Development of Large Numbers of Mast Cells at Sites of Idiopathic Chronic Dermatitis in Genetically Mast Cell-Deficient WBB6F1-/-W/W' Mice

By Stephen J. Galli, Naoki Arizono, Tatsuo Murakami, Ann M. Dvorak, and James G. Fox

The normal skin and other tissues of adult mast cell-deficient WBB6F1-/-W/W' or WCB6F1-SI/SI' mice contain <1.0% the number of mast cells present in the corresponding tissues of the congeneric normal (+/+ +) mice. As a result, genetically mast cell-deficient WBB6F1-/-W/W' or WCB6F1-/-SI/SI' mice are widely used for studies of mast cell differentiation and function. We found that mast cells developed at sites of idiopathic chronic dermatitis in WBB6F1-/-W/W' mice and that the number of mast cells present in the skin of WBB6F1-/-W/W' mice was proportional to the severity of the dermatitis (in ear skin, there were 3.1 ± 0.4 mast cells/mm² of dermis at sites of severe dermatitis x 9 ± 3 at sites of mild dermatitis, 0.8 ± 0.3 in skin without dermatitis, and 100 ± 7 in the normal skin of congenic WBB6F1-/-W/W' +/+/ mice; in back skin, the corresponding values were 2.0 ± 0.6, 1.1 ± 0.9, 0.025 ± 0.025, and 26.2 ± 3.2). The development of mast cells was a local, not systemic, consequence of the dermatitis. Thus, WBB6F1-/-W/W' mice with severe dermatitis lacked mast cells in skin not showing signs of dermatitis and also in the peritoneal cavity, stomach, cecum, and tongue. Idiopathic chronic dermatitis was not associated with the local development of mast cells in WCB6F1-/-SI/SI' mice, a mutant whose mast cell deficiency is due to a mechanism distinct from that of WBB6F1-/-W/W' mice. These findings may have implications for understanding the nature of the mast cell deficiency in WBB6F1-/-W/W' and WCB6F1-/-SI/SI' mice and for the use of these mutants to analyze mast cell differentiation and function.

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MATERIALS AND METHODS

Mice. Male mast cell-deficient W/W' mice and their normal (+/+) littermates (WB/ReJ-W/+ × C57BL/6J-W'/+ )F1r (W/W', +/+) and male mast cell-deficient SI/SI' mice and their normal (+/+) littermates (WC/ReJ-SI/+ × C57BL/6J-SI'/+ )F1r (SI/SI', +/+) were purchased from the Jackson Laboratories, Bar Harbor, ME, at 4 to 8 weeks of age. One group of pooled littermate WBB6F1-/-W/W', +/+) mice and a group of pooled littermate WCB6F1-/-SI/SI', +/+) mice were housed at the Beth Israel Hospital (BIH) Animal Care Facility. Another group of pooled littermate W/W' and congenic +/+ mice were housed at the Massachusetts Institute of Technology (MIT) Animal Care Facility. Both facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC), and the mice were maintained in accordance with guidelines established by the BIH and MIT Committees on Animal Research and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHHS publication 86-23, revised 1985).

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Submitted October 27, 1986; accepted January 21, 1987.

Supported in part by US Public Health Service Grants No. AI 20292, AI 22674, AI 23990, CA 28834, and RR 01046.

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0006-4971/87/6906-0018$3.00/0
Development of chronic dermatitis. Mice of the C57BL/6 and related strains develop a noncontagious and progressive severe dermatitis, apparently unrelated to known infections or nutritional factors. Murphy reported that SI/Sif and W/W' mutants were more susceptible to the development of such dermatitis than the congenic normal (+/+ +) animals. The dermatitis characteristically becomes apparent in older mice and presents as areas of erythema, hair loss, and cutaneous thickening, sometimes associated with the development of ulceration, that involves the skin of the ears and adjacent head, neck, dorsal part of the back, and axilla. Histologic assessment of dermatitis and morphological evaluation and quantitation of mast cells. Mice exhibiting evidence of dermatitis involving the ears and control mice with grossly normal ear skin were killed by cervical dislocation. The ears were then amputated and fixed and processed for 1-μm-thick, Epon-embedded, Giemsa-stained sections or for transmission electron microscopy as previously described. We also determined whether the mast cells that appeared at sites of idiopathic dermatitis in W/W' mice were stained with berberine sulfate, a fluorescent cationic dye that binds to the heparin in the cytoplasmic granules of mature "connective tissue-type" mast cells such as those normally present in the skin of mice. For these studies, representative skin specimens were fixed, processed, and stained with berberine sulfate (Sigma Chemical Co, St Louis) as previously described and examined in a Zeiss fluorescence microscope (Carl Zeiss, Inc, Thornwood, NY) equipped for epillumination. Biopsy samples were also obtained from areas of W/W' back skin exhibiting evidence of dermatitis as well as from the grossly normal back skin of W/W' and congenic +/+ mice. In some cases, additional, grossly normal tissues of W/W' mice with severe dermatitis were prepared for 1-μm sections (normal back skin, tongue, stomach, cecum), and toluidine blue-stained cytocoentrifuge preparations were made of the resident peritoneal cells. Peritoneal cells were collected by lavaging the peritoneal cavity with Hanks' balanced salt solution (HBSS, GIBCO, Grand Island, NY) containing 0.1% bovine serum albumin (Sigma). For quantitation of mast cell numbers, the coded 1-μm sections were examined by light microscopy at 400 x, and the number of mast cells present was recorded. The same slide was then projected onto a piece of paper with a Leitz Type XI C Xenon slide projector (Leitz, Rockleigh, NJ), and the following structures were traced: epidermal surface, dermal-epidermal junction, cartilage (in ear specimens), or panniculus carnosus (in back skin specimens). The area of dermis (mm²) was determined by analyzing the projected images using a MOP-3 digitizer (Zeiss) interfaced to an HP86 computer (Hewlett-Packard Co, Palo Alto, CA). The area of dermis for ear specimens was taken as the total area of ear minus the sum of the area of epidermis plus the area of cartilage; for back skin specimens, the area of dermis was taken as the total area between the dermal-epidermal junction and the superficial surface of the panniculus carnosus. The number of mast cells was expressed as the number of cells per square millimeter of dermis. Differences in mast cell counts were examined for statistical significance by the Mann Whitney U test (two-tailed).

RESULTS
Mast cells occur at sites of chronic dermatitis in WBB6F1-W/W' mice. We first examined 1-μm Epon-embedded, Giemsa-stained sections prepared from W/W' mouse ears exhibiting gross evidence of dermatitis as well as sections of grossly normal ears from W/W' and congenic +/+ mice. Based on the histologic findings, the dermatitis was classified as severe or mild (Fig 1). Ears with severe dermatitis exhibited marked epidermal and dermal thickening, dermal infiltration of leukocytes, and numerous mast cells (Fig 1A to E). By transmission electron microscopy (Fig 1E), the ultrastructure of mast cells at sites of severe dermatitis in W/W' mice closely resembled that reported previously for normal mouse mast cells. Moreover, these mast cells stained with berberine sulfate (Fig 1E, insert), a fluorescent dye that binds to the heparin in the cytoplasmic granules of mature skin mast cells. Ears with mild dermatitis exhibited slight epidermal thickening, little or no dermal thickening, sparse leukocytic infiltration, and occasional mast cells (Fig 1F).

We quantitated dermal mast cells in the ears of W/W' mice with severe or mild dermatitis as well as in the ears of normal W/W' or congenic +/+ mice (Table 1). Two different groups of pooled littermate W/W' mice were analyzed. One group (group A) was housed exclusively at B1H; these mice were killed at ~8 months of age. The other group (B), which included pooled littermate WBB6F1+/+ mice, was housed exclusively at MIT; these mice were killed at ~15 months of age. Approximately 50% of the W/W' mice in each group exhibited gross evidence of dermatitis involving at least one ear. By contrast, none of the pooled littermate +/+ mice in group B developed evidence of dermatitis.

In both groups, the ears of representative normal W/W' mice contained rare dermal mast cells (0.8/mm² of dermis). This value, representing <1% of the number of mast cells present in the ears of the congenic +/+ mice, is in good agreement with previous reports. However, dermal mast cells were increased approximately 11-fold at sites of mild dermatitis and 41-fold at sites of severe dermatitis (both values, P < .001 v the value in normal ears of W/W' mice). The number of mast cells in W/W' mouse ears with severe dermatitis, when expressed as the number per square millimeter of dermis, was significantly less than the number in the ears of +/+ mice (33.0 ± 7.5 v 100.0 ± 7.3, P < .001). But the distribution of mast cells in W/W' ears with dermatitis was uneven, with some areas of dermis containing many mast cells and others containing none (Fig 1B to D). Thus, the concentration of mast cells in some regions of W/W' ears with dermatitis probably approached or exceeded that in the normal ears of the congenic +/+ mice.

The development of mast cells at sites of chronic dermatitis is a local, not a systemic, consequence of the dermatitis. Two findings indicated that the development of mast cells at sites of dermatitis reflects a local consequence of the dermatitis. First, the number of dermal mast cells that developed in the ears of W/W' mice appeared to depend on the severity of dermatitis. This was true whether all ears exhibiting similar degrees of dermatitis were pooled, as in Table 1, or when the three W/W' mice that exhibited different degrees of involvement of their two ears were considered separately. The extent of dermatitis (none, mild, severe) and mast cell counts (number per square millimeter of dermis) for the left (L) and right (R) ears of these mice were as follows: mouse 14, L: mild, 24.1, R: none, 1.5; mouse 19, L: severe, 25.2, R: mild, 4.9; mouse 28, L: severe, 33.3, R: mild, 5.2.

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We also selected four W/W^v mice that had dermatitis and high mast cell counts in at least one ear (range, 20.3 to 57.7 mast cells/mm^2 of dermis) and examined multiple other anatomic sites or organs for the presence of mast cells. No mast cells whatsoever were detected in the normal back skin, tongue, forestomach, glandular stomach, cecum, or peritoneal cavity of these mice.

The number of mast cells at sites of chronic dermatitis varies according to anatomic site. Many of the W/W^v mice analyzed in Table I exhibited dermatitis involving the cephalad regions of the back as well as the ears. We therefore sampled the affected and unaffected back skin of these mice for histologic analysis and mast cell counts. Dermal mast cell counts in the normal back skin of both W/W^v and congenic...
other comparisons within group A, group B, or the combined group were significant at the P value indicated (Table 3). The data (no. of mast cells per square millimeter of dermis) are presented as mean ± SEM (no. of ears). In group A, the mast cell counts in ears with mild dermatitis were not significantly different (P < 0.05) than those in normal ears of W/W mice. All other comparisons within group A, group B, or the combined group were significant at the P < .001 level by the Mann Whitney U test (two-tailed).

Abbreviation: ND, not determined.

*The extent of dermatitis was assessed histologically.

+ / + mice (Table 2) were lower than those in the ear skin of mice of the same genotype (Table 1). At sites of severe dermatitis, the numbers of dermal mast cells in W/W mice were significantly elevated compared with the baseline levels (2.0 ± 0.6 v. 0.025 ± 0.025 mast cells/mm² of dermis, an 80-fold increase). Nevertheless, the number of mast cells at sites of severe dermatitis involving the back skin was only 6% of the corresponding figure for ear skin with severe dermatitis (2.0 v. 33.0 mast cells/mm², respectively, P < .001).

Chronic dermatitis is not associated with the local development of mast cells in WCB6F1-S1/S1 mice. Like WBB6F1-W/W mice, WCB6F1-S1/S1 mice are semisyn- geneic to C57BL/6 mice. Sl/S1 and WCB6F1-S1/S1 mice are similar in phenotype: both have a macrocytic anemia, lack cutaneous melanocytes, are sterile, and exhibit a profound deficiency in mast cells.22,23 Sl/S1 mice also spontaneously develop chronic dermatitis.13 However, the mechanisms of mast cell deficiency in W/W and Sl/S1 mice are different.22,23 W/W mice have a defect of hematopoietic stem cells (CFU-S)22,23; their mast cell deficiency (and anemia) can be repaired by intravenous (IV) transplantation of bone marrow cells derived from the congenic +/+ mice.26 By contrast, Sl/S1 mice have apparently normal hematopoietic stem cells.24 The mast cell deficiency of this mutant is thought to reflect an abnormality in the microenvironmental factors promoting mast cell differentiation/maturation,22,23 and neither the anemia nor the mast cell deficiency of Sl/S1 mice can be cured by IV transplantation of the congenic +/+ bone marrow cells.21

Twelve Sl/S1 mice were sacrificed at 12 months of age: 2 had no evidence of dermatitis, 3 had mild dermatitis, and 7 had severe dermatitis involving at least one ear and/or the adjacent neck and back skin. Virtually no mast cells were identified in the ear or back skin of Sl/S1 mice with dermatitis (Table 3). In other respects (extent of epidermal and dermal changes, inflammatory cell infiltration), the histologic features of the dermatitis in Sl/S1 and W/W mice were similar.

**DISCUSSION**

We found that large numbers of mast cells developed at sites of idiopathic chronic dermatitis in W/W mice. Several lines of evidence indicated that the development of mast cells at a site of dermatitis was a local, not a systemic, effect of the dermatitis. In ears with dermatitis, the number of dermal mast cells was greater in ears with severe dermatitis than in ears with mild dermatitis, and the greatest concentrations of mast cells in individual ears were at the sites exhibiting the most severe dermatitis. In a mouse with unilateral dermatitis, only the affected ear exhibited increased numbers of mast cells. Finally, no mast cells were detected in the normal skin, forestomach, glandular stomach, cecum, or peritoneal cavity of four W/W mice that had large numbers of mast cells at a site of severe dermatitis.

Although chronic dermatitis was associated with significantly elevated dermal mast cell counts in both the affected ears and back skin of W/W mice, the elevation of mast cell numbers was greater in the ears than in back skin. Thus, mast cell counts were 33.0/mm² of dermis in W/W mouse

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Dermatitis</th>
<th>Group A (8 mo old)</th>
<th>Group B (15 mo old)</th>
<th>Combined A + B</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/W</td>
<td>None</td>
<td>1.0 ± 1.0 (3)</td>
<td>0.7 ± 0.4 (7)</td>
<td>0.8 ± 0.3 (10)</td>
</tr>
<tr>
<td>W/W</td>
<td>Mild</td>
<td>3.2 ± 1.4 (4)</td>
<td>10.2 ± 3.3 (16)</td>
<td>8.8 ± 2.7 (20)</td>
</tr>
<tr>
<td>W/W</td>
<td>Severe</td>
<td>32.7 ± 5.1 (7)</td>
<td>33.2 ± 4.7 (14)</td>
<td>33.0 ± 3.5 (21)</td>
</tr>
<tr>
<td>+ / +</td>
<td>None</td>
<td>ND</td>
<td>100.0 ± 7.3 (16)</td>
<td>100.0 ± 7.3 (16)</td>
</tr>
</tbody>
</table>

Mast cell counts were performed as described in the legend to Table 1 (dermis equals the area from the epidermal-dermal junction to the superficial surface of the panniculus carnosus). The data, presented as mean ± SEM (no. of biopsy samples), are from the same mice shown in Table 1 (combined groups A and B).

*P < .001 v values for lines 1 or 4.

†P < .001 v values for lines 1, 2, or 3.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Dermatitis</th>
<th>No. Mast Cells/mm² of Dermis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. W/W</td>
<td>None</td>
<td>0.025 ± 0.025 (16)</td>
</tr>
<tr>
<td>2. W/W</td>
<td>Mild</td>
<td>1.1 ± 0.9 (5)</td>
</tr>
<tr>
<td>3. W/W</td>
<td>Severe</td>
<td>2.0 ± 0.6 (18)[*]</td>
</tr>
<tr>
<td>4. + / +</td>
<td>None</td>
<td>26.2 ± 3.2 (4)[†]</td>
</tr>
</tbody>
</table>

Mast cell counts were performed as described in the legend to Table 1 (dermis equals the area from the epidermal-dermal junction to the superficial surface of the panniculus carnosus). The data, presented as mean ± SEM (no. of biopsy samples), are from the same mice shown in Table 1 (combined groups A and B).

**Table 3. Dermal Mast Cell Counts in Normal WCB6F1-S1/S1 and WCB6F1-+ / + Mice and in WCB6F1-S1/S1 Mice With Idiopathic Dermatitis**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Dermatitis</th>
<th>A. Ear</th>
<th>B. Back Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. S1/S1</td>
<td>None</td>
<td>0 ± 0 (4)</td>
<td>0.03 ± 0.03 (13)[*]</td>
</tr>
<tr>
<td>2. S1/S1</td>
<td>Mild</td>
<td>0 ± 0 (8)</td>
<td>0 ± 0 (3)</td>
</tr>
<tr>
<td>3. S1/S1</td>
<td>Severe</td>
<td>0.03 ± 0.03 (10)[*]</td>
<td>0 ± 0 (2)</td>
</tr>
<tr>
<td>4. + / +</td>
<td>None</td>
<td>103.5 ± 9.8 (10)[†]</td>
<td>33.3 ± 2.6 (8)[†]</td>
</tr>
</tbody>
</table>

Mast cell counts were performed as described in the legends to Tables 1 and 2. The data are presented as mean ± SE (no. of ears or back skin biopsy samples).

*These values reflect the identification of a single mast cell in each of the two groups of specimens.

†P < .001 v any of the other values in columns A or B including the other value for + / + mice.

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**Table 1. Dermal Mast Cell Counts (per Square Millimeter of Dermis) in the Ears of Normal WBB6F1-W/W and WBB6F1-+ / + Mice and in WBB6F1-W/W' Mice With Idiopathic Dermatitis**

<table>
<thead>
<tr>
<th>Genotype</th>
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<tr>
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<td>None</td>
<td>1.0 ± 1.0 (3)</td>
<td>0.7 ± 0.4 (7)</td>
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<td>+ / +</td>
<td>None</td>
<td>ND</td>
<td>100.0 ± 7.3 (16)</td>
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</tr>
</tbody>
</table>

Mast cell counts were performed on 1-µm, Epon-embedded, Giemsa-stained sections of ears, and the area of dermis was calculated by planimetry of the projected image of the slide (see the text for details). The data (no. of mast cells per square millimeter of dermis) are presented as mean ± SEM (no. of ears). In group A, the mast cell counts in ears with mild dermatitis were not significantly different (P < 0.05) than those in normal ears of W/W mice. All other comparisons within group A, group B, or the combined group were significant at the P < .001 level by the Mann Whitney U test (two-tailed).

Abbreviation: ND, not determined.

*The extent of dermatitis was assessed histologically.
ears with severe dermatitis (33.0% of the corresponding value for normal +/+ mice) v 2.0/mm² of dermis in W/W° mouse back skin with severe dermatitis (7.6% of the corresponding value for normal +/+ mice). In part, this finding may be related to the fact that back skin normally contains fewer mast cells than ear skin (26.2 ± 100 mast cells/mm² of dermis in normal +/+ mice [P < .001], 0.025 ± 0.8 mast cell/mm² of dermis in normal W/W° mice [P < .1]). If the differences in the baseline mast cell counts in the normal ear and back skin of W/W° mice are taken into account, the elevations of mast cell numbers associated with chronic dermatitis are similar in the two anatomic sites (a 41-fold elevation over the normal value in the ear and an 80-fold elevation over the normal value in the back skin). There may be an interesting parallel to this finding in the effect of certain W locus mutations on melanocytes. Most mice with a double dose of mutations at the W locus totally lack cutaneous melanocytes.25 But certain of these mutants (eg, W/W°, W/W°) routinely or occasionally exhibit some pigmentation of the ear skin.25

The etiology of the chronic dermatitis that occurs in mice of the C57BL/6 and related strains is unknown.12,13 Attempts to identify conventional infectious agents have been unsuccessful,12,13 and neither histologic nor microbiologic examination (data not shown) of the mice used in our experiments revealed any clues concerning the pathogenesis of the problem. In accord with previous studies of SI/SI and W/W° mice, we found that our W/W° or SI/SI° mice developed a higher incidence of idiopathic dermatitis than did the congenic +/+ mice. Whether the increased susceptibility of the mutants for the development of idiopathic dermatitis has any relationship to the mast cell deficiency expressed by W/W° and SI/SI° mice is unclear.

The findings reported here are important for two reasons. First, they offer a new perspective concerning the nature of the mast cell abnormality expressed by W/W° mice. Although it is well known that the tissues of W/W° mice permit mast cell differentiation/maturation from competent precursor cells such as those derived from congenic +/+ mice,17 our data represent clear evidence that the mast cell deficiency of WBB6F°/W/W° mice can undergo local self-repair in vivo. This finding must reflect a response of the small number of mast cells present in the normal skin of W/W° mice and/or W/W° mast cell precursors to a dermatitis-associated alteration of the W/W° skin microenvironment. It is of interest, in this context, that several investigators have reported that mast cells of W/W° origin can be generated in vitro when hematopoietic cells of W/W° mice are cultured in media containing high levels of interleukin 3 and other growth factors.7,26,27 Moreover, such in vitro analysis indicates that the relative concentrations of mast cell precursors in the bone marrow, spleen, and peripheral blood of W/W° mice are similar to those in the congenic +/+ mice.27 These findings raise the possibility that one microenvironmental alteration at the sites of chronic dermatitis that might contribute to the local development of W/W° mast cells is the production of growth factors similar to those present in the in vitro systems.

On the other hand, W/W° mast cells generated in suspension cultures exhibited diminished proliferative potential in vitro26 and failed to survive and mature after injection into normal W/W° mice in vivo.7 By contrast, many of the mast cells present at sites of idiopathic dermatitis in W/W° mice were mature according to light and electron microscopic criteria and as judged by staining of the cytoplasmic granules with berberine sulfate. Thus, the local alterations produced in association with chronic idiopathic dermatitis resulted in both the marked elevation of the number of dermal mast cells and the expression, by these cells, of a mature phenotype. These effects might reflect the continuous local production of soluble mast cell growth/maturation factors and/or other significant alterations at the site of dermatitis. But whatever the reason(s) for mast cell development at sites of idiopathic dermatitis, elucidation of the mechanisms responsible for this effect is likely to provide additional insight into the nature of the mast cell defect expressed by W/W° mice.

The second important implication of our findings concerns the use of genetically mast cell–deficient mice to study mast cell function in vivo. W/W° mice are widely used to analyze the roles of mast cells in diverse biologic responses.8,9,10,28 Our findings show that it is critical to search for the “spontaneous” appearance of mast cells at sites of inflammatory or pathological processes under investigation in W/W° mice, particularly in those studies involving models of chronic disease processes. It is of interest that the changes associated with the idiopathic dermatitis that occurred in SI/SI° mice apparently were unable to alter significantly the microenvironmental defect thought to be responsible for the failure of mast cell differentiation/maturation in this mutant.22 This result indicates that for certain studies of mast cell biology WCB6F°(-SI/SI°, -/+ /+) mice may represent a more appropriate choice than the WBB6F°(-W/W°, -/+ /+) animals.

ACKNOWLEDGMENT

We thank Susan Kissel for expert technical assistance with the electron microscopy and an anonymous reviewer for calling our attention to the presence of melanocytes in the ears of some W mutant mice.

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