

NECESSITY OF IgE ANTIBODIES AND MAST CELLS FOR MANIFESTATION OF RESISTANCE AGAINST LARVAL *Haemaphysalis longicornis* TICKS IN MICE¹

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Genetically mast cell-deficient WBB6F₁-W/W^m mice showed an apparent defect in manifestation of the resistance against larval *Haemaphysalis longicornis* ticks, but their serum IgE levels increased more than 100-fold after the second tick infestation. Immune sera obtained from the WBB6F₁-W/W^m mice were adoptively transferred to the other WBB6F₁-W/W^m mice which had received intracutaneous injections of WBB6F₁-+/+ mouse-derived cultured mast cells. Because the resistance against ticks was detectable only when both mast cells and IgE antibodies were available, immediate hypersensitivity reaction appeared to have a physiologic role in the manifestation of the resistance against *H. longicornis* ticks.

Mast cells have high affinity IgE receptors on their surface, and the immunologic activity of mast cells is mediated through these IgE receptors (1). Binding of Ag to IgE molecules results in the formation of linkages between IgE receptors, and then the release of the granules themselves or chemical mediators in the granules. This process constitutes an essential step in the immediate hypersensitivity reaction. In addition to having a role in allergic diseases, mast cells have a physiologic role as an effector of host defense mechanisms in intestinal helminth infection (2-5) and dermal tick infestation (6-10). Although the mechanism by which IgE antibodies contribute to host resistance is not always clear, there is a large amount of evidence indicating that IgE- (or, in guinea pigs, IgG1-) dependent mechanisms of mast cell or basophil degranulation occur during immune reactions associated with resistance to infection with intestinal and cutaneous parasites (11). In particular, IgE or IgG1 antibodies have been demonstrated to be involved in resistance to feeding of larval *Amblyomma americanum* ticks in the guinea pig (12, 13).

Genetically mast cell-deficient WBB6F₁-W/W^m mice are used to investigate the defense mechanism against ticks.

When larval *Haemaphysalis longicornis* ticks are applied to the skin of WBB6F₁-W/W^m mice and control WBB6F₁-+/+ mice, the WBB6F₁-+/+ mice acquired the resistance against ticks, but the WBB6F₁-W/W^m mice did not (6). After the bone marrow transplantation from WBB6F₁-+/+ mice, mast cells developed in the skin of WBB6F₁-W/W^m mice, and the rescued WBB6F₁-W/W^m mice acquired the resistance. Moreover, the resistance was observed in the skin pieces grafted from WBB6F₁-+/+ mice onto the back of WBB6F₁-W/W^m mice. Since these results suggested a significant role of mast cells, we directly injected bone marrow-derived cultured mast cells into the skin of WBB6F₁-W/W^m mice (7). The resistance was detectable only at the injection sites where mast cells appeared, confirming the involvement of mast cells in the tick rejection.

In the present study, we examined whether IgE antibodies are also involved in the rejection. Immune sera were obtained from WBB6F₁-W/W^m mice, which did not reject ticks at their own skin, and were adoptively transferred to the other WBB6F₁-W/W^m mice which had received intradermal injections of cultured mast cells. We found that both immune sera containing anti-tick IgE antibodies and the presence of mast cells at the infestation site were prerequisite for manifestation of the tick rejection.

MATERIALS AND METHODS

Mice. Genetically mast cell-deficient WBB6F₁-W/W^m mice and control WBB6F₁-+/+ mice were raised in our laboratory (14); male mice of 10 to 15 wk of age were used.

Ticks. Parthenogenetic *H. longicornis* of the Okayama strain was supplied by Drs. K. Fujisaki and S. Kitaoka of the National Institute of Animal Health, Ibaragi, Japan. Ticks of all stages were fed on ears of Japanese White rabbits according to the method described by Saito (15). Engorged ticks were maintained at continuous darkness, 100% relative humidity, and 25°C. Larvae of 4 to 8 wk of age were used for cutaneous infestation on mice.

Cultured mast cells. Bone marrow cells of WBB6F₁-+/+ mice were cultured at 10⁶ cells/ml in 2 medium supplemented with 10⁻⁴ M 2-ME, 10% FCS and 10% PWM-SCM.³ The method to prepare PWM-SCM has been described (16), and PWM-SCM contains both IL-3 and IL-4 (17). Culture flasks (Nunc, Roskilde, Denmark) were incubated at 37°C in a humidified atmosphere of 5% CO₂, 95% air. Half of the medium was replaced every 7 days. As described by Nakano et al. (18), more than 95% of cells were identified as mast cells 4 wk after the initiation of the culture; the cells were harvested, washed, and resuspended in Eagle's medium at the concentration of 10⁶ cells/0.2 ml.

Cell injection. The method has been described (7). Ten intracutaneous injections (each injection volume, ~0.02 ml) were done within a circle (16 mm in diameter) on the left flank of a WBB6F₁-

³ Abbreviations used in this paper: PWM-SCM, PWM-stimulated spleen cell-conditioned medium; PCA, passive cutaneous anaphylaxis.

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W/W^u mouse (total number of injected cells, 10⁶). India ink was mixed with the suspension medium for later identification of the injection site (19). Control WBB6F₁-W/W^u mice were injected with the suspension medium containing India ink alone.

Tick infestation. Hair on the left flank of mice was clipped; an acrylic ring (16 mm in diameter) was held in place by an adhesive (Aron Alpha A, Sankyo Co., Tokyo, Japan) on the day before tick infestation. Larval ticks were chilled and counted in Petri dishes on ice. Within 0.5 to 1 h, 40 larvae were confined on the skin inside of the acrylic ring. To inhibit the escape of ticks, the open end of the acrylic ring was covered with nylon gauze. The infestation was continued for 10 days in which larval ticks completed the feeding. Only ticks that detached over a period up to 10 days were defined as being engorged; the wet weight of engorged ticks was recorded on the day of detachment. The percent tick yield (number of engorged ticks ÷ number of applied ticks × 100) was calculated.

Immune serum. WBB6F₁-W/W^u mice were infested with 40 larval ticks, and were reinfested 2 wk after the initiation of the first infestation. Ten days after the initiation of the second infestation, blood samples were collected from the axillary artery of the mice under ether anesthesia. Sera were obtained by centrifugation, and were divided into two parts. An aliquot of sera was heated at 56°C for 2 h to inactivate IgE antibodies. The inactivated sera and the remaining nontreated sera were stored at -20°C until use.

Assay for total IgE. Total IgE levels in sera were measured by a sandwich ELISA technique by using two kinds of rat anti-mouse IgE mAb according to the method described by Watanabe et al. (20).

Histologic examination. The mice were killed 10 days after the initiation of the infestation; skin pieces of the infestation site were removed. Small pieces were cut and fixed in Carnoy's fluid. Paraffin sections (5 µm thick) were made by the routine method and were stained with toluidine blue (21). In some of cases, sections were stained with berberine sulfate, and then the same specimens were stained with Alcian blue. Berberine sulfate is a fluorescent dye which specifically stains heparin (22, 23). The method and specificity of berberine sulfate staining have been described elsewhere (18).

Tick Ag. Larval ticks were frozen and thawed in PBS, and then sonicated for 30 s at 130 W; this procedure was repeated five times. The sonicated preparations were centrifuged at 10,000 × g for 20 min, and pooled supernatants were used as tick Ag.

PCA. Immune sera (0.5 ml) were i.v. injected to WBB6F₁-W/W^u mice which had received intracutaneous injections of cultured mast cells. One day after the transfer of serum, 0.2 ml of Evans blue solution (0.25% wt/vol in PBS) was i.v. injected and then 20 µl of tick Ag (5 µg protein) was injected at the skin site where cultured mast cells had been injected; dye infiltration into skin tissues was examined 20 min after the injections of tick Ag. Data were expressed as the mean of two perpendicular diameters.

Statistical analysis. Student's *t*-test was done for statistical approval of the data.

RESULTS

Mast cell-deficient WBB6F₁-W/W^u mice were infested with larval *H. longicornis* ticks. As described in our previous report (6), both tick yields and tick weights were not decreased even in the second infestation, indicating the inability to acquire the resistance. When concentration of total IgE in sera was examined, the concentration after the second infestation (2.7 µg/ml, mean of 8 mice) was more than 100 times as great as the value observed in nontreated WBB6F₁-W/W^u mice (0.016 µg/ml, mean of 5 mice).

The immune sera obtained from WBB6F₁-W/W^u mice were i.v. injected into WBB6F₁-W/W^u mice 6 wk after the intradermal injections of cultured mast cells. Three groups of mice were prepared as controls; 1) the immune sera were i.v. injected into WBB6F₁-W/W^u mice that had received intradermal injections of medium alone; 2) pooled sera of nontreated WBB6F₁-W/W^u mice were i.v. injected into WBB6F₁-W/W^u mice that had received the injections of cultured mast cells; 3) the immune sera were heated and then i.v. injected into WBB6F₁-W/W^u mice that had received the injections of cultured mast cells. All groups of mice were infested with larval *H. longicornis* ticks 1 day after the injection of sera. Attachment of ticks was observed within a day after the infestation in

all groups of mice. Numbers and weights of engorged ticks were significantly decreased in WBB6F₁-W/W^u mice which had received both cultured mast cells and immune sera, whereas these parameters did not change significantly in three control groups of mice (Table I).

Histologically, no mast cells were detectable in the infestation site of WBB6F₁-W/W^u mice which had received injections of medium alone instead of injections of cultured mast cells. Even in such infestation sites, hyperplasia of the epithelium was observed (Fig. 1). When WBB6F₁-W/W^u mice had received intradermal injections of cultured mast cells, numbers of mast cells at the infestation sites were not significantly influenced by the type of i.v. injected sera, i.e., immune, nonimmune, or heated immune sera (data not shown). Degranulation of mast cells was marked in the infestation sites of WBB6F₁-W/W^u mice which had received both cultured mast cells and immune sera but was moderate in the infestation sites of mice which had received intradermal injections of cultured mast cells and the i.v. injection of either nonimmune sera or heated immune sera (Fig. 1).

Cultured mast cells used in the present experiment were not stained with berberine sulfate, suggesting no heparin content. However, most mast cells that appeared at the injection sites of cultured mast cells stained with either Alcian blue or berberine sulfate. This is consistent with the result of the previous study (7).

PCA was examined to confirm the interaction of tick Ag with IgE molecules, which were bound to the receptors on the surface of mast cells. When tick Ag were applied to the injection site of cultured mast cells 1 day after the transfer of immune sera, extravasation of Evans blue occurred (Table II and Fig. 2).

DISCUSSION

Although mast cell-deficient WBB6F₁-W/W^u mice did not manifest the resistance against *H. longicornis*, the serum IgE levels increased more than 100-fold after the second infestation. This appears to be consistent with the result of Kojima et al. (3) who demonstrated the increase of IgE levels in WBB6F₁-W/W^u mice infested with *Nippostrongylus brasiliensis*. Kojima et al. showed nonspecific elevation of anti-DNP IgE antibodies during the infestation of *N. brasiliensis*. However, two experiments of the present study demonstrated the increase of specific anti-tick IgE antibodies: 1) the capacity of the immune sera to transfer the anti-tick resistance was abolished by heating and 2) PCA was successful by using the immune sera.

Mast cells appeared at the injection sites of cultured mast cells in the skin of WBB6F₁-W/W^u mice. Because these mast cells were stained with Alcian blue, toluidine blue, and berberine sulfate, the cells appear to be connective tissue-type mast cells that contain heparin.

The present result clearly demonstrates the necessity of both IgE antibodies and mast cells for the manifestation of the resistance against ticks. The PCA reaction with tick Ag was observed 1 day after the systemic administration of the immune sera, and attachment of ticks to the skin was observed within a day after the infestation. Therefore, IgE antibody-mediated immediate hypersensitivity reaction is considered to have a physiologic role for the resistance against ticks.

In a similar experimental system, Werthil et al. (24) demonstrated that the ability of the skin of mice to ex-

TABLE I
Adoptive transfer of immune sera to WBB6F₁-W/W^v mice of which mast cell deficiency was locally rescued by injections of cultured mast cells

Treatment of Infestation Sites ^a	Serum Transferred ^b	No. of Mice	Mean ± SE	
			Tick Yield (%)	Tick Weight (mg)
Injection of medium	Immune	7	98.9 ± 0.7	0.679 ± 0.010
Injection of cultured mast cells	Nonimmune ^c	7	95.7 ± 1.9	0.694 ± 0.012
Injection of cultured mast cells	Immune	7	58.9 ± 10.4 ^d	0.651 ± 0.006 ^d
Injection of cultured mast cells	Immune but heated ^e	7	90.4 ± 5.1	0.692 ± 0.010

^a Cultured mast cells (10⁶ cells) were injected into the skin of WBB6F₁-W/W^v mice 6 wk before the serum transfer.

^b Donor WBB6F₁-W/W^v mice were infected with 40 larval ticks, and reinfested 2 wk later. Sera were obtained 10 days after the second infestation. WBB6F₁-W/W^v mice were injected i.v. with 0.5 ml of serum, and on the next day 40 larval ticks were infested.

^c Pooled sera of nontreated WBB6F₁-W/W^v mice.

^d $p < 0.02$, when compared to other groups.

^e Immune sera were heated at 56°C for 2 h.

TABLE II

PCA by intracutaneous injection of tick Ag 1 day after i.v. injection of immune sera in WBB6F₁-W/W^v mice locally rescued by injections of cultured mast cells

Serum Transferred ^a	No. of Mice	Reaction Size (mm) ^b
Nonimmune ^c	5	2.7 ± 0.7
Immune	4	12 ± 1.1 ^d
Immune but heated ^e	4	2.5 ± 0.9

^a Cultured mast cells (10⁶ cells) were injected into the skin of WBB6F₁-W/W^v mice 6 wk before the serum transfer. Sera were obtained 10 days after the second infestation. WBB6F₁-W/W^v mice were injected i.v. with 0.5 ml of serum, and on the next day 20 µl of tick (5 µg protein) was injected intracutaneously at the skin where cultured mast cells had been injected.

^b Each value is expressed as mean ± SE.

^c Pooled sera of nontreated WBB6F₁-W/W^v mice.

^d $p < 0.001$, when compared to other groups.

^e Immune sera were heated at 56°C for 2 h.

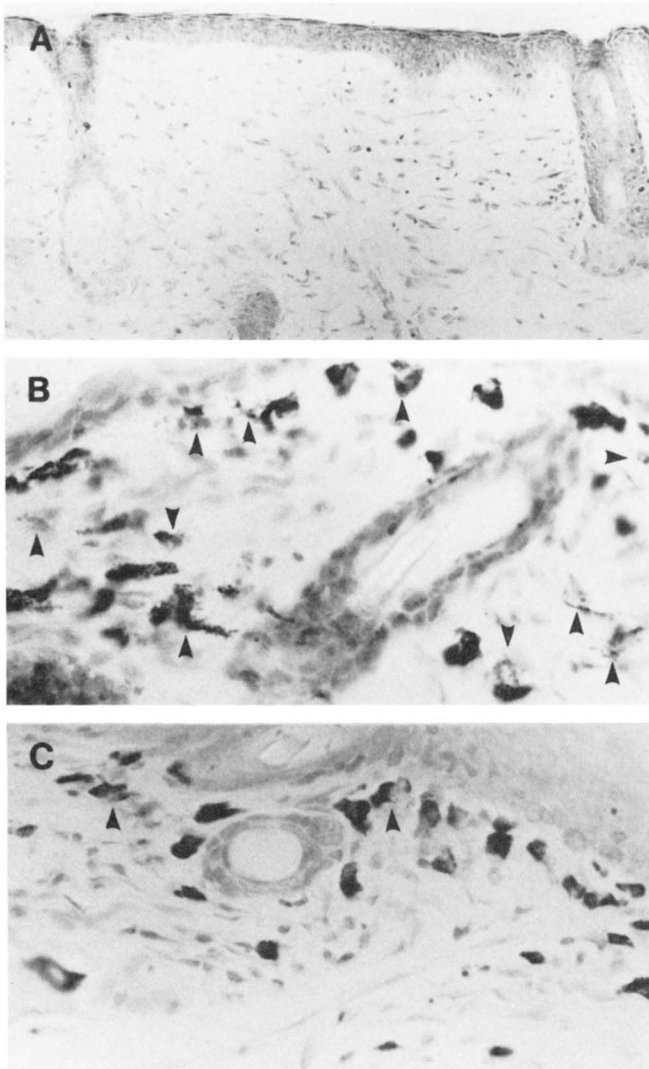


Figure 1. Histologic features of the skin 10 days after the initiation of infestation, toluidine blue stain. A. The feeding site of a control WBB6F₁-W/W^v mouse that had been injected with immune sera 6 wk after the intracutaneous injections of the suspension medium alone (×150). Hyperplasia of the epithelium is marked but no mast cells are detectable. B. The feeding site of a WBB6F₁-W/W^v mouse that had been injected with immune sera 6 wk after the intracutaneous injections of cultured mast cells (×450). Degranulation of numerous mast cells is observed (arrowheads). C. The feeding site of a WBB6F₁-W/W^v mouse that had been injected heated immune sera 6 wk after the intracutaneous injections of cultured mast cells (×450). Degranulation of relatively small number of mast cells is observed (arrowheads).

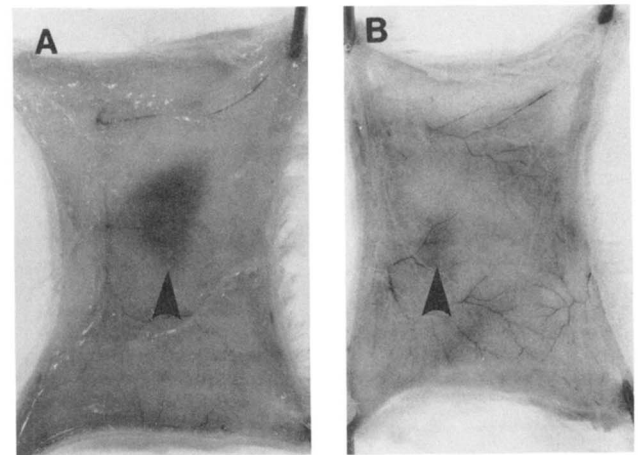


Figure 2. PCA (arrowheads) by intracutaneous injection of 20 µl (5 µg) of tick Ag at the injection site of cultured mast cells, 1 day after i.v. injection of immune sera (A) or heated immune sera (B). Apparent dye infiltration is detectable in (A) but not in (B).

press IgE-dependent PCA reactions was dependent on the presence of mast cells as well as IgE. WBB6F₁-W/W^v mice locally reconstituted with cultured mast cells were injected with monoclonal anti-DNP IgE. When the WBB6F₁-W/W^v mice were challenged with DNP-conjugated human serum albumin, ¹²⁵I-fibrinogen influx and ¹²⁵I-fibrin deposition associated with PCA reactions were induced at the injection sites of the cultured mast cells.

Several investigators (8, 25, 26) found marked infiltration of basophils at the tick feeding sites of guinea pigs, and discussed the importance of basophils in manifestation of resistance against ticks. Brown et al. (12) and Brown and Askenase (26) reported that rejection of *A. americanum* ticks was associated with extensive local

basophil degranulation in guinea pigs and considered that IgG1 antibody-mediated PCA reactions were involved in the resistance against ticks. In cattle, Schleger et al. (10) described numerous degranulated mast cells at attachment sites of *Boophilus microplus* ticks and suggested a role of mast cells in manifestation of the resistance. Although basophils were detected in the bone marrow (27) and blood (28) of mice, we could not find the significant participation of basophils in manifestation of the resistance against larval *H. longicornis* ticks.

Kemp and Bource (29) demonstrated early detachment of *B. microplus* ticks in cattle after the injection of histamine into the feeding sites. Moreover, administration of antihistamine drugs was effective to block manifestation of resistance against *B. microplus* and *Dermacentor andersoni* ticks in cattle (30, 31) and guinea pigs (32), respectively. There is a possibility that histamine released from mast cells may inhibit feeding of ticks. There is another possibility that histamine result in itchy skin. This may induce the animal to scratch the itch, thereby either kicking ticks off the animal or crushing engorged ticks (10). However, in the present experiment, ticks were confined on the skin inside of the acrylic ring; the open end of the acrylic ring was covered with nylon gauze. Therefore, the decrease in number of ticks cannot be explained by kicking off or crushing induced by the mast cell-derived histamine. Moreover, in *A. americanum* infestation of guinea pigs (13), resistant responses were not affected by histamine H-1 and H-2 receptor antagonists, suggesting that mediators other than histamine from basophils or mast cells may be involved in the rejection of *A. americanum* ticks.

WBB6F₁-W/W^u mice have been also used to demonstrate a role of mast cells against helminths. The infestation of *Strongyloides ratti* (4) and that of *Trichinella spiralis* (2, 5) prolonged in WBB6F₁-W/W^u mice, and the bone marrow transplantation from WBB6F₁-+/+ mice normalizes the resistance against helminths. However, Watanabe et al. (33) recently raised a possibility that the mechanism of anti-helminth reaction may be different from that of anti-tick reaction. The IgE-mediated immediate hypersensitivity reaction might not be used in the anti-helminth reaction of mast cells, because the anti-helminth reaction was observed even in genetically IgE-deficient SJA/9 mice (33).

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