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Intraepithelial Infiltration by Mast Cells with Both Connective Tissue-Type and Mucosal-Type Characteristics in Gut, Trachea, and Kidneys of IL-9 Transgenic Mice

Catherine Godfraind,† Jamila Louahed,‡ Helen Faulkner,‡ Anne Vink,‡ Guy Warnier,‡ Richard Grencis,‡ and Jean-Christophe Renauld‡

IL-9 transgenic mice were analyzed for the presence of mast cells in different tissues. In these mice, increased mast cell infiltration was found in the gastric and intestinal epithelium as well as in the upper airways and kidney epithelium, but not in other organs, such as skin. IL-9 transgenic mast cells do not show signs of massive degranulation such as that found in IL-4 transgenic mice and are not involved in spontaneous pathologic changes. Gastric mast cells showed a phenotype related to connective-type mast cells, since they were stained by safranin, and strong expression of mouse mast cell protease-4 and -5 was found in this organ. However, they also expressed proteases related to the mucosal cell type, such as mouse mast cell protease-1 and -2. In vitro, although IL-9 by itself did not induce mast cell development from bone marrow progenitors, it strongly synergized with stem cell factor for the growth and differentiation of mast cells expressing the same protease pattern as that observed in IL-9 transgenic mice. Since constitutive stem cell factor expression was observed in vivo, and anti-c-Kit Abs inhibited IL-9 transgenic mastocytosis in the gut, this synergistic combination of factors is likely to be responsible for the mastocytosis observed in IL-9 transgenic mice. Taken together, these data demonstrate that IL-9 induces the in vivo amplification of a nonclassical mast cell subset with a mucosal localization but expressing proteases characteristic of both connective tissue-type and mucosal mast cells. The Journal of Immunology, 1998, 160: 3989–3996.

IL-9 is a cytokine produced by activated Th2 lymphocytes and is active on various cell types from the hemopoietic and lymphoid systems (1). Originally identified as a T cell growth factor (2), IL-9 also acts as a potent mast cell growth factor in vitro in murine systems, alone or in synergy with IL-3 (3). In vivo, infections of mice by helminth parasites typically induce intestinal mastocytosis as well as a strong expression of Th2 cytokines, including IL-9 (4). The protective role of Th2 activation in such infections has been demonstrated recently, as IL-12 injection during a primary Nippostrongylus brasiliensis infection completely abolished the IL-4, IL-5, and IL-9 expression induced by the parasite as well as the intestinal mastocytosis, resulting in increased parasite survival and egg production (5).

While all tissue mast cells are derived from a common hemopoietic progenitor cell, it is now apparent that they exist in vivo and in vitro as a heterogeneous family of effector cells. Based on their secretory granule proteoglycans and proteases, the differentiated mast cells in rodents are classified into at least two phenotypically distinct populations: connective tissue-type mast cells (CTMC) and mucosal mast cells (MMC) (6). Safranin-positive granules of CTMC contain large amounts of heparin proteoglycans and mouse mast cell protease-4 (mMCP-4), -5, and -6, but no mMCP-1 or -2 (7–10). In contrast, the safranin-negative MMC showed no major abnormality in the immune system. Here, we report that mast cell infiltration is found in the intestinal tract and upper airways of IL-9 transgenic mice. These mast cells are characterized by an intraepithelial localization and a mixed phenotype sharing MMC and CTMC properties, similar to the phenotype of mast cells cultured in vitro in the presence of SCF and IL-9.

Materials and Methods

Transgenic mice

IL-9 transgenic mice were generated using a fusion gene consisting of an IL-9 genomic fragment linked to the promoter of the murine pim-1 gene.

Abbreviations used in this paper: CTMC, cutaneous-type mast cell; MMC, mucosal mast cell; mMCP, mouse mast cell protease; BMMC, bone marrow-derived mast cell; SCF, stem cell factor.
including the TATA box and the cap site, followed by two copies of the Eμ enhancer and one copy of the Moloney murine leukemia virus long terminal repeat (17). Two independent strains of homozygous transgenic mice, designated Tg5 and Tg54, were used in this study. Both strains have circulating IL-9 levels >1 μg/ml while IL-9 is undetectable in the serum of control FVB mice.

**Tissue preparation and sections for conventional histology and electron microscopy**

Organs were fixed by immersion for 24 h in Bouin’s fixative before embedding in paraffin. Five-micron sections were prepared and stained with hematoxylin-eosin (18). Gene expression in these sections was investigated using in situ hybridization and immunohistochemistry.

**RT-PCR analysis of mMCP transcripts**

Total cellular RNA was isolated by the guanidine-thiocyanate/CsCl ultracentrifugation method, and reverse transcription was performed on 10 μg of total RNA with an oligo(dT) primer. cDNA corresponding to 100 ng of total RNA was amplified for 14 cycles by PCR with specific primers as indicated in Table I. For mMCP-1, -2, and 4, a single PCR amplification was performed with primers designed from regions that were perfectly conserved between the various mouse and human mMCP genes. For mMCP-7, a nested amplification was performed using primers designed from regions that were perfectly conserved between the various mouse and human mMCP genes. For mMCP-5, a single PCR amplification was performed using primers designed from regions that were perfectly conserved between the various mouse and human mMCP genes. For mMCP-6, a single PCR amplification was performed using primers designed from regions that were perfectly conserved between the various mouse and human mMCP genes.

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<tr>
<th>Target</th>
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<td>IL-9</td>
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<td>5′-GGTACCGTCTTCCCTGGAGTAC-3′</td>
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**Bone marrow derived in vitro cultures**

Murine rIL-3 produced in CHO cells was provided by Dr. T. Burgess (The Ludwig Institute, Melbourne, Australia). Murine rIL-9 was produced in the baculovirus system and purified as previously described (22). The cDNA encoding the murine SCF was amplified by PCR based on the published sequence (23) with a 3′ primer introducing a stop codon just upstream of the region encoding the transmembrane domain. This cDNA was expressed in COS cells, and the activities of supernatants were assessed by their ability to induce Mo7e cell proliferation. These supernatants contained 60 U/ml of SCF, corresponding to approximately 600 ng/ml based on the comparison with recombinant human SCF (PeproTech, Rocky Hill, NJ).

Mouse BMNC were obtained by culturing bone marrow from 4-wk-old BALB/c mice for 15 days in enriched medium (RPMI 1640 containing 0.55 mM l-arginine, 0.24 mM l-asparagine, 1.25 mM l-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin, 50 μg/ml 2-ME, and 20% FCS) supplemented with various combinations of murine rIL-3 (1 ng/ml), IL-9 (200 U/ml), and SCF-transfected COS cells (5%). Supernatants from mock-transfected COS cells were used as a control and proved completely inactive. Every 4 days, the nonadherent cells in the cultures were transferred into new flasks and suspended into fresh culture medium supplemented with the appropriate combination of cytokines.

**Results**

**Mast cell infiltration in the digestive tract of IL-9 transgenic mice**

Since during helminth infections, mast cells frequently accumulate in the digestive tract concomitantly with IL-9 production, we investigated the possible causative role of IL-9 in this process by examining the gut of IL-9 transgenic mice. While the epidermoid esophagus was very similar in transgenic and normal mice, the...
glandular stomach in IL-9 transgenic mice showed greater numbers of mast cells, located mainly between epithelial cells from the upper part of the mucosa (Fig. 1). Not only were the total numbers of mast cells increased by a factor of 5 to 10 in transgenic animals, but those observed in normal mice were mostly located in the connective tissue. In IL-9 transgenic mice, mast cells appeared metachromatic with Giemsa staining and positively stained with chloroesterase-specific staining. Unexpectedly, they were also stained with safranin (Fig. 1A), a feature considered a marker of serosal mast cells found in the skin and the peritoneal cavity. They also had the capacity to bind biotinylated IgE (data not shown). By electron microscopy, these cells bore nonuniform electron-dense granules whose membranes were ill defined, and some cells showed partially degraded granules (data not shown).

In the small and large intestines, two distinct types of cells were detected specifically in IL-9 transgenic mice. Increased numbers of chloroesterase-positive mast cells were found in the muscularis mucosae of the small intestine of IL-9 transgenic mice compared with those in normal mice. These cells were observed mainly in close proximity to mucosal lymph nodes, as illustrated in Figure 2, E and F, pointing to a possible role for lymphocytes in this process. However, we did not observe any significant increase in mast cells in other lymphoid organs, including the thymus, spleen, and lymph nodes of IL-9 transgenic mice, compared with the control strain (data not shown).

On the other hand, after hematoxylin-eosin staining, IL-9 transgenic mice showed an infiltration between enterocytes of many round cells with a granular eosinophil content (Fig. 2A). Although these cells are morphologically related to mast cells and were stained by toluidine blue, we failed to characterize them as mature mast cells by other current staining methods. They were not metachromatic with Giemsa staining (Fig. 2C), did not stain for chloroesterase (Fig. 2D), and showed no detectable IgE binding (data not shown). These cells were not detected in normal control mice, whereas they were abundant (~400 cells/mm²) in the lower part of the villi and the upper part of the crypts in IL-9 transgenic mice. By electron microscopy, these cells showed granules of a size compatible with mast cell granules. Many of them were characterized by the presence of heterogeneous material and crystal-like inclusions, but could easily be distinguished from eosinophil granules (Fig. 3). Taken together, these histologic and morphologic features suggest that these cells represent mast cells that have not (yet) completed the conventional differentiation pathway, pointing to a relationship with recently identified mast cell progenitors (24).

Analysis of mast cell infiltration in other tissues

Analysis of sections from the respiratory tract from control and IL-9 transgenic animals also revealed an increase in mast cell numbers in IL-9 transgenic mice. These cells were characterized by positive staining for chloroesterase and contained metachromatric granules. By contrast, in control mice, mast cells were observed only very rarely in the respiratory tract. Noticeably, in IL-9 transgenic mice, mast cells were much more numerous in the upper tract (trachea: Fig. 4, A and B), whereas they were only occasionally found in bronchioles and alveoli (data not shown). A striking feature of these cells is their location within the epithelial cell layer (Fig. 4A). In adipose tissue surrounding the trachea, only a small increase in mast cell numbers was observed in IL-9 transgenic vs control mice (data not shown).

Examination of other tissues from transgenic animals indicated that the mastocytosis was not uniformly distributed. Mast cells were indeed not detected in liver; endocrine tissues, such as thyroid, pancreas, and adrenal glands; or the central nervous system. For the skin, no difference in the number or location of mast cells was observed in IL-9 transgenic mice compared with control mice (data not shown). We did not find circulating mast cells in the blood of these mice, but increased concentrations of mast cell protease mMCP-1 were observed in the serum of IL-9 transgenic mice (12,000 ng/ml, compared with 5 ng/ml in normal mice), most likely reflecting mast cell infiltration in gut and lungs.

In addition to the respiratory tract, kidneys of IL-9 transgenic mice contained increased numbers of mast cells. Interestingly, these cells were located in the epithelial cell layer of both proximal and distal tubes (Fig. 4C). In kidneys from control animals, mast cells were exclusively found in the organ capsule, where only a slight increase was found in IL-9 transgenic mice (data not shown). No significant difference was noticed for ureter or bladder.

Intestinal IL-9 transgenic mast cells display characteristics of both mucosal and connective tissue-type mast cells

As previously shown in Figure 1, mast cells found in the glandular stomach were stained by safranin, a characteristic feature of
CTMC, and thereby contrast with mast cells found in the intestine of parasite-infected mice, referred to as MMC, which are not stained by safranin (6). To further determine the phenotype of the IL-9 transgenic mast cells, we analyzed the expression of mast cell proteases of the mMCP family, which are differentially expressed in MMC and CTMC (14). RNA was prepared from the stomachs of IL-9 transgenic and control mice, and a semiquantitative PCR analysis was performed for FcεRI, granzyme B, and mMCP-1, -2, -4, -5, and -7. As shown in Figure 5, IL-9 transgenic mice showed a strongly increased expression of the α- and β-chains of FcεRI, reflecting the mast cell infiltration described above. In addition, granzyme B, which was previously shown to be induced by IL-9

**FIGURE 2.** Intestinal mast cell infiltration in IL-9 transgenic mice. The small intestine from IL-9 transgenic (A, C, D, and E) or control FVB (B and F) mice was analyzed after hematoxylin-eosin staining (A and B), Giemsa staining (C), or chloroesterase-specific staining (D–F). Arrows and boxes indicate intra-epithelial mast cells showing a granular eosinophilic content after hematoxylin-eosin staining (A) and appearing as slightly pink blue with Giemsa staining (C) but negative after chloroesterase-specific staining (D). The large arrow in D points to a chloroesterase-positive submucosal mast cell. In the muscularis mucosae, chloroesterase staining reveals the presence of increased numbers of mast cells in IL-9 transgenic mice (E) compared with those in normal FVB mice (F), particularly in the vicinity of lymph nodes as illustrated here.

**FIGURE 3.** Electron microscopy of intestinal IL-9 transgenic mast cells. Electron microscopy of intraepithelial granulated cells (large arrow) in IL-9 transgenic mice shows features compatible with mast cells in the small gut (A) as well as in the stomach (B). The granule content in the small intestine seemed more crystalline (inset). In both pictures, comparison can be made with eosinophilic granules (small arrows).
in mast cells in vitro (25), together with every mMCP tested were overexpressed in IL-9 transgenic mice, including mMCP-4 and -5, characteristic of CTMC, as well as mMCP-1 and -2, representative of MMC proteases. By PhosphorImager quantification, a 10- to 30-fold increase was observed in mMCP-1, -2, -4, and -5, whereas mMCP-7 expression, a marker of immature mast cells (26), was only 3- to 6-fold increased.

Similar mast cell phenotypes induced by IL-9 in vivo and in vitro

To further analyze the role of IL-9 in the growth and differentiation of mast cells, we derived in vitro cell lines from bone marrow progenitors in the presence of SCF, IL-3, and IL-9. As shown in Figure 6, when these cytokines were used separately, only IL-3 led to the proliferation of mast cells (based on the IgE binding). However, the combination of IL-9 and SCF allowed for the development of mast cell lines in vitro, to a similar extent as IL-3. These mast cell populations were further characterized by RT-PCR analysis of their protease expression. In line with previous reports, BMMC cultured with IL-3 alone expressed only mMCP-5 and -7 along with granzyme B (Fig. 7). When SCF was added to IL-3, mMCP-1, -2, and 4 were induced, confirming the activity of SCF as a mast cell differentiation factor. Most importantly, a similar extended protease expression pattern was found in the presence of IL-9 and SCF, with even higher levels of mMCP-1, -2, and -4.

Role of SCF in intestinal mastocytosis of IL-9 transgenic mice

The observations that 1) neither IL-9 nor SCF by itself was sufficient to induce mast cell growth and differentiation in vitro; and 2) their combination lead to a protease phenotype similar to that observed in vivo in IL-9 transgenic mice raise the possibility that these factors are indeed involved in this mast cell hyperplasia. In line with this possibility, the SCF mRNA was constitutively expressed in both FVB and IL-9 transgenic mice (Fig. 8).

To assess the in vivo role of SCF, IL-9 transgenic mice were treated for 4 days with the ACK-2 mAb raised against c-Kit, the receptor of SCF, which has previously been shown to ablate *Trichinella spiralis*-induced intestinal mastocytosis (21). As shown in Figure 9, anti-c-Kit Abs inhibited 80 to 90% of intestinal and gastric mastocytosis, demonstrating that endogenous SCF was required for this in vivo activity of IL-9.

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**FIGURE 4.** Mast cell infiltration in IL-9 transgenic lungs and kidneys. In between epithelial cells of IL-9 transgenic tracheal cells, a large number of chloroesterase-positive cells (A, arrowheads) was observed, while they were not found in FVB normal mice (B). Quantitatively, six or seven mast cells were found per square millimeter of IL-9-transgenic tracheal epithelium compared with <0.1 in wild-type mice. The same observation was made in the kidney of IL-9 transgenic mice stained with Giemsa (C) compared with that of normal FVB mice (D).

**FIGURE 5.** Expression of mast cell differentiation markers in the glandular stomach of IL-9 transgenic mice. Total RNA was extracted from the glandular stomach of 6- to 8-wk-old Tg5, Tg54, or normal FVB mice (three mice per group). RT-PCR amplification was performed as described in Materials and Methods, using the primers described in Table I. For mMCP-1, -2, and -4 (left panel), cDNAs were amplified by a single pair of primers corresponding to identical sequences in these genes, and the PCR product was hybridized with three specific probes, whose specificities are shown using cloned mMCP-1, -2, and -4 cDNAs. For all other genes, specific oligonucleotides were used for both PCR amplification and hybridization.
Discussion

This study shows that mice constitutively expressing IL-9 contain increased numbers of mast cells that accumulate in the intestinal and respiratory mucosa, demonstrating the activity of IL-9 on mast cells in vivo. These observations contrast with the fact that in vitro, IL-9 by itself is unable to induce mast cell growth and differentiation from bone marrow progenitors. A likely explanation is the synergistic activity of IL-9 and SCF on mast cell progenitors. Thus, while SCF alone was not sufficient to induce mast cell development in vitro, IL-9 and SCF together were potent mast cell induction stimuli. Moreover, SCF mRNA was constitutively expressed in both normal and transgenic mice, in agreement with the fact that ubiquitous cell types such as fibroblasts may be a source of this factor (27). In vivo treatment with anti-c-Kit Abs inhibited most of the intestinal mastocytosis observed in IL-9 transgenic mice. Finally, the protease pattern of mast cell lines obtained in vitro with SCF and IL-9 parallels that observed in RNA from IL-9 transgenic gastric mucosa.

Although it is well established that SCF is required for MMC and CTMC development in vivo (28), its role in mast cell differentiation remains less understood. When IL-3-driven BMMC were restimulated with SCF and IL-9, SCF was found to preferentially up-regulate mMCP-4 (15), which is considered a marker of CTMC, while IL-9 increased the expression of mMCP-1 and -2.

FIGURE 6. Derivation of mast cell cultures from bone marrow progenitors in the presence of IL-3, IL-9, and SCF. Bone marrow cells from 4-wk-old BALB/c mice were cultured for 15 days in enriched medium supplemented with the indicated combinations of IL-3 (1 ng/ml), IL-9 (200 U/ml), and SCF-transfected COS cell supernatant (5%). Supernatants from mock-transfected COS cells were used as a control and proved completely inactive. Every 4 days, the nonadherent cells in the cultures were transferred into new flasks and suspended in fresh culture medium supplemented with the appropriate combination of cytokines. After 15 days, the binding of biotinylated IgE was measured by FACS analysis (A). Mast cell numbers shown in B correspond to the numbers of cells positive for IgE binding.

FIGURE 7. Mast cell protease expression pattern of BMMC. RNA from bone marrow-derived cultures, obtained as described in Figure 6, was analyzed by RT-PCR as described in Materials and Methods. For mMCP-1, -2, and -4, cDNAs were amplified by a single pair of primers corresponding to identical sequences in these genes, and the PCR product was hybridized with three specific probes. For all other genes, specific oligonucleotides were used for both PCR amplification and hybridization.

FIGURE 8. SCF and IL-9 expression in the glandular stomach of IL-9 transgenic and control mice. Total RNA was extracted from the glandular stomach of 6- to 8-wk-old Tg5, Tg54, or normal FVB mice (three mice per group). Nonsaturating RT-PCR amplification and hybridization were performed as described in Materials and Methods, using the oligonucleotides described in Table I.
Involvement of some antigenic stimulation through the respiratory airways reflects the role of lymphocyte-derived factors. In line with this, motaxis. In this regard, the observation that mast cells were preferentially stained by safranin, one of the hallmarks of MMC dichotomy and further suggests that proteases of these two types are expressed in mucosal mast cells of IL-9-transgenic mice. In the present study, simultaneous expression of these proteases was observed in vivo and in vitro in the presence of IL-9 and SCF. This observation raises the possibility that a combination of these cytokines induces the development of a heterogeneous population of mast cells, including IL-9-driven mucosal and SCF-driven serosal mast cells, even though neither SCF nor IL-9 by itself induces any in vitro mast cell development from bone marrow progenitors. Our data do not support this hypothesis, as all IL-9 transgenic mast cells were homogeneously stained by safranin, one of the hallmarks of CTMC, thereby suggesting that these mast cells represent a homogeneous population at a distinct stage of differentiation, with the expression of both serosal and mucosal characteristics. Taken together, our data therefore support an alternative hypothesis, namely that mast cell heterogeneity extends far beyond the CTMC/MMC dichotomy and further suggests that proteases of these two patterns may be simultaneously expressed. This observation also reinforces the recent finding that mast cells can reversibly alter their phenotype protease, and that a static nomenclature is inadequate to describe mast cell populations (29).

An important observation for the mast cell infiltrate in IL-9 transgenic mice is that of its selectivity for the intestinal and respiratory mucosa and particularly its intraepithelial niche. This feature is unlikely to result from tissue-specific transgene expression, since IL-9 was produced ubiquitously in the IL-9 transgenic mice used in this study (17). One possible explanation could lie in the SCF expression for a cofactor present only in these tissues. Although SCF expression is not restricted to these tissues, it is possible that a third factor may be involved in mast cell development or chemotaxis. In this regard, the observation that mast cells were preferentially found in the vicinity of mucosal lymph nodes might reflect the role of lymphocyte-derived factors. In line with this hypothesis, a potential factor involved in tissue specificity is the involvement of some antigenic stimulation through the respiratory or digestive tract. This might also explain the observation that in the respiratory airways, mast cells accumulate mainly in the trachea and that in the intestinal tract, they vary both in numbers and in histologic characteristics among the esophagus (that did not show any mast cell increase), the glandular stomach (with an increase in mature mast cells), and the small intestine (with an increase in both mature and immature mast cells). Another potential explanation might be related to a yet undefined activity of IL-9 on adhesion molecules expressed by mast cells, endothelial cells, or epithelial cells.

In this respect, site-restricted mast cell infiltration was reported for IL-4 transgenic mice that showed increased numbers of mast cells in the eyelids (30). Interestingly, in these mice, mast cell infiltration resulted in a marked inflammatory reaction involving “piecemeal” degranulation of the mast cells. By contrast, IL-9 transgenic mice do not seem to be affected by their intestinal and respiratory mastocytosis. However, preliminary observations suggest that these mice are more resistant to intestinal dwelling parasitic helminths (31). Further studies will be needed to assess whether they might also be more sensitive to the development of food allergy. Combined with the fact that most IL-9 transgenic mice have a relatively normal survival and exhibit no spontaneous mast cell-associated pathology, our observations indicate that these mast cells represent a valuable tool to analyze the role of mast cells in various biologic situations.

REFERENCES


