

Mast cells: Ontogeny, homing, and recruitment of a unique innate effector cell

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Mast cells (MCs) are found principally in peripheral tissues yet are of bone marrow origin. Recent studies in mice trace the MC lineage from the common myeloid progenitor through the granulocyte-macrophage progenitor in the bone marrow to a committed MC progenitor (MCP). Additionally, at least in the mouse, a bipotent basophil-MC progenitor has been identified in the spleen, suggesting a physiologic role for this organ in MC development. MCPs are especially abundant in the mouse intestine, likely ensuring the capacity for a rapid expansion of MCs in the intestinal epithelium during the effector response to helminth infection and perhaps providing a pool of committed cells capable of redistribution to other tissues. Migration of MCPs to the intestine is constitutive and controlled by α chemokine receptor 2 and $\alpha 4\beta 7$ integrins expressed on the MCPs, with the latter integrin interacting with endothelial vascular cell adhesion molecule 1 and mucosal addressin cell adhesion molecule 1. In contrast, normal mouse lung tissue contains few MCPs and MCs, and these cellular reservoirs are not affected by the lack of α chemokine receptor 2 or $\alpha 4\beta 7$ integrin. Nonetheless, robust recruitment of MCPs to the lung occurs during experimentally induced allergic pulmonary inflammation and requires $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrins interacting with vascular cell adhesion molecule 1 but not with mucosal addressin cell adhesion molecule 1. Thus although MCs are present in all organs, the pathways responsible for the trafficking of MCPs from the circulation are organ specific and include both constitutive and inducible systems, ensuring both resident MCs and the potential for incremental recruitment in accord with the requirements of the immune response. These findings in mice await confirmation in human subjects. (*J Allergy Clin Immunol* 2006;117:1285-91.)

Key words: Mast cells, basophils, progenitors, homing, recruitment

Abbreviations used

BaP:	Basophil progenitor
BMCP:	Basophil-mast cell progenitor
CCR:	β Chemokine receptor
CMP:	Common myeloid progenitor
CTMC:	Connective tissue mast cell
CXCR:	α Chemokine receptor
GMP:	Granulocyte-macrophage progenitor
MAdCAM-1:	Mucosal addressin cell adhesion molecule 1
MC:	Mast cell
MCP:	Mast cell progenitor
MMC:	Mucosal mast cell
PI-3K:	Phosphoinositol-3 kinase
SCF:	Stem cell factor
VCAM-1:	Vascular cell adhesion molecule 1

Mast cells (MCs), long regarded as a key effector cell of human allergic disease and of immune responses to helminthic parasites in the small intestine, are now considered primary inducers and amplifiers of both innate and adaptive immune responses.¹ MCs have also been implicated in an array of autoimmune and inflammatory disease models.² MCs are constitutive tissue residents and are distributed throughout all vascularized organs. More than 20 years ago, seminal studies revealed that MCs arose from cells in the bone marrow and that committed precursors of MCs (MC progenitors [MCPs]) resided constitutively in the intestinal mucosa of normal mice.^{3,4} These observations implied the existence of pathways permitting trafficking of bone marrow-derived precursors to peripheral organs for subsequent development into MCs. Models of various diseases and responses to infections have implicated roles for MCs by using adoptive transfer of bone marrow or bone marrow-derived cultured MCs from congenic wild-type mice into MC-deficient strains. Some of these pathologic conditions are associated with increments in the numbers of MCs (reactive MC hyperplasia), implying that the pathways and mechanisms responsible for regulating MCP recruitment and trafficking are likely to be dynamic and susceptible to modification during inflammation. We have focused our recent studies on defining these pathways as they relate to MC development in both health and disease. The anticipated parallels to human MC development remain to be explored.

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ONTOGENY OF THE MC

MC subsets and heterogeneity

MCs were first recognized in the tissues of various organs on the basis of the unique metachromatic staining characteristics of their secretory granules.⁵ Subsequent studies discriminated 2 distinct MC subpopulations in the rodent intestine.^{6,7} One MC population possesses safranin-positive granules and resides in the submucosal connective tissues and was termed *connective tissue MCs* (CTMCs). The granules of CTMCs stained even after formalin fixation of the tissues. The second MC population resides in the mucosal epithelial surface of the intestine and was termed *mucosal MCs* (MMCs). These MCs were safranin negative and lost their staining after formalin fixation. CTMCs and MMCs were subsequently shown to differ in protease expression, quantity and profile of eicosanoid release with activation, and proteoglycan content, the latter of which in part accounts for their different staining characteristics.⁸ Experimental infection of rodents with intestinal helminths produces a sharp increment in intestinal MCs (reactive mastocytosis) that preferentially involves the MMC subset.⁹ This observation is similar to the selective increases in the numbers of MCs that are observed in the mucosal epithelium of the nose, bronchi, and gastrointestinal tracts of human subjects with allergic diseases.^{1,10} Thus T_H2 -type inflammatory responses are associated with reactive mastocytosis in both rodents and human subjects.¹¹ Moreover, MMCs, but not CTMCs, were absent in athymic nude mice, implying that T-cell products were necessary for the derivation of the former population of MCs but not for the latter.¹² Likewise, a morphometric study of surgically resected intestinal specimens from human subjects revealed that individuals with deficient T-cell function selectively lacked MCs in the intestinal mucosa but had normal numbers of MCs in the adjacent submucosa.¹³ Studies with knockout mice and neutralizing antibodies revealed key roles for IL-3 and IL-4 in the development of the MMC population; again, CTMCs were unaffected.¹⁴ Thus MC subsets, in addition to differences in anatomic location, staining properties, and protease composition, differed strikingly in their requirement, or lack thereof, for stimulation by accessory growth factors derived from T cells.

Despite the sharp histochemical and functional contrasts between MMCs and CTMCs, extensive experimental evidence supports a common lineage for these cells.^{15,16} Adoptive transfer of congenic bone marrow from normal mice restored both MC subpopulations to the tissues of W/Wv mice, a strain that is severely deficient in MCs because of a loss-of-function mutation in c-kit, the receptor tyrosine kinase for stem cell factor (SCF) that is obligate for MC development. The MC defect in the W/Wv mice is paralleled by Sl/Sl mice, which possess a defect in the gene encoding the membrane-bound isoform of SCF. Collectively, these observations support the concept that all MC subpopulations arise from a single population of bone marrow-derived progenitors. Although these subpopulations share a requirement for

c-kit and SCF for their *in situ* maturation, only the subpopulation in the intestinal and bronchial mucosal epithelial surface requires accessory T cell-derived growth factors. Moreover, the fact that MC numbers, especially in the intestinal mucosal epithelium, sharply increase during helminthic infection indicates that MC development is dynamic and formed the logical basis for pursuing mechanistic studies of the developmental and recruitment mechanisms of MCPs. It is important to note that MCs in the human intestine also segregate into subpopulations that are T cell dependent and independent, respectively, suggesting an important parallel to the mouse, and at least some of the developmental and recruitment mechanisms for MCPs and MCs are conserved between the species.

Characteristics of MCPs

The first putative MCP identified in mice was a "lymphocyte-like" cell population isolated from the intestinal mucosa that gave rise to MCs with *in vitro* culture.^{4,17} These cells were positive for the Thy-1 antigen, a membrane marker that is generally associated with thymocytes. Subsequently, Rodewald et al¹⁸ isolated a population of committed mouse MCPs by sorting rare cells that were transiently detected in mouse fetal blood and expressed high levels of c-kit and low levels of Thy-1. The c-kit^{hi}/Thy-1^{lo} fetal blood cell population, termed *promastocytes*, lacked the high-affinity receptor for IgE, FcεRI, and did not respond to cytokines active for the differentiation of lymphocytes, monocytes, and granulocytes in colony-forming assays; however, they gave rise to pure colonies of primitive FcεRI-positive MCs when cultured in the presence of recombinant SCF plus IL-3. Fetal blood-derived promastocytes injected into the tail veins of W/Wv mice induced mature MCs to develop in the peritoneal cavity, reflecting their trafficking to the tissues and differentiation *in situ*. Thus this study provided the first cytofluorographic definition of an MCP, arising during a short period of embryonic development and seeding the fetal tissues with nascent MC populations.

In a recent study our group sought to trace the ontogeny of MCPs in adult mice using a strategy of fluorescence-activated cell sorting of cell subpopulations, followed by *ex vivo* culture under conditions conducive to colony formation by all myeloid lineages.¹⁶ In the bone marrow of C57BL/6 mice, MCs arose from the myelomonocytic pathway of development. The first defined differentiation step in the bone marrow separates the common lymphocyte progenitor (CLP) from the common myeloid progenitor (CMP), the first cell type committed to the myelomonocytic pathway. CMPs can subsequently differentiate into either megakaryocyte-erythrocyte progenitors or into a granulocyte-macrophage progenitor (GMP). GMPs are distinguished from the CMPs by their increased expression of the low-affinity IgG receptor FcγRIII. Culturing these bone marrow GMPs *in vitro* with a nonselective cocktail of cytokines (SCF, IL-3, IL-5, IL-6, and IL-9) gave rise to all granulocytes, as well as monocytes and MCs (Fig 1). Within the bone marrow, CMPs and

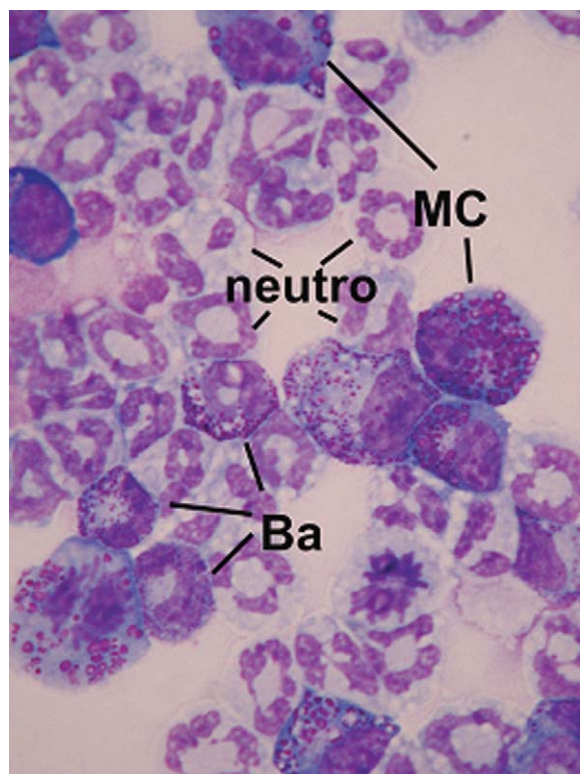


FIG 1. Morphologic characteristics of cells arising from cytofluorographically isolated GMPs from bone marrow of C57BL/6 mice. The depicted cells arose from the culture of a single GMP in the presence of SCF, IL-3, IL-5, IL-6, and IL-9, giving rise to a colony containing both MCs and basophils (Ba), as well as monocytes, neutrophils (neutro), and other granulocytes. Magnification 1000 $\times$.

GMPs accounted for approximately 0.2% and 0.4%, respectively, of the lineage marker-negative, Sca-1⁺, c-kit⁺ bone marrow cells. The presence of CMPs and GMPs in the bone marrow and their capacity to differentiate *ex vivo* into MCs explains the relative ease with which mouse MCs can be grown to high purity from unfractionated bone marrow cells by using the appropriate inductive cytokines (typically IL-3 or a combination of SCF and IL-3).¹⁹

Although these studies revealed the potential of CMPs and GMPs to give rise to MCs, they failed to identify a bone marrow cell population that is truly restricted to the MC lineage (ie, pure MCPs). This implied that commitment of this cell type might uniquely occur in extramedullary tissues. On the basis of earlier studies that had used clonogenic assays and MC colony enumeration, the spleen and the intestine appeared to contain especially abundant pools of MCPs. A subsequent analysis of these 2 organs, however, revealed strikingly different respective progenitor cell populations and surprising insights into MC ontogeny. In the intestine a population of cells expressing CD34, Fc ϵ RI, and high levels of β 7 integrin was identified that was completely committed to the MC lineage on the basis of *in vitro* culture of the isolated cells (Fig 2). These committed intestinal MCPs were further defined by their

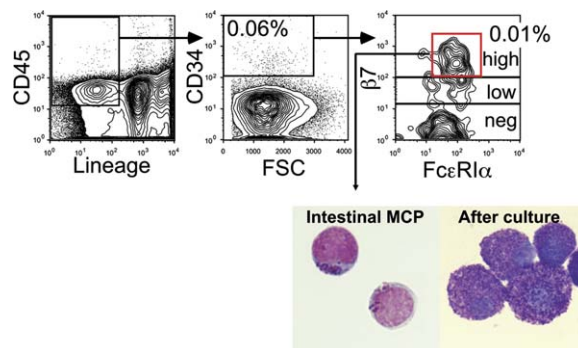


FIG 2. Cytofluorographic sorting of intestinal MCPs. The CD45⁺, lineage marker-negative (left), CD34⁺ (center) subpopulation of mononuclear cells from mouse intestine were sorted for high expression of β 7 integrin and Fc ϵ RI (right) and stained with hematoxylin and eosin before (lower left) and after (lower right) culture in the presence of myeloerythroid cytokines¹⁶ for 7 days. This cell population gives rise only to pure colonies of MCs. Magnification = 1000 $\times$. FSC, Forward scatter.

cytofluorographic profile as Sca-1⁺, c-kit⁺, Fc γ RII/III⁺. This cell phenotype shares some features of cells isolated from human peripheral blood that were CD34⁺, c-kit⁺, CD13⁺ and gave rise to MCs and monocytes in culture.²⁰

The splenic progenitor cell population, like the intestinal MCPs, expresses high levels of the β 7 integrin and is lineage marker-negative, c-kit⁺, Fc γ RII/III⁺ but differs from MCP in that it is Fc ϵ RI^{lo} (Fig 3). Surprisingly, in clonogenic cultures this splenic cell population gave rise not only to MC colonies but also to basophil colonies, as well as colonies containing mixtures of the 2 cell types, and is thus a true bipotent basophil-MC progenitor (BMCP). BMCPs could not be detected in either the intestine or bone marrow. Interestingly, the bone marrow (but not spleen or intestine) contains β 7 integrin^{lo}, c-kit^{lo/-}, Fc γ RII/III⁺, Fc ϵ RI⁺ cells that are committed basophil progenitors (BaPs; ie, not capable of differentiating into MCs or mixed colonies *in vitro*; Fig 3). These BaPs represent approximately 0.06% of the total bone marrow cell population. Although MC-deficient W/Wv mice have reduced numbers of BaPs in the marrow, these mice totally lack both intestinal MCPs and the splenic BMCPs, supporting the ontogenic relationship of these latter 2 cell populations to MCs. This relationship is confirmed by the observation that MCs appear in the stomach mucosa, peritoneal cavity, and spleens of W/Wv mice that receive isolated BMCPs or MCPs from congenic wild-type mice. BMCPs are strikingly more efficient than MCPs in reconstituting the tissues with MCs. As few as 400 BMCPs are capable of fully reconstituting the peritoneal cavity of W/Wv mice with normal-appearing mature MCs, whereas the injection of a similar number of intestinal MCPs reconstituted peritoneal MCs to levels only approximately 10% of normal. Furthermore, BMCPs proliferate *ex vivo* more vigorously than do MCPs, expanding by greater than 10⁶-fold over a 2.5-week period of culture compared with 10⁴- to 10⁵-fold expansion of MCPs under the same conditions. In contrast, BaPs undergo expansion only for the

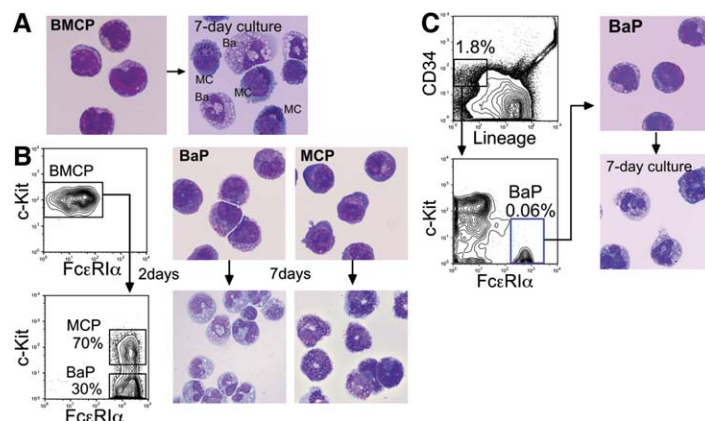
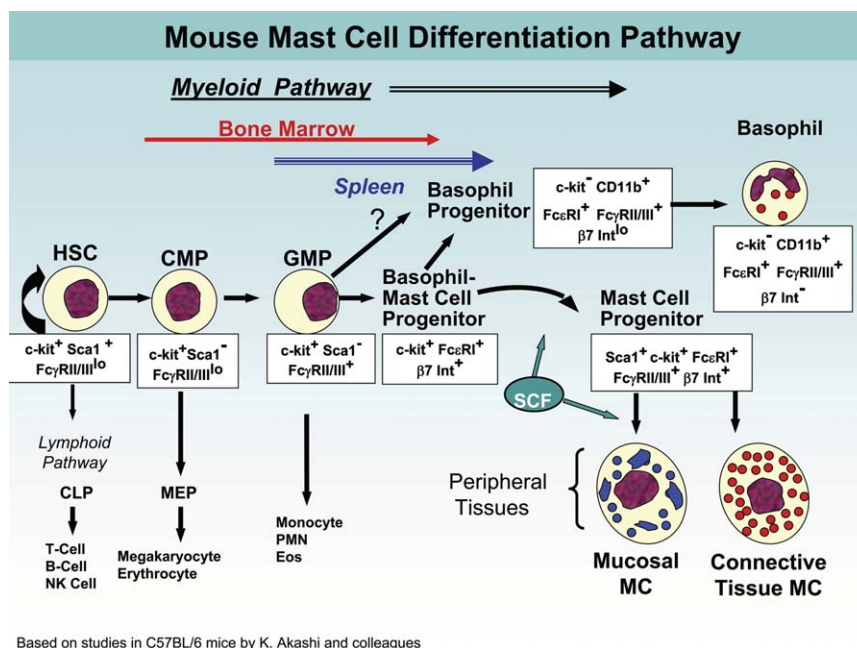


FIG 3. Cytofluorographic sorting and characterization of splenic BMCPs and bone marrow BaPs. **A**, Lineage marker-negative, c-kit⁺, FcγRII/III⁺, β7^{hi}, FcεRI^{lo} spleen cells stained before (left) and after (right) culture. Only 3 colony types arise; pure MCs, pure basophils (Ba), and colonies containing both basophils and MCs (right). **B**, Only 2 populations arise in cultures of splenic β7^{hi}, FcεRI^{lo} cells, which differ in their expression of c-kit (bottom left) and are characterized as BaPs or MCPs (right). **C**, BaPs, but not MCPs, are identified in the bone marrow and are identical to cells arising from splenic BMCPs. Magnification = 1000×



Based on studies in C57BL/6 mice by K. Akashi and colleagues

FIG 4. Mouse MC differentiation pathway. MC development in C57BL/6 mice proceeds along the myeloid pathway through the CMPs and then through the GMPs. In the bone marrow GMPs are the immediate precursor of the MCPs and BaPs. BMCPs are found exclusively in the spleen and differentiate into both MCPs and BaPs on culture in myeloid growth factors. HSC, Hematopoietic stem cell; CLP, common lymphoid progenitor; MEP, megakaryocyte erythrocyte progenitor; NK cell, natural killer cell.

first 6 to 10 days and then begin to die off in culture in accordance with previous reports.²¹ We also noted that after inflammation induced by *Trichinella spiralis* infection or by ovalbumin sensitization and challenge, all 3 progenitor populations, intestinal MCPs, bone marrow BaPs, and splenic BMCPs, underwent expansion.

Together, these studies support an ontogenic relationship between MCs and basophils (Fig 4), which, although they share certain characteristics, were long thought to be completely separate and distinct cell lineages. Several

questions remain, however. It is uncertain whether the splenic BMCPs can be mobilized into the circulation or whether it is only the committed progeny that are released into the circulation. The reservoir of BaPs in the bone marrow suggests that this is the principal source for these cells, but derivation from the splenic BMCPs, which expand with T_H2-polarized inflammation, remains a possibility. In addition, the potential cross-talk between the spleen and the bone marrow in “mastopoiesis” is now a more pressing question and open to exploration.

Although our studies support the requirement for conditioning of progenitor cells in the spleen or peripheral tissues for MC lineage commitment, other investigators have identified MC lineage-restricted populations in mouse bone marrow. Jamur et al,²² using a unique antibody, identified a population of cells in BALB/c bone marrow comprising 0.02% of the bone marrow population that they believed was a committed MCP. Pennock and Grecis²³ identified a $\beta 7$ integrin–positive cell population that expands in the bone marrow after helminth infection and then moves into the blood on day 5 or 6, just before observing the expansion of MCs within the small intestine. Using $\beta 7$ integrin and the T_H2 cell/MC marker T1/ST2, Chen et al²⁴ identified a population of immature cells in C57BL/6 marrow that was distinct from either the CMP or GMP populations. No estimate of cell frequency was described, and our group did not identify such a cell population. Nevertheless, we were able to consistently derive MCs from populations of GMPs that were either $\beta 7^{lo}$ or $\beta 7^-$. Furthermore, on culture, both populations of bone marrow–derived GMPs gave rise to $c\text{-kit}^+$, $CD11b^+$, $Fc\epsilon RI^+$ BaPs and to $c\text{-kit}^+$, $CD11b^-$, $Fc\epsilon RI^+$ MCPs, indicating that this cell, the GMP, is upstream of both cell types.

MCP TRAFFICKING: BASAL HOMING VERSUS INFLAMMATION-INDUCED RECRUITMENT AND EVIDENCE FOR ORGAN-SPECIFIC PATHWAYS

Intestinal homing

The remarkable abundance of committed MCPs in the small intestine provides an opportunity to understand some of the constitutive homing mechanisms of this lineage. Clonogenic MCP enumeration assays revealed that C57BL/6 mice bearing a targeted deletion of $\beta 7$ integrins completely lacked intestinal MCPs at baseline.²⁵ These mice also lacked mature MCs in both the submucosal and mucosal compartments, indicating that the missing MCP population was essential for the development of both anatomic subsets.²⁶ The defect in basal MCPs and mature MCs was remarkably compartmentalized because the stomach, lung, and spleen contained wild-type numbers of mature MCs, and cells isolated from these organs yielded normal MC colony counts. Mice lacking the αE integrin chain (one of 2 partners of the $\beta 7$ integrin chain) showed normal numbers of intestinal MCPs, implicating the $\alpha 4\beta 7$ integrin as the functionally relevant heterodimer. The requirement for $\alpha 4\beta 7$ integrin in MCP homing to the intestine was confirmed in wild-type mice by means of experiments involving sublethal irradiation, which eliminates MCPs from peripheral tissues.^{25,27} When irradiated mice receive bone marrow cells intravenously, the recovery of MCPs in the intestine occurred after a short delay of 4 to 5 days and then progressed steadily until the MCPs in the intestines were fully reconstituted after approximately 2 weeks. When these irradiated mice were treated during their

reconstitution with neutralizing antibodies against various integrin subunits, anti- $\alpha 4$, anti- $\beta 7$, or anti- $\alpha 4\beta 7$ blocked the recovery of MCPs, whereas antibodies to αE or $\beta 1$ integrins had no effect. In subsequent analyses, antibody blockade of either vascular cell adhesion molecule (VCAM-1) or mucosal addressin cell adhesion molecule 1 (MAdCAM-1), both of which are endothelial counterligands for $\alpha 4\beta 7$, each suppressed the recovery of MCPs in irradiated mice.²⁸ Furthermore, blocking antibody treatment of normal wild-type (nonirradiated) mice depleted MCPs in the intestine as well, indicating that the MCP pool was dynamic and replaced with a half-life of approximately 4 days. Taken together, these studies highlight a unique, organ-specific requirement for the $\alpha 4\beta 7$ integrin in constitutive homing of MCPs to the small intestine. The constitutive expression by this organ of the counterligands for $\alpha 4\beta 7$ integrin likely accounts for the maintenance of the large pool of committed MCPs that is unique to the intestine and ensures the rapid development of a reactive mucosal mastocytosis in response to intestinal helminth infection. These studies also highlight the fact that other pathways must be responsible for recruitment of MCPs to other organs and even to other parts of the gastrointestinal tract.

As is the case for all blood-borne leukocytes, recruitment of MCPs to the peripheral tissues requires not only adhesive interactions but also directed migration. A cytofluorographic analysis of human cord blood–derived MCPs, defined by a $c\text{-kit}^{lo}$, $Fc\epsilon RI^{lo}$, $CD13^+$ membrane phenotype, revealed that these cells expressed 4 chemokine receptors: α chemokine receptor (CXCR) 2, CXCR4, β chemokine receptor (CCR) 3, and CCR5.²⁹ On the basis of analysis of CCR3-, CCR5-, and CXCR2-null mouse strains, only CXCR2-null mice showed a decrease (by approximately 70%) in resident intestinal MCPs.²⁸ Reconstitution of irradiated wild-type BALB/c mice with bone marrow from CXCR2-null mice versus wild-type BALB/c bone marrow showed similar decreases in the number of intestinal MCPs, the same as in the CXCR2-null donors, confirming that the defect in MCP homing was due to CXCR2 expressed by the MCP rather than by the endothelium or other tissue elements.

Chemoattractants, such as the CXCR2 ligands, act by simultaneously inducing directed migration while increasing the avidity of integrins through an inside-out signaling mechanism that involves phosphoinositide-3 kinase (PI-3K).^{30,31} Furthermore, mice lacking the PI-3K p85 regulatory subunit are markedly deficient in intestinal MCs, which likely reflects both deficiencies in activation of adhesion pathways and a consequence of the established effect of PI3K on $c\text{-kit}$ –dependent proliferation.^{31,32} It thus seems likely that CXCR2 ligands, which are constitutively expressed in the intestines of mice, activate adhesion through the requisite $\alpha 4\beta 7$ integrin heterodimer by means of CXCR2 stimulation of PI-3K, resulting in upregulation of the affinity of the $\alpha 4\beta 7$ integrin for the endothelial ligands MAdCAM-1 and VCAM-1. This system, driving the unique constitutive recruitment of MCPs to the intestine, likely reflects the microbial burden of this organ, as well

as the requirement to mount a reactive mastocytosis efficiently in response to helminths.

Lung recruitment

Similar to the mastocytosis that arises in the epithelium of helminth-infected intestine, the numbers of MCs present in the bronchial epithelium of subjects with asthma are markedly increased compared with the numbers in biopsy specimens from nonasthmatic control subjects.^{10,33} Moreover, the numbers of circulating CD34⁺ cells capable of giving rise to MC colonies *in vitro* (presumably reflecting MCPs in human subjects) are increased by several fold in the blood of subjects with asthma compared with in the blood of healthy control subjects.³⁴ Both C57BL/6 and BALB/c mice have very few resident MCPs in the lung. Moreover, mature MCs are sparse in the lungs of either strain. Nevertheless, chronic allergen-induced pulmonary inflammation induces a reactive mastocytosis in the bronchial epithelial surface of the mouse lung, implying the capacity for this organ to undergo inducible changes in adhesion-chemotaxis pathways necessary for the recruitment of MCPs.³⁵ To explore these potential mechanisms, we sensitized mice to chicken egg ovalbumin, followed by repetitive inhalation challenge with aerosolized chicken egg ovalbumin. The mononuclear cells isolated from enzymatically dispersed lungs of these mice were used in the same clonogenic assay as was used for the studies of intestinal MCPs. After as few as 3 inhalation challenges, the numbers of MCPs in the lungs increased sharply in both the C57BL/6 and BALB/c strains (approximately 30-fold increases in total number of MCPs per lung relative to the low baseline value in saline-challenged animals). In contrast to homing of MCPs to the intestine, antibody blockade of MAdCAM-1 had no effect on the numbers of MCPs recruited to the lung, whereas anti-VCAM-1 antibodies substantially inhibited MCP recruitment. Moreover, mice with a conditional deletion of VCAM-1 restricted to the vascular endothelium showed sharp decreases in the recruitment of MCPs consistent with the antibody neutralization data. Blocking antibodies directed against $\alpha 4$, $\beta 1$, $\beta 7$, and the $\alpha 4\beta 7$ integrin heterodimer were all inhibitory of MCP recruitment during the allergen challenge, whereas anti- αE was inactive. Moreover, allergen-challenged $\beta 7$ integrin-deficient C57BL/6 mice showed an approximately 70% decrease in MCPs compared with that seen in wild-type control animals, with no substantial decrease in the recruitment of other cell types. Taken together, these observations implicate the induction of VCAM-1 (an event attributed to cytokine stimulation of endothelial cells) as a key permissive event for the recruitment of MCPs to the lung through interactions with the $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrins. The key chemoattractants necessary for recruitment of MCPs to the lung are yet to be defined but are likely to include inducible ligands for the chemokine receptors expressed by the circulating MCPs. It seems logical that MCP recruitment is a necessary prerequisite for the development of a reactive intraepithelial mastocytosis observed with longer periods of allergen challenge. Whether the VCAM-1-dependent

pathways contribute to MC accumulation in the airway smooth muscle, a feature unique to bronchial asthma, remains to be explored.

SUMMARY

The involvement of MCs in multiple disease processes, as well as their importance as a therapeutic target in asthma, allergy, and potentially other inflammatory diseases, highlights a need to understand the mechanisms for their development and widespread distribution. Although studies done in the mouse can be extended to the human system only with caution, the unique lineage pathway of MC development, with the terminal stages taking place in peripheral tissues, presents a challenge for understanding trafficking mechanisms that are most easily addressed in the mouse. A clear paradigm has been established, explaining the constitutive MCP pool in the intestine, and the mechanisms controlling recruitment to the lung with allergen-induced inflammation are now emerging. These studies demonstrate that both tissue-specific homing and inflammatory requirement are highly controlled processes. The constitutive presence of MCs in the skin, central nervous system, and other tissues, where they are not only sentinels of the immune system but also inducers of disease, implies the existence of heretofore unrecognized, organ-specific pathways for MCP recruitment that might have direct bearing on therapeutic development. These mouse studies should permit parallel studies in human subjects to isolate and characterize committed MCPs, to clarify the fascinating role of the spleen, and to determine whether the lineage pathways of the MC and basophil intersect in the human subject as they do in the mouse. Likewise, observations recently made *in vitro* in human cells, mouse cells, or both (ie, the chemotactic pathways necessary for the MC infiltration of airway smooth muscle in asthma³⁶ and the potent chemotactic activity of leukotriene B₄ for immature MCs from both human subjects and mice³⁷) provide potentially further exciting insights into trafficking mechanisms that can readily be tested by using available experimental systems.

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