Therefore, only mature B cells rely on natural IgM to boost BCR signals and promote their survival.

Mature B cell maintenance and survival are influenced by signals received through the BCR, as well as by the B cell survival factor BAFF, which prevents B cell apoptosis via Bim inhibition (3, 38). The provision of BAFF in vitro or in vivo protected splenic B cells from undergoing apoptosis secondary to the lack of secreted IgM. Furthermore, the abnormal ratio of MZ to FO B cells in Sμ− mice was partly reversed by BAFF administration, suggesting that B cell survival and entry into different splenic compartments are closely linked. Although the overexpression of BAFF leads to increased MZ B cells (39, 40), alternate selection effects may dominate in the context of diminished BCR signals. This reinforces the notion of cross-talk between signals received from the BCR and BR3 and their interdependence for B cell survival and selection (29). In contrast, the administration of BAFF had no effect on peritoneal B cells, consistent with their already high levels of BAFF engagement. The high BAFF binding by peritoneal B cells may be attributed to increased expression of TACI on B cells in that compartment compared with the spleen (25, 26). TACI is essential for B cell responses to T cell–independent Ags and efficient plasma cell generation, and it may play a role in the production of anti-nuclear Ags (41–43). Indeed, the increased BAFF binding in the peritoneum, as noted by the authors and other investigators (44), could partly account for the differential
B cell fate in this environment. Moreover, it is tempting to speculate that the high level of BAFF in the peritoneum could increase the BCR signaling threshold required for B cell deletion, thus affording protection to B cells from increased levels of cognate Ag. Limiting the availability of BAFF impairs the survival of autoantigen-binding B cells (44), which are known to be overrepresented in the peritoneum (15, 16). Competition for Ag could also play a role in the maintenance of B cell subsets and the elimination of autoreactive B cells in the peritoneum (45). A reduction in BCR signaling due to the absence of secreted IgM would favor the persistence of autoreactive B cell clones through reduced negative selection. Thus, the increased levels of BAFF in the peritoneal cavity, coupled with a reduction in peritoneal B cell apoptosis, could account for the increased levels of autoantibodies present in Sm mice (22).

Intriguingly, the reduction in peritoneal B1a cell death was more marked compared with the other peritoneal B cell subsets, which might explain their relative expansion in the absence of IgM (24, 31). It is unclear why B1a cells are affected more than other peritoneal B cells. The explanation could be linked to the observation that the increased availability of cognate Ag in the peritoneum is thought to influence the phenotype of B1 cells. Thus, transfer of splenic B cells into the peritoneal environment leads to splenic B cells acquiring a B1 cell-like phenotype (46, 47). However, all B cells in the peritoneum display unique features separate from their splenic counterparts, very likely due to environmental influences. Indeed, peritoneal B2 cells show some characteristics of B1b cells (48). This could account for the contrasting impact of secreted IgM deficiency on the survival of B2 cells in the peritoneum compared with FO B cells in the spleen.

In conclusion, we propose that secreted IgM acts as an adjuvant in the spleen and peritoneum to enhance the interaction between Ag and BCR, thereby regulating B cell survival. However, the consequences of a lack of secreted IgM are very different in the two compartments, illustrating the complex interaction between environment and B cell homeostasis. In addition, our observations support a role for BAFF in modulating secreted IgM- and ligand-dependent interactions in the maintenance of the splenic B cell pool.

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Disclosures
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