Antigen-Driven Induction of Polyreactive IgM during Intracellular Bacterial Infection

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Polyreactivity is well known as a property of natural IgM produced by B-1 cells. We demonstrate that polyreactive IgM is also generated during infection of mice with *Ehrlichia muris*, a tick-borne intracellular bacterial pathogen. The polyreactive IgM bound self and foreign Ags, including single-stranded and double-stranded DNA, insulin, thyroglobulin, LPS, influenza virus, and *Borrelia burgdorferi*. Production of polyreactive IgM during infection was Ag driven, not due to polyclonal B cell activation, as the majority of polyreactive IgM recognized ehrlichial Ag(s), including an immunodominant outer membrane protein. Monoclonal polyreactive IgM derived from T cell-independent spleen plasmablasts, which was germline-encoded, also bound cytoplasmic and nuclear Ags in HEp-2 cells. Polyreactive IgM protected immunocompromised mice against lethal bacterial challenge infection. Serum from human ehrlichiosis patients also contained polyreactive and self-reactive IgM. We propose that polyreactivity increases IgM efficacy during infection but may also exacerbate or mollify the response to foreign and self Ags. *The Journal of Immunology*, 2012, 189: 000–000.

Polyreactivity, the ability of an Ig to bind two or more unrelated Ags, is a characteristic of natural Abs produced by B-1 cells. Polyreactive natural Abs, commonly germline or near-germline encoded, exhibit structural flexibility, which allows for more promiscuous binding to Ags (1–3). Polyreactive IgM is thought to aid in the neutralization of pathogens prior to the development of high-affinity, Ag-specific Abs (1, 4, 5). Polyreactivity is characterized by low-affinity interactions with Ag, although IgM polyvalency allows for higher-avidity interactions. Although polyreactive Ab is found in normal serum, it is often bound to self Ag, from which it must be dissociated to be detected (2, 6).

Polyreactivity, as a property of an Ig molecule, is distinguished here from apparent polyreactivity, a property of polyclonal serum. The latter may occur via non-Ag-specific Ab production, often in response to stimulation of B cells by parasitic membrane proteins, or bacterial LPS and/or CpG motifs (7–11). Polyreactivity is not a unique property of IgM, as it has been observed in IgG induced by some viral infections and in IgA secreted by intestinal plasmablasts (12–14). Although acute viral infections can drive the production of polyreactive IgM, such Abs have not been reported to be induced by bacterial infection (15).

Various models have been proposed to explain how natural and immune polyreactive Abs function. Polyreactivity may serve to increase the overall affinity of an Ab by enhancing binding to a pathogen during instances where homotypic bivalent binding is not possible (described as heteroligation); such a model may explain why Ab elicited during HIV-1 infection is broadly polyreactive (12). Alternately, naturally occurring polyreactive IgM may serve to facilitate the clearance of apoptotic cells and/or autoantigen-containing immune complexes, thereby contributing to immune surveillance (16–19).

Our previous studies described the induction of T cell-independent (TI) IgM by a large population of CD11c-expressing spleen plasmablasts during infection with the intracellular bacterium *Ehrlichia muris* (20). The plasmablasts are responsible for the generation of nearly all the IgM produced in the spleen during acute infection, and IgM is sufficient for both short- and long-term protection against ehrlichial infection (20, 21). In the current study, we demonstrate that the IgM produced by the spleen plasmablasts is polyreactive, a characteristic that has not been described for infection-induced IgM. We demonstrate that the polyreactive IgM is pathogen-specific but also binds a number of unrelated self and foreign Ags and is produced during human ehrlichiosis. We propose that polyreactive IgM serves to facilitate host defense but also may modify host responses to self. These studies highlight a novel aspect of the host humoral response that may be characteristic of many bacterial infections that induce strong TI immunity.

**Materials and Methods**

**Animals**

The mice used in the studies were obtained from The Jackson Laboratory (Bar Harbor, ME) or were bred under microisolator conditions at the Wadsworth Center Animal Care Facility in accordance with institutional guidelines for animal welfare. Sex-matched C57BL/6, RAG1-deficient (B6.129S7-Rag1<sup>tm1Mmg</sup>/J), MHC class II-deficient (B6.129S2-H2<sup>Dab1-Ea</sup>/J), and CD1d-deficient (B6.C129S-Cd1<sup>tmGor</sup>/J) mice 6–12 wk of age were used for the studies. As institutional guidelines do not allow the use of death as an endpoint in animal studies, mice were humanely sacrificed when judged to be moribund.

**Infections and immunizations**

Mice were infected i.p. with 5 × 10<sup>4</sup> copies of *E. muris*, as previously described (22). Mice were administered purified recombinant outer membrane protein-19 (OMP-19) in alum (Imject; Thermo Scientific, Rockford, IL), prepared according to the manufacturer’s instructions.

**Quantification of bacteria**

Bacterial copy number was determined by probe-based PCR using primers and probes for the *E. muris* dsb gene, as described previously (23).
PCR products were analyzed with an Applied Biosystems 7500 Fast Real-Time PCR System (Applied Biosystems, Foster City, CA). The copy number of the E. muris dsb gene was determined using known quantities of dsb ampiclon as standards. We have made the simplifying assumption that bacterial copy number and numbers of viable bacteria were equivalent in our experimental model.

ELISA
Microtiter plates (Immulon; VWR) were adsorbed overnight with 10 μg/ml recombinant E. muris or Ehrlichia chaffeensis OMP-19 or the following Ags: 10 μg/ml single-stranded bovine DNA, 5 μg/ml porcine insulin, 10 μg/ml thyroglobulin, 10 μg/ml LPS from Salmonella enterica (all from Sigma); 10 μg/ml dsDNA (EMD Biosciences); heat-inactivated influenza virus (A/PR/8; generously provided by Dr. L. Haynes, Trudeau Institute, Saranac Lake, NY); or Borrelia burgdorferi (a gift from Dr. T. Sellati, Albany Medical College, Albany, NY). The microtiter plates were blocked with 20% FBS in PBS. Primary Abs were detected with alkaline phosphatase-conjugated anti-IgM or anti-IgG secondary Abs (Southern Biotech). The use of human serum samples was approved by the Wadsworth Center Institutional Review Board.

Analysis of human samples
Sera from human ehrlichiosis patients or normal human controls were generously provided by Dr. S. Wong of the Wadsworth Center and by Dr. H. Prince of Focus Diagnostics. The use of human serum samples was approved by the Wadsworth Center Institutional Review Board.

HEp-2 immunofluorescence assays
Human sera were diluted 1:80 and applied to HEp-2 cell-coated microscope slides (Bio-Rad, Hercules, CA) according to the manufacturer’s instructions. Serum Abs were detected with biotin-conjugated goat anti-human IgM or IgG followed by a streptavidin–Alexa Fluor 488 conjugate (Invitrogen, Eugene, OR). For hybridomas, supernatants were applied to microscope slides, and Ab binding was detected with biotin-conjugated goat anti-mouse IgM. Cells were visualized using a Zeiss Axioskop2 epifluorescence microscope equipped with a Hamamatsu ORCA-ER camera and analyzed using OpenLab software.

Results
Ehrlichial infection induces a TI polyreactive IgM response
Our previous studies have revealed an important role for TI IgM in mediating short- and long-term immunity during ehrlichial infection. IgM is produced during infection by a population of extracellular splenic CD11c-expressing plasmablasts (20), among which 10–20% recognized an immunodominant Ag, OMP-19. IgM production was highest during acute infection but was maintained for at least as long as 366 d, at least in part by a population of bone marrow IgM-producing plasmablasts/plasma cells (21). In the course of these studies, we observed that the IgM elicited during E. muris infection was highly polyreactive. The IgM bound double- and single-stranded DNA, insulin, and thyroglobulin (Fig. 1A–D). These self Abs are commonly used to assay polyreactivity because their distinct structures reduce the likelihood that binding is due to cross-reactivity [i.e., binding to related epitopes on different Ags (14, 25)]. Polyreactive IgM was not detected in normal sera from C57BL/6 mice. Polyreactive IgM was observed beginning on days 7–9 postinfection, was maximal on day 14, and declined thereafter, reaching modest titers that were maintained for at least 396 d postinfection. We also observed reactivity of immune sera to whole influenza virus A/PR/8 and Borrelia burgdorferi, pathogens to which the mice had not been previously exposed (Fig. 1E, 1F). Self- and foreign-reactive IgM-secreting B cells were detected in the spleens of infected mice, indicating that the splenic CD11c-positive plasmablast cells we have described previously were partly or wholly responsible for the generation of the polyreactive IgM (Fig. 1G, 1H) (20). Polyreactivity was not detected as a property of IgG at any point during infection (data not shown).

Our previous study demonstrated that the IgM response induced during ehrlichial infection occurred independently of CD4 T cells (20). Consistent with these findings, we detected self-reactive IgM during infection of MHC class II- and CD1d-deficient mice (26), indicating that neither CD4 T cells nor CD1d-restricted cells (i.e., NKT cells) were required for the generation of polyreactive IgM (Fig. 2A, 2B).

Polyreactivity is associated with OMP-19 specificity
Although our data suggested that the infection-induced IgM was polyreactive, we could not discount the possibility that E. muris stimulated the production of non-polyreactive IgM of unrelated specificities via polyclonal B cell activation or by BCR ligation by a B cell superantigen (27). To address whether polyreactivity was a property of monoclonal IgM, we generated B cell hybridomas from spleen B cells of infected mice on day 14 postinfection. We first tested whether the hybridomas produced pathogen-specific IgM using a dot immunoblot assay to detect IgM binding to intact bacteria. Of 329 IgM-secreting hybridomas isolated, nearly 85%
produced ehrlichial-specific Abs (Fig. 3A, 3B). These findings were confirmed by immunofluorescence microscopy of ehrlichia-infected splenocytes (data not shown). Among all IgM-secreting hybridomas, 30% (96 of 329) bound OMP-19 (Fig. 3C); these data are reflective of our published data, which reported a similar frequency of OMP-19–specific IgM-producing cells in the spleen, as detected by ELISPOT assay (20). The non-OMP-19–reactive ehrlichia-specific hybridomas produced IgM that bound to yet unidentified Ag(s) that were not detected by Western analysis, indicating that the Abs bound conformational epitopes, or non-protein Ags. Because the majority of monoclonal IgM was pathogen specific, our data indicate that nonspecific B cell activation does not play a major role in the generation of the polyreactive IgM.

To test whether the monoclonal IgM exhibited polyreactivity, the hybridoma supernatants were tested for reactivity to the panel of self and foreign Ags used in the studies described in Fig. 1. More than 20% of the OMP-19–specific IgM was highly polyreactive (i.e., they bound to three to five unrelated Ags), and >75% of the OMP-19–specific IgM bound at least one unrelated Ag (Fig. 3C). In contrast, among the non-OMP-19–specific IgM, only 36.5% exhibited polyreactivity; moreover, none of the non-OMP-19–specific IgM bound all five Ags examined, and only a few (3%) were highly polyreactive (Fig. 3C). In contrast, IgM produced by hybridomas generated from uninfected mice were largely non-polyreactive, as only 2.9% (2 of 68) of the Abs bound two unrelated Ags (Fig. 3C).

Because polyreactivity was correlated with OMP-19 specificity, we addressed whether polyreactivity was an intrinsic property of OMP-19–specific IgM. Immunization with recombinant OMP-19 failed to induce polyreactive IgM (Fig. 3D), indicating that polyreactivity was not a consequence of OMP-19 recognition per se. These data provide additional support for the conclusion that polyreactive IgM was elicited during infection by pathogen-specific B cells and was not generated by natural Ab-producing cells.

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FIGURE 1. *Ehrlichia muris* infection induces a long-term polyreactive IgM response. (A–F) Serum IgM was tested for reactivity against the indicated Ags by ELISA on the indicated days postinfection. The data represent Ab titers detected in individual mice; the horizontal lines indicate the mean titers. Titers lower than 10 were considered background. (G and H) ELISpot analysis was used to determine the frequency and number of Ag-specific IgM-secreting B cells in the spleen on day 14 postinfection. Spots produced by cells from uninfected mice (which were negligible) were subtracted from values obtained for infected mice. The data are representative of at least three experiments. A Student t test was used to calculate statistical significance. *p < 0.05.

FIGURE 2. Polyreactive IgM was produced independent of CD4+ T cells or CD1d+ NKT cells. Sera were obtained from MHC class II-deficient (A) and CD1d-deficient (B) mice on day 14 postinfection. IgM reactivity to self Ags was determined by ELISA. The data are representative of two experiments.
specifecity; that is, they bound only to particular Ags in the panel tested (e.g., compare Em622 and Em749). These data suggested that the polyreactive Abs were structurally distinct. This was confirmed by nucleotide sequence analysis of the IgH genes encoding regions of six highly polyreactive IgM, which revealed that the genes used distinct V, D, and J segments (Table II). Moreover, the IgM were all encoded by germline Ig genes, consistent with their TI, extrafollicular origin (20).

Polyreactive IgM is sufficient to protect against ehrlichial infection

We next tested whether monoclonal polyreactive IgM was sufficient to protect mice against *E. muris* infection in immunodeficient mice. IgM was produced in vivo by administering polyreactive IgM-producing hybridoma cells s.c. into RAG-deficient mice (28, 29). This approach generated relatively high serum IgM titers in the recipient mice within 7 d (1:100 to 1:6400). The recipient mice survived for at least 2 wk after myeloma cell administration, which provided sufficient time to test whether the IgM was sufficient to control acute *E. muris* infection. The recipient mice were infected with *E. muris* 3 d after myeloma cell administration, and splenic bacterial colonization was determined on day 10 postinfection. Mice implanted with irrelevant IgM-secreting myeloma cells exhibited splenic bacteremia comparable to that observed in infected mice that had not been administered hybridoma cells. In contrast, mice implanted with polyreactive OMP-19–specific IgM-secreting hybridoma cells exhibited low to no bacterial infection (Fig. 4A). Moreover, the reduction in bacterial colonization was

Table I. Ag reactivity of polyreactive IgM

<table>
<thead>
<tr>
<th>Hybridoma</th>
<th>OMP-19</th>
<th>dsDNA</th>
<th>ssDNA</th>
<th>Insulin</th>
<th>LPS</th>
<th>Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Em400</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Em504.1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Em622</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Em638</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Em720.1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Em749</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Ag reactivity, as determined by ELISA: +, A405 > 0.25, −, A405 < 0.25.

Table II. H chain gene utilization by infection-induced polyreactive IgM

<table>
<thead>
<tr>
<th>Hybridoma</th>
<th>VH</th>
<th>DH</th>
<th>JH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Em504.1</td>
<td>J558.84.190</td>
<td>DSP2.9</td>
<td>JH3</td>
</tr>
<tr>
<td>Em702.1</td>
<td>7183.20.37</td>
<td>DFL16.1</td>
<td>JH4</td>
</tr>
<tr>
<td>Em703.1</td>
<td>J558.67.166</td>
<td>DFL16.1</td>
<td>JH2</td>
</tr>
<tr>
<td>Em720.1</td>
<td>J558.18.108</td>
<td>DQ52-C57BL/6</td>
<td>JH3</td>
</tr>
<tr>
<td>Em785.1</td>
<td>J558.31.121</td>
<td>DFL16.1</td>
<td>JH3</td>
</tr>
</tbody>
</table>

Sequence alignments were performed using IgBLAST (http://www.ncbi.nlm.nih.gov/igblast/).
directly correlated with high serum OMP-19–specific IgM in the recipient mice (Fig. 4B; i.e., mice with the highest IgM titers exhibited the lowest infections). Although most polyreactive IgM tested in the assay were OMP-19–specific, a non-OMP-19–specific ehrlichial-specific IgM (Em412) also reduced bacterial infection below the limit of detection. These data indicate that polyreactive IgM is sufficient to mediate host defense.

**Ehrlichial infection induces IgM autoantibodies**

We next addressed whether the polyreactive IgM bound nuclear and cytoplasmic Ags. Anti-nuclear Abs are characteristic of systemic lupus erythematosus and other autoimmune disorders. Non-polyreactive irrelevant IgM generated from uninfected mice did not bind HEp-2 cells (Fig. 5, irrelevant IgM). In contrast, all of the polyreactive IgM tested bound HEp-2 cells, although each of the IgM exhibited distinct binding specificities, underscoring our observation that many of the IgM were quasi-specific. Anti-cytoplasmic (Fig. 5; mAb Em504.1), anti-nuclear (mAbs Em553.2 and Em662.2), mixed nuclear and cytoplasmic (mAb Em720.1), and anti-cytoskeletal (mAb Em785.1) specificities were detected. Thus, the polyreactive IgM generated during infection was also autoreactive.

**Autoreactive IgM was detected in sera from human ehrlichiosis patients**

Although autoimmunity has not been reported to be associated with ehrlichiosis in humans, our finding from the mouse model led us to address whether IgM from human ehrlichial patients exhibited polyreactivity and/or autoreactivity. Sera from 32 human monocytic ehrlichiosis (HME) patients and from normal controls were evaluated for reactivity to *E. chaffeensis* OMP-19, dsDNA, and insulin. Sera from HME patients exhibited nearly 10-fold higher titers against each of these Ags relative to healthy human control sera (Fig. 6A). Moreover, autoreactivity in HME patients was directly correlated with OMP-19 specificity: the patients with the highest anti–OMP-19 IgM titers also exhibited high reactivity to dsDNA and insulin (Fig. 6A). We also addressed whether patient sera exhibited autoreactivity by assay for HEp-2 cell-reactive IgM. The majority of normal control sera (90%) contained non-HEp-2–reactive IgM; in contrast, most HME patients produced autoreactive IgM that exhibited mixed nuclear and cytoplasmic specificity (Fig. 6C). HME patients also produced autoreactive IgG, which was also correlated with high anti–OMP-19 reactivity (Fig. 6B). Although anti-nuclear IgG specificities were observed in both HME patients and normal controls, the overall frequency of autoreactive IgG was significantly higher in HME patients (Fig. 6C; 97 versus 38%). Although it was not possible to determine whether the monoclonal Igs detected in ehrlichial patients were polyreactive, the data from the mouse suggest such an interpretation and raise the possibility that ehrlichial as well as other bacterial infections may play a role in the generation or exacerbation of autoimmunity in humans via the induction of polyreactive IgM and/or IgG.

**Discussion**

Although polyreactive Ab is often considered to be a property of natural Ab produced by B-1 cells or is a consequence of polyclonal B cell activation, our study shows that polyreactive IgM can be produced by Ag-specific B cells in response to bacterial infection. We also demonstrate the production of polyreactive and/or autoreactive IgM by human ehrlichiosis patients. Our findings from the
Polyreactivity is not a universal property of IgM molecules, although a significant portion of circulating natural IgM has been reported to bind multiple Ags (30, 31). In our studies, we did not detect polyreactive IgM in uninfected mice, indicating that the IgM we characterized were not derived from natural Ab-secreting B cells. Other studies have also described the production of Abs of irrelevant specificity during infection; however, it has been unclear whether the apparent polyreactivity observed in other studies was a consequence of polyclonal or Ag-specific B cell activation (7, 10, 11, 32, 33). For example, during influenza infection, polyreactive Ab is secreted by B-1a cells; however, these cells were apparently activated in a polyclonal fashion, as the majority of Ab produced is non-Ag-specific (5, 34). In contrast, during ehrlichial infection, most B cells were triggered via their BCRs, as nearly 85% of hybridomas we generated produced ehrlichia-specific IgM and insulin by ELISA. Data from five representative patients are indicated in the plots by pseudocoloring. The differences between HME patients and normal controls were statistically significant.*p < 0.05, **p < 0.01, ***p < 0.001 (Student t test). (C) Sera from HME patients (n = 27 to 30) and normal controls (n = 27 to 29) were tested for auto-reactivity by HEP-2 assay. Bar graphs summarize the frequency of patients exhibiting cytoplasmic, nuclear, or nuclear plus cytoplasmic specificities. The differences in the frequencies of patients exhibiting self-reactivity were statistically significant. The error bars indicate the SD. ***p < 0.001 (Fisher’s exact 2 × 4 test).

Mice infected with Ehrlichia chaffeensis exhibit polyreactive IgG Abs that are Ag-specific (46), and have not yet been encountered by the host. Thus, polyreactivity, as a property of IgM, is more likely to benefit the host, rather than cause harm.

Sera from HME patients were also apparently polyreactive. Although it was not determined whether polyreactivity was a property of monoclonal IgM in patients, our findings from the mouse model suggest that this was the case. Whereas we only detected polyreactive IgM in mice, apparently polyreactive IgG was detected in the sera of HME patients. This difference may be a consequence of subsequent exposure to Ags or pathogens in humans, which can drive autoreactive IgM-expressing B cells to class switch to IgG-secreting plasma cells (43–45). These findings suggest that the induction of polyreactive IgG in human patients may contribute to the development of autoimmunity. Autoantibodies are produced during infection of humans with a related rickettsial pathogen, Anaplasma phagocytophilum (46), and have been observed in Ehrlichia canis-infected dogs (47, 48). Thus, autoantibody production may be a common feature of rickettsial infections and may be a consequence of induced polyreactivity. Although a correlation between human ehrlichial infections and autoimmunity has not been reported, this remains a possibility that warrants further investigation.

How or if polyreactive IgM may contribute to autoimmunity in mice or humans is not understood. Anti-dsDNA IgM has been shown to be associated with reduced pathology in various models of autoimmunity (17, 49–51). Another study reported a protective effect of IgM anti-β2 glycoprotein I Abs in systemic lupus erythematosus patients (52). In contrast, class switching of autoreactive IgM-expressing B cells can lead to the production of pathogenic IgG Abs (43–45). In the context of parasitic infection, nonspecific IgM production during leishmaniasis has been sug-
gested to exacerbate disease (53). Although the aforementioned studies did not address a role for polyreactive IgM, our findings indicate that ehrlichial infection drives the production of polyreactive and autoreactive IgM in mice and humans and suggest that polyreactivity may be associated with the exacerbation or amelioration of autoimmune disease.

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Disclosures

The authors have no financial interests of conflict.

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