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Accelerated Ischemia/Reperfusion-Induced Injury in Autoimmunity-Prone Mice

Sherry D. Fleming,*† Marc Monestier,*‡ and George C. Tsokos3*†

Natural Abs have been implicated in initiating mesenteric ischemia/reperfusion (I/R)-induced tissue injury. Autoantibodies have affinity and self-Ag recognition patterns similar to natural Abs. We considered that autoimmunity-prone mice that express high titers of autoantibodies should have enhanced I/R-induced injury. Five-month-old B6.MRL/lpr mice displayed accelerated and enhanced intestinal I/R-induced damage compared with 2-mo-old B6.MRL/lpr and age-matched C57BL/6 mice. Similarly, older autoimmune mice had accelerated remote organ (lung) damage. Infusion of serum IgG derived from 5-mo-old but not 2-mo-old B6.MRL/lpr into I/R resistant Rag-1−/− mice rendered them susceptible to local and remote organ injury. Injection of monoclonal IgG anti-DNA and anti-histone Abs into Rag-1−/− mice effectively reconstituted tissue injury. These data show that like natural Abs, autoantibodies, such as anti-dsDNA and anti-histone Abs, can instigate I/R injury and suggest that they are involved in the development of tissue damage in patients with systemic lupus erythematosus. The Journal of Immunology, 2004, 173: 4230–4235.

Mesenteric ischemia/reperfusion (I/R) results in local intestinal inflammation and damage, and progresses to an inflammatory response in remote organs, including the lungs (1, 2). The influx and activation of neutrophils into the ischemic tissue has a critical role in the tissue damage (3, 4), although neutrophils alone are not sufficient to cause damage (5). Complement activation is involved in the development of local and remote organ injury as demonstrated by the ability of various complement activation inhibitors to prevent tissue damage (1, 2, 5–9).

Complement activation in I/R-induced injury occurs through the classical pathway (10–12), although it may involve the alternative pathway (13). Rag-1-deficient (Rag-1−/−) mice are protected from intestinal damage after I/R (11), but infusion of normal murine IgM reconstitutes the I/R-induced tissue damage (10–12). Similarly, Rag-1−/− mice are protected from skeletal muscle I/R-injured injury (14). Complement receptor 2 deficient (C5′2−/−) mice are also resistant to mesenteric I/R-induced injury that is reconstituted following the infusion of normal IgM and IgG (10, 12). Interestingly, the infusion of normal IgM alone restored complement activation, whereas infusion of normal IgG alone caused neutrophil influx and activation (10). These data suggest that naturally occurring Abs are critical in initiating I/R-induced tissue injury.

Produced primarily by B-1 B cells, natural Abs are frequently polyreactive with a low affinity for multiple self-Ags. Germfree nonimmunized mice express levels of natural Abs similar to strain-controlled normal mice, suggesting that the Abs arise in the absence of nonself antigenic stimulation (15, 16). Autoantibodies found in mice and humans with systemic lupus erythematosus (SLE) usually display features similar to those of natural Abs including reactivity against multiple autoantigens (17). Autoantibodies considered to be of pathogenic importance, such as anti-DNA Abs, may arise from natural Abs following somatic mutation (18, 19), but they still retain reactivity against multiple autoantigens including phospholipids (20, 21).

The MRL/lpr mouse develops clinical and serologic features similar to human SLE (22). The production of autoantibodies with multiple specificities, including ssDNA, Sm, chromatin, RNA protein complexes, and phospholipids, typifies the disease (17). The C57BL/6-lpr/lpr (B6.MRL/lpr) mouse shows characteristics of lymphadenopathy and autoimmunity, although the levels of certain autoantibodies are lower than those in the MRL/lpr/lpr mouse (23, 24). We hypothesized that autoantibodies present in the sera of mice with systemic autoimmunity should initiate I/R-induced organ injury in a fashion similar to natural Abs (10, 12, 25). This hypothesis predicts that autoimmunity-prone mice should display enhanced and accelerated I/R-induced intestinal damage, and that infusion of autoimmune sera into I/R-resistant Rag-1−/− mice should restore organ damage. In this study, we show that, indeed, B6.MRL/lpr mice display both enhanced and accelerated organ damage and that serum IgG from 5-mo-old B6.MRL/lpr mice and anti-DNA and anti-histone-specific mAbs effectively reconstitute mesenteric injury in Rag-1−/− mice subjected to I/R.

Materials and Methods

Mice

Adult male B6.MRL.Tnfrsf9b610 (B6.MRL/lpr), B6.Rag-1 (Rag-1−/−), and control C57BL/6 mice were obtained from The Jackson Laboratory (Bar Harbor, ME), and housed in the Uniformed Services University for the Health Sciences animal facility.

Experimental protocol

After at least a 7-day acclimation period, mice were prepared for surgery. Anesthesia was induced with ketamine (16 mg/kg) and xylazine (8 mg/kg) administered by i.p. injection. All procedures were performed with the animals breathing spontaneously and body temperature maintained at 37°C.
using a water-circulating heating pad. Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals, and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 1996 edition. All procedures were reviewed and approved by the University’s Animal Care and Use Committee, and performed in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Animals were subjected to I/R as previously described (5, 10). Briefly, a midline laparotomy was performed before a 30-min equilibration period. The superior mesenteric artery was then identified, isolated, and a small nontraumatic vascular clamp (Roboz Surgical Instruments, Rockville, MD) applied for 30 min. After this ischemic phase, the clamp was removed and the intestine was allowed to reperfuse for 1 or 2 h. In some experiments, 30 min before laparotomy, animals were given 200 μg of purified Ig, by i.v. injection. Sham animals were subjected to the same surgical intervention, except they did not undergo superior mesenteric artery occlusion. The laparotomy incisions were sutured and the animals were monitored during the reperfusion period. Additional ketamine and xylazine was administered by i.m. injection immediately before euthanasia. There was no significant difference in survival between treatment and control groups. After euthanasia, the small intestine 10–20 cm distal to the gastroduodenal junction was removed for histologic and immunohistochcmical analysis and for the measurement of inflammatory mediators as described below. Immediately after removal of intestinal tissue, a bronchial alveolar lavage was performed with sterile saline. The number of cells in the recovered lavage fluid was counted and expressed as cells per milliliter.

Histology and immunohistochemistry

Immediately after euthanasia, 2-cm segments of small intestine specimens were fixed in 10% buffered Formalin phosphate, embedded in paraffin, sectioned transversely in 5- to 7-μm sections, and stained with Giemsa. In each section, 50–100 villi were graded on a six-tiered scale as described previously and the mean score was recorded (5, 10). Briefly, a score of 0 was assigned to a normal villus; villi with tip distortion were scored as 1; villi lacking goblet cells and containing Gugenheims’ spaces were scored as 2; villi with patchy disruption of the epithelial cells were scored as 3; villi with exposed but intact lamina propria and epithelial cell sloughing were assigned a score of 4; villi in which the lamina propria was exuding were scored as 5; and finally, villi displaying hemorrhage or denuded villi were scored as 6. All histological analysis was performed in a blinded manner.

Ex vivo eicosanoid determination

The ex vivo generation of eicosanoids by small intestine tissue was determined as previously described (5, 10). Briefly, fresh midjejunum sections were minced, washed, and resuspended in 37°C oxygenated Tyrode’s buffer (Sigma-Aldrich, St. Louis, MO). After incubating for 20 min at 37°C, supernatants were collected and stored at −80°C until assayed. The concentration of leukotriene B4 (LTB4) was determined using an enzyme immunoassay (Cayman Chemical, Ann Arbor, MI). The tissue protein content was determined using the bicinchoninic acid assay (Pierce, Rockford, IL) adapted for use with microtiter plates. LTB4 levels were expressed per mg protein per 20 min.

Ig preparation and purification

Serum from B6.MRL/lpr mice was obtained by cardiac puncture and diluted 1/2 with PBS. The solution was incubated with protein L-conjugated agarose (Pierce) for 2 h. The agarose was washed three times with phosphate buffer, pH 7, before eluting with glycine buffer, pH 2.5, for 15 min. The eluted material was dialyzed into sterile saline. The purity of each preparation was determined by Western blot analysis using alkaline phosphatase-conjugated anti-mouse Ig (Innogenetix Life Technologies, Carlsbad, CA). Murine anti-DNA (PL-9-11) or anti-histone H2A-H2B (PL-9-7) mAbs were purified from culture supernatants by affinity chromatography on recombinant protein G-agarose as described previously (26). The isotype control Ab (IgG3, clone FLOPC-21) was obtained from Sigma-Aldrich and dialyzed to exchange the buffer.

Statistical analysis

Data are presented as mean ± SEM and were compared by one-way ANOVA with post hoc analysis using the Newman-Keuls test (GraphPad Instat Software, Philadelphia, PA) or Kruskal-Wallis test with Dunn post analysis for the nonparametric analysis of mucosal injury. The difference between groups was considered significant when p < 0.05.

Results

Mesenteric I/R-induced damage is accelerated and enhanced in B6.MRL/lpr mice

Two- and 5-mo-old B6.MRL/lpr or C57BL/6 mice were subjected to mesenteric ischemia followed by 1-h or 2-h reperfusion. Similar to previous results, damage of the villi was noted 1 h after reperfusion and increased by the second hour in control mice. There was no significant difference between the 2- and 5-mo-old C57BL/6 mice, and data were combined for these control animals. Similar to C57BL/6 mice, young (2 mo) B6.MRL/lpr mice displayed injury that increased over the first 2 h of reperfusion (Fig. 1, A and B, and Fig. 2, A and B). The maximal injury score of 2-mo-old B6.MRL/lpr mice (2 h after reperfusion) was not significantly different from that of C57BL/6 mice (2.1 ± 0.4 vs 2.4 ± 0.5). In contrast, 5-mo-old B6.MRL/lpr mice had severe injury after 1-h reperfusion (Fig. 1C, and Fig. 2, C and D) as indicated by the presence of numerous villi with exposed or exuding lamina propria and epithelial sloughing. In addition, the injury was significantly increased compared with the intestinal injury observed in C57BL/6 mice (3.4 ± 0.7 vs 1.6 ± 0.4) (Fig. 1, A and C). The 2-h reperfusion injury score was comparable in all three groups of mice, however, the villi were shorter in the 5-mo-old B6.MRL/lpr mice, suggesting reannealing and healing of the epithelium.

To determine the inflammatory component influencing the early injury in the B6.MRL/lpr mice, ex vivo intestinal LTB4 production was determined. Production of LTB4 ex vivo has been shown previously to correlate with polymorphonuclear cell (PMN) infiltration and inflammation (27–29). In C57BL/6 mice, intestinal I/R-induced LTB4 production was significantly elevated at 1 and 2 h after reperfusion (Fig. 3A). Two-month-old B6.MRL/lpr mice produced comparable levels of LTB4 at 1 and 2 h after reperfusion...
Increased susceptibility to remote tissue injury in B6.MRL/lpr mice following mesenteric I/R

C57BL/6 mice subjected to mesenteric I/R develop lung injury 4 h after the beginning of reperfusion (1, 2). One measure of lung damage is the increased cell numbers in the bronchoalveolar lavage fluid (30). Accordingly, to determine whether the B6.MRL/lpr mice develop lung damage earlier than C57BL/6 mice, we counted the number of cells in the bronchoalveolar lavage fluid of 2- and 5-mo-old B6.MRL/lpr mice after 1 h of reperfusion. As shown in Fig. 4, 2-mo-old B6.MRL/lpr mice had a slight but not significant increase in cell numbers compared with animals subjected to sham treatment. However, there was a significant increase in lavage fluid cell numbers in 5-mo-old B6.MRL/lpr mice, indicating that remote I/R-induced organ injury also occurs earlier in these mice. The cell numbers in the bronchoalveolar lavage fluid of C57BL/6 mice after 2 h of reperfusion were not increased compared with sham-operated animals.

Transfer of serum IgG from B6.MRL/lpr mice induces tissue damage in Rag-1−/− mice

B6.MRL/lpr mice produce multiple autoantibodies, the titers of which increase as the mouse ages (24, 31). To determine whether these autoantibodies were responsible for the accelerated mesenteric I/R, we purified IgG from 2- and 5-mo-old B6.MRL/lpr mice and injected it into Rag-1−/− mice before performing mesenteric I/R. Similar to previous studies (11), Rag-1−/− mice infused with PBS failed to develop significant mesenteric I/R-induced injury (Fig. 5, A, B, and E). Rag-1−/− mice injected with IgG from 2-mo-old B6.MRL/lpr mice had increased mesenteric injury, albeit not significantly different from that observed in mice infused with PBS (Fig. 5, A and C). The average villus was vacuolated with Gugenheim’s spaces, and patchy epithelial disruption of the tips of the villi. In contrast, Rag-1−/− mice infused with IgG from 5-mo-old B6.MRL/lpr mice displayed significantly enhanced tissue damage compared with Rag-1−/− mice infused with either PBS or 2-mo-old B6.MRL/lpr IgG (Fig. 5). The villi had exposed lamina propria with epithelial sloughing, exuding lamina propria, hemorrhage, or they were denuded.

Next we asked whether the intestinal injury that was observed in Rag-1−/− mice injected with 5-mo-old B6.MRL/lpr serum IgG

FIGURE 3. LTBA4 production is enhanced in 5-mo-old B6.MRL/lpr mice. Intestinal sections were collected from C57BL/6 (A), 2-mo-old B6.MRL/lpr (B), and 5-mo-old B6.MRL/lpr (C) mice after sham or I/R treatment. Ex vivo eicosanoid production by tissue sections from each treatment group was determined by enzyme immunoassay as described in Materials and Methods. Each bar is average ± SEM with n = 3–6 animals/group. Using ANOVA with Newman Keuls post hoc test, * indicates significant difference from sham treatment group, p < 0.05.

FIGURE 4. Mesenteric ischemia reperfusion increases cell numbers in the bronchoalveolar lavage fluid of 5-mo-old B6.MRL/lpr mice. Two- and 5-mo-old mice were subjected to sham treatment or ischemia, followed by 1-h reperfusion before bronchoalveolar lavage. The number of cells in the bronchoalveolar lavage fluid was counted and expressed as cells per milliliter lavage fluid collected. Each bar is the average ± SEM with 3–6 mice/group. Using ANOVA with Newman Keuls post hoc test, * indicates significant difference from sham treatment group, p < 0.05.
was associated with increased LTB₄ production as it was observed in B6.MRL/lpr serum IgG treated to I/R. After 2-h reperfusion, Rag-1⁻/⁻ mice treated with IgG from 5-mo-old B6.MRL/lpr mice produced significantly increased amounts of LTB₄ (Fig. 6). In contrast, there was no significant increase in LTB₄ production by Rag-1⁻/⁻ mice treated with IgG from 2-mo-old B6.MRL/lpr mice (Fig. 6). The increased LTB₄ production correlated with a significant increase in neutrophils in the villi of 5-mo-old B6.MRL/lpr mice compared with 2-mo-old mice (5-mo-old, 16 ± 1.1 PMN/high power field vs 2-mo-old, 7 ± 0.9 PMN/high power field). These data indicate that local production of LTB₄ is involved in the autoantibody-initiated I/R injury.

**Anti-DNA and anti-histone mAbs reconstitute I/R injury in Rag-1⁻/⁻ mice**

Sera from mice with lupus contain anti-nuclear Abs with various specificities, including dsDNA and histones (26). To establish that prevalent autoantibodies present in the sera of B6.MRL/lpr IgG were responsible for the reconstitution of the I/R injury, we infused Rag-1⁻/⁻ mice with 50 µg of IgG3 anti-DNA or anti-histone murine mAb or with equal amounts of isotype (IgG3) control Ab 30 min before mesenteric I/R or sham treatment. Treatment with either mAb did not induce tissue damage in sham-treated animals. Infusion of either anti-DNA or anti-histone mAbs induced significant intestinal injury in response to I/R compared with either untreated Rag-1⁻/⁻ or isotype control Ab (Fig. 7). In contrast though, to mice infused with 5-mo-old IgG, in which we noted only scarce deposition of complement to the intestinal tissue, Rag-1⁻/⁻ mice injected with IgG3 monoclonal autoantibodies displayed complement deposition (data not shown). These data indicate that anti-nuclear Abs play a pathogenic role in mesenteric I/R-induced injury.

**FIGURE 5.** Five-month-old B6.MRL/lpr serum IgG restores tissue injury in Rag-1⁻/⁻ mice. Rag-1⁻/⁻ mice were infused with serum IgG purified from 2- or 5-mo-old B6.MRL/lpr mice (2 mo (C) or 5 mo (D), respectively), or with PBS (sham (A) or I/R (B)), before mesenteric I/R. Representative intestinal tissue sections from each treatment group are illustrated in A–D. Solid arrow head indicates villi with small epithelial break (solid line; injury score = 3) or Gugenheim’s space (dashed line; injury score = 2); open arrow head indicates villi with exposed lamina propria (solid line; injury score = 4) or exuding lamina propria (dashed line; injury score = 5). The injury score (E) was determined from Giemsa-stained intestinal sections as described in Materials and Methods. Each bar is the average ± SEM with 3–6 mice/group. Using Kruskal-Wallis test with Dunn post analysis, * indicates significant difference from sham treatment group, p < 0.05.

**FIGURE 6.** Five-month-old B6.MRL/lpr serum IgG enhances LTB₄ production in Rag-1⁻/⁻ mice. After infusion of IgG from either 2- or 5-mo-old B6.MRL/lpr mice, Rag-1⁻/⁻ mice were subjected to sham or I/R treatment, and intestinal sections collected. As described in Materials and Methods, ex vivo intestinal LTB₄ production was determined by enzyme immunoassay and expressed as picograms per microgram tissue. Each bar is the average ± SEM with 3–6 mice/group. Using ANOVA with Newman Keuls post hoc test, * indicates significant difference from sham treatment group, p < 0.05.

**FIGURE 7.** Anti-DNA or anti-histone mAbs reconstitute I/R injury in Rag-1⁻/⁻ mice. Rag-1⁻/⁻ mice were infused with PBS or 50 µg of the indicated Ab 1 h before ischemia, followed by 2-h reperfusion. Immediately after reperfusion, intestinal sections were formalin fixed, stained, and scored for intestinal injury as described in Materials and Methods. Each bar is the average ± SEM with 3–6 mice/group. Using Kruskal-Wallis test with Dunn post analysis, * indicates significant difference from sham treatment group, p < 0.05.
Discussion

Natural Abs have been implicated in initiating mesenteric I/R-induced tissue injury (10, 12, 25). Because autoantibodies share autoantigen recognition patterns that are reminiscent of natural Abs, we hypothesized that they should share ability to initiate I/R-induced injury. If correct, this hypothesis predicts that autoimmune-prone mice that express high levels of diverse autoantibodies should experience enhanced, and possibly accelerated, I/R-induced injury. Also, it predicts that serum Ig from mice with overt autoimmune disease should restore I/R injury in the I/R-induced injury resistant Rag-1<sup>−/−</sup> mice. In this study, we showed that indeed B6.MRL/lpr mice have enhanced and, more importantly, accelerated intestinal tissue damage following I/R. In mice injected with whole IgG from old B6.MRL/lpr mice, the injury was associated with increased production of the chemotaxant LT<sub>B</sub> and followed by significant remote organ (lung) injury. The observation that autoantibodies are implicated in this observation is supported by the experiments that show that transfer of serum IgG from 5-mo-old B6.MRL/lpr mice, but not from younger mice, effectively reconstituted I/R-induced injury in Rag<sup>−/−</sup> mice. The fact that transfer of anti-dsDNA and anti-histone Ab effectively reconstitutes I/R injury in Rag<sup>−/−</sup> mice indicates that autoantibodies present in the 5-mo-old B6.MRL/lpr are responsible for the recorded tissue damage.

The role of natural Abs in the initiation of mesenteric I/R injury has been demonstrated by transferring Ig into two strains of mice, Cr2<sup>−/−</sup> (10, 12) and Rag<sup>−/−</sup> (11, 25), both of which are resistant to I/R injury. The lack of Ig in the Rag<sup>−/−</sup> mouse suggests the role of Ig in the initiation of the tissue injury. The Cr2<sup>−/−</sup> mouse displays practically normal levels of Ig with the exception of IgG3, which appears to be slightly decreased (32, 33). The experiments reported using the Cr2<sup>−/−</sup> mice, in which the I/R injury can be reconstituted with normal murine Ig but not Cr2<sup>−/−</sup> Ig, strongly suggest the presence of a “injured-tissue-binding” repertoire that is missing in the Cr2<sup>−/−</sup> mouse (10). This concept of the existence of tissue injury-igniting specific Abs is further supported by the isolation of an IgM clone from normal peritoneal B-1-enriched B cells that was able to restore I/R injury in the Rag<sup>−/−</sup> mouse (25).

Ig transfer experiments into Cr2<sup>−/−</sup> mice revealed that restoration of the mesenteric injury following the infusion of IgG is associated with the production of the chemoattractant LT<sub>B</sub> and profound infiltration of neutrophils (10). In contrast, the injury that ensues following the injection of IgM Ab is associated with the deposition of complement in the injured intestine (10, 12, 25). Similarly, infusion of IgM, total (12), or cloned (25) Ab into the Rag<sup>−/−</sup> mouse is associated with the deposition of complement. In the experiments that we show in Fig. 2, we noted that the damaged intestine in the 5-mo-old B6.MRL/lpr mouse was characterized by profound infiltration of neutrophils, suggesting a dominant role for IgG in the initiation of the injury. This assumption was further supported by the fact that the injured intestine in these animals produced increased levels of LT<sub>B</sub> (Fig. 3) and was proven to be true by the observation that IgG from 5-mo-old and not from 2-mo-old B6.MRL/lpr mice was capable of restoring injury in the Rag<sup>−/−</sup> mouse. Five-month-old mice, unlike the 2-mo-old B6.MRL/lpr mice that were included in this study, display known clinical features of autoimmunity, that is, autoantibody production and lymphadenopathy (24, 31). Obviously, this does not exclude the possibility that IgM Abs also contribute to the expression of I/R injury. It is known that both PMN infiltration and complement activation are involved in variable degrees in the expression of mesenteric I/R injury. It appears that infusion of whole IgG from old B6.MRL/lpr mice into Rag<sup>−/−</sup> mice causes primarily inflammatory cell infiltration, whereas IgG3 monoclonal anti-DNA and anti-histone Abs are associated with complement activation and deposition. In addition, the reconstitution of I/R injury by autoantibody in the Rag<sup>−/−</sup> mouse does not exclude the possibility that T or other cells may also be involved in the expression of I/R injury in the normal mouse.

The autoantibody specificities found in the sera of B6.MRL/lpr mice include, among others, anti-DNA Ab and rheumatoid factor (23, 34). Our studies and those reported previously (10, 25) indicate that more than one specificity can bind to injured tissue and initiate injury. Recently, it was shown that during apoptosis, nuclear fragments are exposed on the cell surface and are recognized by anti-DNA and anti-histone Abs (35). Intestinal I/R results in TUNEL-positive epithelial cells that can be inhibited by treatment with a caspase inhibitor or in Bcl-2 transgenic mice (36, 37) indicating that apoptosis plays a role in I/R-induced damage. Therefore, we believe that anti-DNA and anti-histone mAbs bind to I/R-generated apoptotic intestinal cells and cause tissue damage in response to I/R. This concept is consistent with previously published work showing that anti-DNA Abs injected into the hippocampus and cortex of mice cause neuronal cell loss (38). Cat-ionic anti-DNA Abs have been shown to bind to the glomerular basement membrane and contribute to renal inflammation and damage (39).

Despite the fact that autoantibodies have been widely considered important in the expression of organ damage in patients with SLE, there is little proof that autoantibodies can ignite on their own organ damage. Anti-cardiolipin Abs injected into pregnant mice cause fetal absorption (40–42). Our study shows that autoantibodies can serve as the second “hit,” following the first hit delivered by the I/R process, and enable the expression of intestinal damage. It appears that autoantibodies alone cannot cause intestinal damage because neither humans nor mice with SLE have profound intestinal disease characterized by profound damage.

We propose that autoantibodies present in the sera of humans and mice with SLE contribute to tissue damage after an organ/tissue has suffered another damaging event such as ischemia. The first damaging event may cause the expression of cell surface Ags that bind readily circulating autoantibody.

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References


