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*J Immunol* 2013; 191:1373-1382; Prepublished online 1 July 2013; doi: 10.4049/jimmunol.1202907

http://www.jimmunol.org/content/191/3/1373

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**Supplementary Material**

http://www.jimmunol.org/content/suppl/2013/06/28/jimmunol.1202907.DC1

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*The Journal of Immunology* is published twice each month by The American Association of Immunologists, Inc., 1451 Rockville Pike, Suite 650, Rockville, MD 20852
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.
Histamine H₂ Receptor Signaling in the Pathogenesis of Sepsis: Studies in a Murine Diabetes Model

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Type 1 diabetes enhances susceptibility to infection and favors the sepsis development. In addition, diabetic mice produced higher levels of histamine in several tissues and in the blood after LPS stimulation than nondiabetic mice. In this study, we aimed to explore the role of mast cells (MCs) and histamine in neutrophil migration and, consequently, infection control in diabetic mice with mild sepsis (MS) induced by cecum ligation and puncture. We used female BALB/c, MC-sufficient (WB/B6), MC-deficient (W/Wv), and NOD mice. Diabetic mice given MS displayed 100% mortality within 24 h, whereas all nondiabetic mice survived for at least 5 d. The mortality rate of diabetic mice was reduced to 57% after the depletion of MC granules with compound 48/80. Moreover, this pretreatment increased neutrophil migration to the focus of infection, which reduced systemic inflammatory response and bacteremia. The downregulation of CXCR2 and upregulation of G protein–coupled receptor kinase 2 in neutrophils was prevented by pretreatment of diabetic mice given MS with compound 48/80. In addition, blocking the histamine H₂ receptor restored neutrophil migration, enhanced CXCR2 expression, decreased bacteremia, and improved sepsis survival in alloxan-induced diabetic and spontaneous NOD mice. Finally, diabetic W/Wv mice had neutrophil migration to the peritoneal cavity, increased CXCR2 expression, and reduced bacteremia compared with diabetic WB/B6 mice. These results demonstrate that histamine released by MCs reduces diabetic host resistance to septic peritonitis in mice. The Journal of Immunology, 2013, 191: 1373–1382.
It was demonstrated that histamine levels are increased in plasma and tissues in diabetic rats, as well as in patients with diabetes mellitus (32, 33). Moreover, levels of histamine are higher in diabetic rats than in nondiabetic animals after LPS administration (34). In agreement, in this study, we found that histamine is increased in diabetic mice undergoing septic peritonitis. Moreover, we observed that histamine released by MCs decreases neutrophil migration to the infection site through interaction with H2, resulting in impaired host defense and a poor sepsis outcome in diabetic mice.

Materials and Methods

**Mice**

Female BALB/c, MC-sufficient (WB/B6), W/Wv, and NOD mice were housed in facilities of Department of Pharmacology, School of Medicine of Ribeirão Preto at 23–25°C with free access to water and food. Animal care and treatment was based on the Guide for the Care and Use of Laboratory Animals (35), and all experiments were approved by the Animal Research Ethics Committee of the School of Medicine of Ribeirão Preto (no. 001/2008).

**Diabetes induction**

Diabetes was induced with a single i.v. injection of alloxan (Sigma Chemical Company, St. Louis, MO) at a dosage of 50 mg/kg in saline (100 μl). The nondiabetic control group received an i.v. injection of saline alone. Blood samples were collected from the tail vein to measure blood glucose levels using a glucometer (Precision Xtra Abbott, Alameda, CA).

**Pharmacological treatment**

Nondiabetic mice were treated s.c. with histamine (3 μg or 10 μg in 100 μl saline) (Sigma Chemical Company, St. Louis, MO), 1 h before CLP and every 24 h afterward for a total of 5 d for survival rate analysis, or treated 1 h before CLP with 10 μg histamine per mouse for neutrophil migration, bacterial load, and CXCR2 expression evaluation. Ten days after alloxan treatment, diabetic mice were injected i.p. with pyrilamine (20 mg/kg, an H3/4 antagonist), or saline 1 h before CLP. Ten days after saline or alloxan administration, diabetic and nondiabetic mice were injected with peritonitis, and the results were reported as the mean ± SEM.

**Detection of serum TNF-α and CXCL-2 levels**

TNF-α and CXCL-2 levels were assessed in serum and PCL 6 h after surgery by ELISA. The results were displayed in picograms per milliliter as the mean ± SEM.

**Histamine measurement**

Mouse plasma histamine concentration was measured 6 h after surgery using an immunoenzymatic method with a manufactured kit (Cayman, Ann Arbor, MI).

**Neutrophil isolation and chemotaxis assay**

Bone marrow or blood neutrophils were isolated using a Percoll gradient as described previously (14). Neutrophil suspensions were incubated with RPMI 1640 (Sigma-Aldrich) or histamine at a concentration of 1 or 10 μM for 1 h, and neutrophil chemotaxis was assessed toward CXCL-2 (30 ng/ml; R&D Systems, Minneapolis, MN) in a Boyden chamber (Neuro Probe, Bethesda, MD). In another set of experiments, the chemotactic activity of blood neutrophils obtained from related experimental groups was assessed for CXCL-2 (30 ng/ml), IFN-γ (10−7 M), or RPMI 1640 (negative control).

**Vascular leakage**

Evans blue dye (2.5% in 100 μl of PBS) was i.v. administered 30 min before CLP. Two hours after CLP, the mice were killed, and the peritoneal cavity was washed with 1.5 ml PBS/EDTA (1 mM). The extent of leukocyte accumulation in the lung was measured by myeloperoxidase activity. Evans blue in peritoneal exudates was determined under a standard curve.

**Determination of the myeloperoxidase activity**

The extent of leukocyte accumulation in the lung was measured by myeloperoxidase assay as previously described (38). The absorbance of the tissue supernatant was compared with a standard curve of mouse peritoneal neutrophils, and the results were reported as the mean ± SEM of the total number of neutrophils per milligram of lung.

**Statistical analysis**

The log-rank test was used to evaluate the survival rate, and the proportional risk model of Cox was used to identify the differences between groups. The Mann–Whitney U test was used to assess the following variables: blood and PCL bacterial count between vehicle-administered MS group and histamine-administered MS group and body weight. The one-way ANOVA, followed by Tukey’s multiple-comparison test, was used for the others variables. A p value < 0.05 was considered statistically significant.

**Results**

**Diabetic mice showed increased MC numbers after MS**

Alloxan-induced diabetes is a common experimental model used to study the pathophysiologic mechanisms involved in type 1 diabetes (39). Blood glucose levels in diabetic mice were increased 10 d after alloxan administration (Supplemental Fig. 1B), and these mice showed reduced body weight compared with nondiabetic mice (Supplemental Fig. 1C). We also evaluated the numbers of MCs (FceRI/CD117+ cells) in the peritoneal cavity during diabetes by flow cytometry. Interestingly, we observed higher

**Flow cytometry**

One hundred microliters of blood was stained using PerCP-Cy5.5-conjugated anti-mouse myeloid lineage differentiation Ag Gr-1 (GR-1) (BD Bioscience, Franklin Lakes, NJ), PE-conjugated anti-CXCR2 mAb (R&D Systems, Minneapolis, MN), or the appropriate isotype controls. The cells were washed, fixed in 2% formaldehyde, and analyzed by flow cytometry in a FACSort flow cytometer using CellQuest software. Neutrophils were identified by their light scatter properties and high GR-1 expression. MC number was determined using double staining with PE-Cy5-conjugated anti-CD117 and FITC-conjugated anti-FceRI (eBioscience, San Diego, CA). The GRK2 staining was evaluated by flow cytometry in neutrophils as previously described (37).
numbers of MCs in the peritoneal cavity of sham-operated (sham) diabetic mice compared with sham nondiabetic mice. In addition, diabetic mice had a significant increase in MCs in their peritoneal cavity compared with nondiabetic mice after MS induction. However, the number of MCs in MS diabetic mice did not differ from sham diabetic mice (Fig. 1A). We also observed a significant increase in the MC numbers in the peritoneal cavity of naive diabetic mice that did not undergo sham surgery compared with related nondiabetic mice (Supplemental Fig. 1D).

**MC degranulation contributes to sepsis onset in diabetic mice**

To evaluate the role of MCs in diabetic mice given sepsis, we pretreated diabetic mice with C48/80, an agent that induces MC-granule depletion (40), for 4 d before MS induction. Diabetic mice exhibited 100% mortality rate after MS, whereas all nondiabetic mice survived for 5 d after surgery (Fig. 1B). C48/80 pretreatment of diabetic mice enhanced survival rate to 42% after MS induction. As a control for sepsis induction, we induced SS in nondiabetic mice and observed that they died within 3 d after surgery (Fig. 1B). The nondiabetic mice pretreated with C48/80 had a 33.3% survival rate after SS, whereas all SS mice that were not pretreated with C48/80 died. The survival rates of the pretreated mice and nonpretreated mice after MS were 85.7 and 100%, respectively, demonstrating that the pretreatment with C48/80 did not alter the MS survival rate (Supplemental Fig. 2D). It is important to mention that the pretreatment of diabetic mice with C48/80 did not increase neutrophil migration to the peritoneal cavity compared with sham nondiabetic mice. Notably, pretreatment of diabetic mice with C48/80 significantly increased neutrophil migration to the peritoneal cavity compared with sham nondiabetic mice (Fig. 1E). In contrast, MS diabetic mice had decreased neutrophil migration in the peritoneal cavity, which were similar to the numbers observed in SS nondiabetic mice. Pretreatment of diabetic mice with C48/80 significantly increased neutrophil migration to the peritoneal cavity compared with MS nontreated diabetic mice (Fig. 1E). We also observed that the pretreatment with C48/80 of diabetic mice restored the random migration (chemokinesis) of blood neutrophils compared with nontreated diabetic mice after MS induction (Fig. 1F).

High systemic levels of proinflammatory cytokines and leukocyte sequestration in the lungs correlate with sepsis severity (41). Accordingly, we found higher levels of leukocytes in the lungs of diabetic MS mice and nondiabetic SS mice than in nondiabetic MS mice. Pretreatment of diabetic mice with C48/80 attenuated this leukocyte infiltration into the lungs after MS induction (Supplemental Fig. 2A). In addition, diabetic MS mice exhibited higher serum concentrations of TNF-α and CXCL-2 than nondiabetic controls.

**FIGURE 1.** MC granule depletion induces septic peritonitis control in diabetic mice. MC numbers were quantified in the peritoneal cavity using MC-specific markers (CD117 and FcεRI) in nondiabetic or diabetic mice 10 d after alloxan administration (A). Nondiabetic mice and diabetic mice were pretreated with saline or C48/80 before induction of MS. SS was carried out in nondiabetic mice. The survival rates were evaluated daily for 5 d after CLP surgery (B). Bacterial burden in the PCL (C), blood (D), and neutrophil numbers (E) into the peritoneal cavity was quantified 6 h after surgery. Blood neutrophils were obtained from sham-operated, nondiabetic (ND), and diabetic mice pretreated with saline or C48/80 after MS surgery. The chemotactic activity of blood neutrophils toward CXCL-2 (30 ng/ml) or RPMI 1640 (negative control) was determined in Boyden chambers (F). The results were expressed as the mean ± SEM (n = 5–7). These are representative graphs of at least two independent experiments. *p ≤ 0.05 compared with the nondiabetic sham-operated group, #p ≤ 0.05 compared with the nondiabetic MS group, &p ≤ 0.05 compared with the diabetic MS group.
abetic MS mice, which were reduced significantly by C48/80 pre-
treatment (Supplemental Fig. 2B, 2C).

**MC degranulation promotes GRK2 upregulation and CXCR2
downregulation in neutrophils**

Reduced neutrophil migration to focus of infection can result from
GRK2-mediated downregulation of CXCR2 in circulating neutrophils (16). To address this possibility, we analyzed CXCR2 ex-
pression by flow cytometry and GRK2 by immunofluorescence in
circulating neutrophils after MS in alloxan-induced diabetic and
nondiabetic mice. As shown in Fig. 2A, circulating neutrophils from
MS diabetic mice exhibited a significant reduction in CXCR2 ex-
pression compared with those from both sham (nondiabetic and
diabetic) and MS nondiabetic mice. Pretreatment of diabetic mice
with C48/80 significantly prevented the CXCR2 downregulation in
MS diabetic mice. Moreover, we observed that GRK2 protein ex-
pression was increased in neutrophils from MS diabetic mice and
SS nondiabetic mice compared with the MS nondiabetic or sham-
operated groups. The pretreatment of diabetic mice with C48/80
prevented this increased GRK2 expression compared with sham-operated nondiabetic mice.

In addition, pretreatment with C48/80 prevented GRK2 induction
in the neutrophils from these mice (Supplemental Fig. 2E).

**H2 antagonist treatment alleviates sepsis in diabetic mice**

As shown in Fig. 2B, MS diabetic mice produced higher levels of
histamine compared with both sham (nondiabetic and diabetic)
and MS nondiabetic mice. As previously shown (Fig. 1B), de-
pleting MC granules with C48/80 decreased the severity of sepsis
in diabetic mice after MS induction. This pharmacologic inter-
vention also significantly decreased serum histamine levels in MS
diabetic mice (Fig. 2B). This finding suggested that the high serum
levels of histamine in diabetic mice may contribute to poor sepsis
outcome. To test this hypothesis, we used histamine receptor
antagonists in diabetic mice given MS. Treatment with an H₁
antagonist (pyrilamine) delayed the death of the mice, but all mice
still died within 4 d of MS induction (Fig. 3A). In contrast,
treating diabetic mice with an H₂ antagonist (cimetidine) in-
creased the survival rate by ∼45%. The treatment of MS diabetic
mice with an H₃/₄ antagonist (thioperamide) did not influence their
survival rate (Fig. 3A). As shown in Fig. 3B, the combination of
H₁ and H₂ antagonists had no effect on survival rates of diabetic
mice after MS induction.

We next evaluated the effects of the H₂ antagonist on neutrophil
recruitment to the focus of infection, blood bacterial load, and
CXCR2 expression in circulating neutrophils in MS diabetic mice.
H₂ blockade significantly restored the neutrophil migration to
the peritoneal cavity of MS diabetic mice (Fig. 3C), resulting in
a significantly lower bacterial load in the blood compared with
nontreated MS diabetic mice (Fig. 3D). In addition, treatment with
the H₂ antagonist increased CXCR2 expression in the neutrophils
of the MS diabetic mice (Fig. 3E). Blood neutrophils from the MS
diabetic mice have a reduced chemotactic response to CXCL-2,
but not to fMLF, compared with the MS nondiabetic mice, ex-
cluding the possibility of cross desensitization for this receptor.

![FIGURE 2.](http://www.jimmunol.org/)

**FIGURE 2.** MC granule depletion prevents CXCR2 internalization and histamine release during polymicrobial peritonitis in diabetic mice. Quantitative analysis of the mean intensity of fluorescence (MFI) for CXCR2 in blood cells with high expression of GR-1 (neutrophils) was evaluated by flow cytometry
(A). Serum histamine levels were determined 6 h after surgery from several experimental groups as described earlier (B). Blue staining by DAPI represents
neutrophil nuclei; red staining represents GRK2 expression in neutrophil cytoplasm (C) (original magnification ×400). An overlay of nuclei and GRK2
expression shows the qualitative analysis from several experimental groups. Results are expressed as the mean ± SEM (n = 5–7). These are representative
graphs of at least two independent experiments. *p ≤ 0.05 compared with the nondiabetic sham-operated group, **p ≤ 0.05 compared with the nondiabetic
MS group, ***p ≤ 0.05 compared with the diabetic sham-operated group, ****p ≤ 0.05 compared with the diabetic MS group.
addition, H₂ pretreatment of the MS diabetic mice significantly restored the chemotactic response to CXCL-2, compared with the chemotactic response of the blood neutrophils of the MS diabetic nontreated mice (Supplemental Fig. 3A).

To determine whether these observations in MS diabetic mice were attributable to differences in vascular permeability between the septic groups, we used Evans blue extravasation in the peritoneal cavity as an index for vascular leakage. The Evans blue content during the first 2 h after MS was prominently increased in both the nondiabetic and diabetic mice compared with nondiabetic sham-operated mice. H₂ antagonist treatment did not alter the Evans blue content in the peritoneal cavity of the MS diabetic mice (Fig. 3F).

**Histamine is involved in septic peritonitis susceptibility**

Our earlier results suggested that histamine negatively regulated neutrophil migration. To test this hypothesis, we first incubated neutrophils with histamine (1 and 10 μM) and observed a reduction in their chemotactic response to CXCL-2 (Fig. 4A). Accordingly, neutrophil incubation with histamine (10 μM) also promoted CXCR2 internalization (Fig. 4B). Pretreatment of >neutrophils with an H₂ antagonist significantly prevented the histamine-induced CXCR2 downregulation (Fig. 4B). In addition, neutrophils incubated with histamine showed increased intracellular GRK2 expression compared with neutrophils incubated with RPMI (control). However, preincubation of neutrophils with an H₂ antagonist significantly diminished the histamine-induced upregulation of GRK2 expression (Supplemental Fig. 3B, 3C).

Enhanced infiltration of neutrophils into the inflammatory site was observed in air-pouch inflammation (42) and bacterial peritonitis (43) in histidine decarboxylase–deficient mice, which cannot produce histamine, indicates that histamine inhibits neutrophil recruitment. Thus, we examined the role of histamine in neutrophil recruitment in the septic peritonitis model. In vivo, administration of 3 or 10 μg histamine per mouse decreased the survival rates by ~30 and 50%, respectively, 5 d after MS surgery (Fig. 4C). Histamine administration also significantly inhibited neutrophil migration to the focus of infection, resulting in impaired infection control as shown by reduced bacterial clearance in the peritoneal cavity and an enhanced bacterial load in the blood (Fig. 4D, 4E). Moreover, systemic histamine administration significantly reduced the CXCR2 expression in the blood neutrophils in MS mice (Fig. 4F). Moreover, the H₂ antagonist treatment significantly prevented the downregulation of CXCR2 expression in neutrophils from mice given MS (Fig. 4F).

**MC deficiency protects diabetic mice from SS**

Next, we evaluated sepsis progression in mice lacking MCs (W/W) and their littermate controls (WB/B6). Our results showed that nondiabetic W/W mice were more susceptible to MS than control WB/B6 nondiabetic mice (Fig. 5A). We observed a significant decrease in neutrophil numbers in the peritoneal cavity accompanied by increased bacterial load at the focus of infection and in the blood of MS W/W nondiabetic mice compared with MS WB/B6 nondiabetic mice (Fig. 5B–D). In contrast, diabetic W/W mice with MS showed ~25% improvement in the survival rate compared with WB/B6 diabetic mice with MS (Fig. 5A). In parallel, we observed that diabetic WB/B6 mice given MS had a significant reduction in neutrophil migration and increased peri-

**FIGURE 3.** H₂ antagonism improves the septic peritonitis outcome in diabetic mice. The survival rates of diabetic mice with MS pretreated and posttreated with H₁, H₂, H₃/4 (A), or a combination of H₁ plus H₂ antagonists were evaluated daily for 5 d after CLP (B). The number of neutrophils into the peritoneal cavity (C) and the bacterial burden in the blood (D) were quantified 6 h after surgery. Quantitative analysis of the mean intensity of fluorescence (MFI) for CXCR2 in blood cells with high expression of GR-1 (neutrophils) was evaluated by flow cytometry (E). Evans blue concentrations were assessed in the PCL 2 h after CLP surgery (F). The results are expressed as the mean ± SEM (n = 5–7). These are representative graphs of at least two independent experiments. *p ≤ 0.05 compared with the nondiabetic sham-operated group; #p ≤ 0.05 compared with the nondiabetic MS group; &p ≤ 0.05 compared with the diabetic MS group.
toneal cavity and blood bacterial loads compared with nondiabetic
WB/B6 MS mice. In contrast, diabetic W/Wv mice displayed
higher neutrophil numbers and reduced bacterial loads in the
peritoneal cavity and blood compared with diabetic WB/B6 mice
after the MS induction (Fig. 5B–D). Analysis of blood neutrophils
by flow cytometry showed that MC deficiency did not affect
CXCR2 expression on neutrophils from nondiabetic mice with
MS, but prevented CXCR2 downregulation on neutrophils after
MS induction in diabetic mice (Fig. 5E).

**Discussion**

The factors that determine whether a particular infection in a di-
abetic mouse or patient will be successfully controlled or progress
to sepsis are not well understood. Neutrophils from diabetic mice
without any apparent infections already have functional abnor-
malities, including decreased phagocytic capacity (44) and che-
motactic responses (45). In addition, increased numbers of tissue
MCs have been found in clinical diabetes (46). Studies using ex-
perimental models also demonstrated that MCs are more abundant
in different tissues of diabetic rats compared with related nondi-
abetic rats (47). Consistent with these findings, we observed that
the increase in peritoneal MC numbers in diabetic mice coincided
with the severity of sepsis and impaired neutrophil migration
during septic peritonitis.

Based on these results, we evaluated the role of MCs in the
increased sepsis susceptibility of diabetic mice using several
approaches. Pretreatment of diabetic mice with C48/80 induced
marked neutrophil migration to the focus of infection, which was
associated with decreased bacteremia and an improvement in the
survival rate after MS. In agreement, we observed that the high
TNF-α and CXCL-2 levels in the serum of diabetic mice undergoing septic peritonitis were decreased by C48/80 treatment. The improved control of septic peritonitis in C48/80-pretreated diabetic mice could not be attributed to glucose metabolism effects, as the drug did not alter hyperglycemia. C48/80 pretreatment was previously demonstrated to prevent neutrophil migration impairment and systemic mediator release after SS (23). A different study showed that, after MC stabilization using cromolyn sodium, mice were protected from a lethal dose of i.v. Gram-negative bacteria (48). Overall, our results implicate MCs in both neutrophil migration impairment and systemic inflammatory mediator release in response to septic stimulus in diabetic mice.

Chemokines and their receptors play a pivotal role in regulating the activation and migration of leukocytes through the extracellular matrix (49). The importance of CXC-ELR+ chemokines and their receptors for host defense against infection has been demonstrated in various models (50, 51). In humans (52) and experimental sepsis (13), reduced neutrophil chemotaxis and migration were associated with decreased CXCR2 expression on circulating neutrophils. Similarly, we found that CXCR2 expression in neutrophils was significantly reduced during MS in diabetic mice, but neutrophils. Similarly, we found that CXCR2 expression in neutrophils was significantly reduced during MS in diabetic mice, but neutrophils. Similarly, we found that CXCR2 expression in neutrophils was significantly reduced during MS in diabetic mice, but neutrophils. Similarly, we found that CXCR2 expression in neutrophils was significantly reduced during MS in diabetic mice, but neutrophils. Similarly, we found that CXCR2 expression in neutrophils was significantly reduced during MS in diabetic mice, but neutrophils. Similarly, we found that CXCR2 expression in neutrophils was significantly reduced during MS in diabetic mice, but...
endothelial cells. These studies support our finding that the antagonist reversed the inhibitory effect of histamine on neutrophil chemotaxis (60). On the other hand, increased adhesion molecule expression in endothelial cells is promoted by histamine via H1 receptor desensitization perhaps via GRK2 upregulation. In support, another study also found that histamine-deficient mice control Escherichia coli infection better than wild-type mice, which was related to high leukocyte migration (43). Also, importantly, histamine is induced during acute M. tuberculosis infection and may dampen protective immunity by augmenting the inflammatory response associated with this disease (65).

MCs have been proposed to enhance survival by augmenting intracellular neutrophil killing through either IL-6 production (66) or through the action of MC proteases (67). In general, our findings support that activation of local MCs is crucial for host defense during bacterial infection because nondiabetic W/Wv mice had more sepsis mortality than WB/B6 nondiabetic mice. In contrast, we showed that diabetic W/Wv mice had lower sepsis mortality than WB/B6 diabetic mice. In agreement, other studies have shown that systemic MC activation exacerbates mortality during SS (24, 68). Although MCs may induce neutrophil recruitment and activation, and could have a protective role during acute local infection, these effects can be overcome and ultimately become detrimental during systemic and severe infections. In addition, along with improved survival, diabetic W/Wv mice undergoing MS had lower numbers of bacteria in the blood and increased neutrophil migration into the peritoneal cavity that were associated with decreased CXCR2 internalization, indicating that MC deficiency confers resistance to septic peritonitis in diabetic mice.

NOD mice spontaneously develop a form of diabetes that closely resembles the human disease (69). Accordingly, NOD mice were more susceptible to MS than prediabetic mice, with 50 and 25% mortality rates, respectively. Septic peritonitis was exacerbated in NOD mice when compared with prediabetic mice because these mice were unable to clear the polymicrobial infection, which then progresses to bacteremia. These effects correlated with increased MC numbers, increased serum histamine levels, impaired neutrophil migration, and downregulation of CXCR2 expression on blood neutrophils. H2 pretreatment of NOD mice promoted neutrophil chemotaxis and migration associated with maintenance of CXCR2 expression and, consequently, a better control of bacterial infection.

In conclusion, this study shows that MC degranulation induces neutrophil migration failure through CXCR2 receptor desensitization by a mechanism that is dependent on augmented GRK2 expression and that ultimately results in sepsis development. In addition, to our knowledge, we provide the first evidence that MCs appear to exert these harmful effects through the systemic release of histamine. Taken together, our results suggest that inhibition of histamine-mediated signaling through H2 antagonism might confer protection against sepsis onset in a diabetic host.

**Acknowledgments**

We are grateful to Giuliana Bertoti Francisco from the Laboratory of Inflammation and Pain of the School of Medicine Ribeirão Preto, University of São Paulo for help in the cytokine, chemokine, and histamine assays.

**Disclosures**

The authors have no financial conflicts of interest.


