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Senescent Jejunal Mast Cells and Eosinophils in the Mouse Preferentially Translocate to the Spleen and Draining Lymph Node, Respectively, During the Recovery Phase of Helminth Infection

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Because mice infected with Trichinella spiralis experience a pronounced, but transient, mastocytosis and eosinophilia in their intestine, this disease model was used to follow the fate of senescent T cell-dependent mast cells (MCs) and eosinophils. Very few MCs or eosinophils undergoing apoptosis were found in the jejunum during the resolution phase of the infection, even though apoptotic MCs were common in the large intestine. Although the mesenteric draining lymph nodes contained large numbers of apoptotic eosinophils, MCs were rarely found at this location. During the recovery phase, large numbers of MCs were present in the spleen, and many of these cells possessed segmented nuclei. These splenic MCs were not proliferating. Although MCs from the apoptotic eosinophils, MCs were rarely found at this location. During the recovery phase, large numbers of MCs were present in the intestine, this disease model was used to follow the fate of senescent T cell-dependent mast cells (MCs) and eosinophils. Very few MCs or eosinophils undergoing apoptosis were found in the jejunum during the resolution phase of the infection, even though apoptotic MCs were common in the large intestine. Although the mesenteric draining lymph nodes contained large numbers of apoptotic eosinophils, MCs were rarely found at this location. During the recovery phase, large numbers of MCs were present in the spleen, and many of these cells possessed segmented nuclei. These splenic MCs were not proliferating. Although MCs from the jejunal and spleen of noninfected mice failed to express mouse MC protease (mMCP-9), essentially all of the MCs in the jejunal submucosa and spleen of T. spiralis-infected mice expressed this serine protease during the recovery phase. The MCs in the jejunal expressed mMCP-9 before any mMCP-9-containing cells could be detected in the spleen. The fact that mMCP-9-containing MCs were detected in splenic blood vessels as these cells began to disappear from the jejunum supports the view that many jejunal MCs translocate to the spleen during the recovery phase of the infection. During this translocation process, some senescent jejunal MCs undergo nuclear segmentation. These studies reveal for the first time different exit and disposal pathways for T cell-dependent eosinophils and MCs after their expansion in the jejunum during a helminth infection. The Journal of Immunology, 2000, 165: 344–352.

Because activated mast cells (MCs) and eosinophils release multiple preformed and newly expressed mediators that can profoundly affect the body’s homeostasis, the numbers of these effector cells of the immune response must be tightly regulated in tissues. Much is known about the factors and mechanisms by which committed hematopoietic progenitors differentiate into mature MCs and eosinophils (for reviews, see Refs. 1–4). However, substantially less is known about the fate of expanded populations of these granulocytes during the recovery phase of an inflammatory response. A commonly used disease model to understand MC and eosinophil development in the mouse is the transient, T cell-dependent eosinophilia and mastocytosis that occurs in the intestines of helminth-infected mice and rats (5–17). In the jejunum of these helminth-infected animals, IL-5 plays a central role in the eosinophilia (11, 17), whereas c-kit ligand, IL-3, IL-4, IFN-γ, and TNF-α play central roles in the mastocytosis (9, 12, 13, 16, 18). Other T cell-derived factors such as IL-9 (19–21) are needed to instruct the expanded population of MCs in the jejunal epithelium to produce mouse MC protease-1 (mMCP-1), mMCP-2 (14, 22–24), and other mediators.

During the recovery phase of a Trichinella spiralis infection that occurs at weeks 2–5, the excess eosinophils and MCs slowly disappear from the jejunum. The MCs initially disappear from the upper villi, and at least some of these cells migrate laterally and downward toward the submucosa (14). Apoptotic MCs are rare but have been found in the jejunum of helminth-infected rats (25), and glucocorticoid treatment of helminth-infected mice results in the rapid engulfment of at least a portion of these jejunal MCs by resident macrophages (26, 27). Because MCs developed in vitro with IL-3 spontaneously undergo apoptosis when their viability-enhancing factors are removed from the culture medium (28), it has been assumed that most jejunal MCs undergo apoptosis locally once the pathogen-specific T cells cease to be prominent in the intestine after the adult T. spiralis helminths are expelled.

Mouse MCs store in their granules various combinations of a carboxypeptidase (29) and at least 13 serine proteases (designated granzyme B, cathepsin G, mMCP-1 to mMCP-10, and transmembrane trypstatin) (22, 23, 30–38). MCs take a number of days to turn over their granule constituents (39). Thus, the particular panel of neutral proteases that a MC expresses in the BALB/c mouse at any time in this cell’s life span appears to be dictated by the combination of regulatory factors the MC encounters in both its current and previous microenvironments (14, 15, 39–43). For example, the v-abl-immortalized V3 MC line expresses mMCP-1 and
mMCP-2 when this mMCP-1/mMCP-2− cell line is adoptively transferred into the jejunum of normal BALB/c mice (43). We previously reported that the MCs in the jejunum of T. spiralis-infected BALB/c mice undergo time- and strata-dependent changes in their expression of mMCP-1, mMCP-2, mMCP-5, mMCP-6, mMCP-7, and mMCP-9 (14, 15). Using a variety of approaches, we now report that during the recovery phase of T. spiralis infection, many of the expanded jejunal MCs and eosinophils exit the intestine and preferentially translocate to spleen and draining lymph nodes, respectively.

Metachromatic cells that express the high-affinity IgE receptor have been found in the blood of humans with various allergic disorders that have some features of MCs (e.g., surface expression of CD117 (c-kit) and granule expression of chymase, carboxypeptidase A, and multiple tryptases) and some features of basophils (e.g., blood location, segmented nuclei, and surface expression of Bsp-1) (44). Although most mouse MCs possess a large, centrally positioned, nonsegmented nucleus, some occasionally possess segmented nuclei (45). We now report that many of the senescent MCs in the intestine of T. spiralis-infected mice undergo sequential changes in their nuclear profiles as they make their way to the spleen. Thus, in this model system, nuclear segmentation of the T cell-dependent population of MCs that expands in the jejunum during a helminth infection is an early indicator of senescence.

Materials and Methods

Enzyme cytochemistry and immunohistochemistry

BALB/c mice were infected orally with 400 freshly isolated stage-3 T. spiralis larvae, as described (14, 15, 41). Mice were killed at various times after helminth infection. The jejunum, large intestine (i.e., cecum; ascending, transverse, and descending colon), spleen, liver, draining mesenteric lymph nodes, and ear were removed and fixed for analysis. All mouse MCs that have been examined to date in fixed, dehydrated, and embedded tissues contain abundant levels of chloroacetate esterase activity (14). Thus, with a modification (46) of the enzyme cytochemistry procedure of Leder (47), fixed tissue sections were incubated at 30°C for 1 h with a solution containing naphthol AS-D chloroacetate. The tissue preparations were rinsed and counterstained with hematoxylin. For histochemical identification of eosinophils, appropriate sections were stained with hematoxylin/eosin/azure II, which stains eosinophils pink (46), or with Congo red, which stains eosinophils orange (48). Wright Giemsa stain was also used in some tissue sections to identify all granulocytes.

For MC immunohistochemistry, tissue sections from noninfected and T. spiralis-infected mice were stained with immunoualkaline phosphatase, as described (14, 15, 49). Collected tissues were fixed for 4 h at room temperature in 4% paraformaldehyde in 0.1 M sodium phosphate (pH 7.6), were washed twice with PBS containing 2% DMSO, and were suspended in a solution containing deoxyribonuclease I (0.6 mg/ml) and 0.5 mg/ml of 0.7% EDTA (pH 8.0). The DNA was digested for 30 min at 37°C. The sections were then treated with 5 μg/ml of anti-McAb for 30 min. The McAbs used were mouse anti-BrdU and goat anti-mouse Ab (Vector Laboratories). MCs were identified in the subsequent serial section with the chloroacetate esterase cytochemistry procedure.

Results

Evaluation of the MCs and eosinophils in the intestine during the recovery phase of helminth infection

Although most of the chloroacetate esterase+/mMCP-2−/mMCP-9+ MCs in the mouse intestine at the height of the T. spiralis infection at week 2 resided in the jejunum, increased numbers of these cells were also found in epithelium of the large intestine (Fig. 1). The MCs in the large intestine at this time point were generally large in size. Although most of these cells possessed a centrally positioned, large-sized, nonsegmented nucleus, a few possessed crescent-shaped, eccentric nuclei. MCs in various stages of apoptosis at this time point in the infection were rarely detected. However, during the recovery phase of the infection at weeks 3–5, nearly all of the chloroacetate esterase+/mMCP-2+ MCs in the large intestine exhibited noticeable morphologic changes. Many were substantially smaller in size. Although a few of these cells possessed the crescent-shaped, eccentric nuclei seen at the height of the infection, most contained either a segmented/bilobed nucleus or a condensed nucleus typical of a cell undergoing the late stages of apoptosis. This continuum of morphologic changes suggests not only that most of the expanded MCs residing in the large intestine undergoing apoptosis locally but also that nuclear segmentation is an early indicator of MC senescence.

As found previously (14), some of the chloroacetate esterase+/mMCP-2−/mMCP-9+ MCs in the small intestine of helminth-infected BALB/c mice resided in the lamina propria, but most resided in the villus epithelium until week 2 (Fig. 2). MCs were occasionally detected in the lumen during the recovery phase of the infection (Fig. 3). Some mMCP-2− MCs with condensed nuclei typical of cells undergoing apoptosis were found in the epithelium at this time point. Moreover, MCs in their earlier stages of apoptosis also were occasionally seen at this location with the TUNEL assay. Nevertheless, unlike the proportion in the large intestine during the recovery phase of the helminth infection (Fig. 1), <5% of the >1000 MCs examined in the jejunum in these varied assays were in their early or late stages of apoptosis. In addition, nearly all of these apoptotic MCs resided in the epithelium rather than in the...
lamina propria or submucosa (Fig. 3, b and e). Macrophages that had engulfed apoptotic MCs were not detected in the jejunum. The discovery that more MCs were detected in the lamina propria during the recovery phase of the infection (Figs. 2c and 3f) than at the height of the infection (Fig. 2b) is consistent with the previous granule morphologic data (14) that had indicated that at least some of the intraepithelial MCs migrated into the lamina propria. The pronounced motility of these MCs raised the possibility that they had the ability to exit the jejunum.

Large numbers of eosinophils were also found in the jejunum at the height of the helminth infection at days 11–14 (Fig. 2, d–f). However, in contrast to where the MCs localized, the eosinophils resided in either the submucosa or lamina propria of the lower villus. None appeared in the epithelium. With the TUNEL assay, apoptotic eosinophils were rarely found in the jejunum at any time point during the infection. Moreover, only rarely could a macrophage be detected in the jejunum that had engulfed an apoptotic eosinophil (data not shown). These findings also raised the possibility that many of the excess jejunal eosinophils were translocating to a different tissue site.

Translocation of jejunal eosinophils to the draining lymph nodes and jejunal MCs and V3 MCs to the spleen

During the recovery phase of the helminth infection, the mesenteric draining lymph nodes contained large numbers of eosinophils but very few MCs (Fig. 4). When a MC was detected, it generally was small in size and possessed a segmented nucleus. As assessed histochemically, many of the eosinophils in the lymph nodes had apoptotic nuclei. Moreover, many macrophages in the lymph nodes had phagocytosed apoptotic cells, including eosinophils.

Although the data indicated that the draining lymph nodes were major repositories for the migrating jejunal eosinophils, it was apparent that these locations were not a significant repository for the senescent MCs that had disappeared from the jejunum. We knew that v-abl-immortalized V3 MCs translocate to both the spleen and liver when injected i.v. (43). However, when given i.p., these transformed MCs translocated to the spleen but not the liver (Fig. 5). This new finding raised the possibility that the spleen was a major repository for the disappearing jejunal MCs. The number of MCs in the spleen at week 4 was >10-fold higher than the number in the spleen of noninfected mice or mice that had been exposed to the helminth for just 1 wk (Fig. 6). Kinetic experiments revealed

**FIGURE 1.** Changes in the nuclear profiles of the MCs residing in the large intestine during *T. spiralis* infection. At the height of the helminth infection (a–c), most of the MCs in the large intestine possessed an oval nucleus (b). However, a few MCs possessed crescent-shaped, eccentric nuclei (c). At weeks 3–5 during the recovery phase of the infection (d and e), the MCs in the large intestine generally contained either a segmented/bilobed (d) or an apoptotic (e) nucleus. MCs (red-stained cells; arrow) were detected with either chloroacetate esterase substrate (a) or anti-mMCP-2 Ab (b–e).

**FIGURE 2.** Location of MCs and eosinophils in the jejunum. MCs were not found in the upper villus of the jejunum of mice that had been exposed to *T. spiralis* for 7 days (a). Although many MCs (arrows; b and c) resided in the mucosal epithelium at the height of the helminth infection at day 14 (b), MCs were found only in the lamina propria (central region of the villus) during the recovery phase of the infection at day 28 (c). Eosinophils (arrows; d–f) were rarely found in uninfected mice (d), but their numbers steadily increased in the lamina propria and submucosa until day 11 of the helminth infection (e). This initial eosinophilia slowly subsided during the subsequent days (f). The chloroacetate esterase cytochemistry (a–c) and Congo red histochemistry (d–f) procedures were used to identify MCs and eosinophils, respectively.
that the rise in MC numbers in the spleen occurred when MCs began to disappear in the jejunum. At no time were MCs detected in the liver of a helminth-infected animal. At week 2 of the infection, when MCs began to increase in number in the spleen, analysis of serial-sectioned tissue revealed a notable absence of MCs that incorporated BrdU into their genomic DNA (Fig. 7). The fact that the MCs were evenly dispersed throughout the sinusoids (Fig. 8) rather than in clusters of two or more also implied that the increased number of MCs in this organ at 4 wk was not the result of local proliferation of a MC-committed progenitor in the spleen.

The only MC population in a noninfected BALB/c mouse that has been found to express mMCP-9 resides in the uterus (36). Nevertheless, we previously showed that during the recovery phase of helminth infection, virtually every nonintraepithelial MC residing in the mid-villus, crypts, and submucosa of the jejunum expresses this highly restricted serine protease (15). At no point did the cutaneous MCs in the ears or the large intestine of the helminth-infected mice express mMCP-9 (data not shown). Splenic MCs before and 3 mo after *T. spiralis* infection also failed to express mMCP-9 (data not shown). However, essentially all of

FIGURE 3. Extruded, migrating, and apoptotic MCs in the jejunum during the resolution phase of the intestinal mastocytosis. Serial (b and c) or nonserial (a and d-f) sections of *T. spiralis*-infected mouse tissue were subjected to the TUNEL biochemical (c), chloroacetate esterase cytochemical (a, b, d, and f), or anti-mMCP-2 Ig immunohistochemistry (e) procedures. Arrows in b, c, and e indicate apoptotic MCs in the jejunal epithelium. Apoptotic MCs were rarely seen in the submucosa at all time points during the helminth infection. The arrow in a indicates a rarely detected MC that has extruded into the lumen.

FIGURE 4. Histochemistry and immunohistochemistry of the eosinophils and MCs in a mesenteric draining lymph node. The mesenteric draining lymph nodes of a noninfected BALB/c mouse (a) and a BALB/c mouse that had been infected with *T. spiralis* 2 wk earlier (b–f) were evaluated for the presence of eosinophils (a–d) and MCs (d–f). The purple (filled arrows) and pink (open arrows) cells in the hematoxylin/eosin/azure II (HAE)-stained tissue section (d) are MCs and eosinophils, respectively. The large number of eosinophils (orange cells) in the lymph nodes can be more easily seen in the Congo red-stained sections (arrows in b). The arrows in c point to macrophages that have engulfed apoptotic cells, including eosinophils. MCs are rare in the draining lymph nodes (d–f). Nevertheless, when present, these chloroacetate esterase (CAE)− cells (data not shown) express mMCP-2 (f) and mMCP-9 (e). Moreover, most of these MCs possess a segmented nucleus (f).
the MCs in the splenic cortex at week 4 of helminth infection expressed this serine protease (Fig. 8). MCs that expressed mMCP-2 and mMCP-9 (Fig. 9) also were occasionally found in the lumen of the blood vessels in contiguity with splenic sinusoids.

Discussion

Although substantial progress has been made during the last decade in our understanding of the factors and mechanisms that regulate MC and eosinophil development in normal and diseased mice, rats, and humans, little is known about the fate of mature MCs or eosinophils when the numbers of these granulocytes are transiently increased during a T cell-dependent inflammatory response. Using the *T. spiralis* infection model, we have now determined that most of the T cell-dependent intraepithelial MCs in the large intestine of the BALB/c mouse undergo apoptosis locally during the recovery phase of the inflammation, whereas substantial numbers of jejunal MCs translocate to the spleen. In contrast, many of the surplus jejunal eosinophils translocate to the draining lymph nodes.

*T. spiralis* infects the small intestine of the mouse to elicit a T cell-dependent (8) eosinophilia and mastocytosis in the jejunum (Figs. 2 and 6). A less pronounced mastocytosis occurs in the large intestine (Fig. 1). Although larvae become encysted in skeletal muscle, mice are able to expel the adult nematode from the intestine if the load of experimentally introduced *T. spiralis* is not excessive. During the recovery phase of the infection at weeks 2–5, the number of MCs in the jejunum slowly and progressively decreases to baseline (Fig. 6). The secondary eosinophilia in the jejunum around day 28 is more systemic and coincides with the peak of *T. spiralis* larvae encystment in skeletal muscle. Despite the dramatic fall in the number of eosinophils during weeks 2–3, we were unable to detect many apoptotic eosinophils in the jejunum. Large numbers of apoptotic intraepithelial MCs were found in the large intestine (Fig. 1), but only a few apoptotic MCs were found in the jejunal epithelium (Fig. 3). Even at that latter site, <5% of the intraepithelial MCs at any time during the infection were in their early or late stages of apoptosis. Dying MCs also were rarely

![FIGURE 5. In vivo fate of V3 MCs. v-abl-immortalized V3 MCs were injected into either the tail vein (a and d) or the peritoneal cavity (b and e); 2 wk later, the numbers of chloroacetate esterase V3 MCs in the spleen (a and b) and liver (d and e) were evaluated. At the depicted magnification, MCs were rarely seen in the spleen (c) and liver (f) of normal, untreated BALB/c mice. The chloroacetate cytochemistry procedure was used to detect the V3 MCs (red-stained cells). The arrow in b points to a cluster of V3 MCs.](http://www.jimmunol.org/)

![FIGURE 6. Time-dependent changes in the number of MCs and eosinophils in tissues. At each time point, sections of jejunum (a), lymph node (b), and spleen (c) of helminth-infected mice were evaluated for their content of MCs (●) and eosinophils (■). At each time point, two to three high power fields (HPF) were examined in a tissue section. Results are the mean ± SEM of cell counts from three animals analyzed at each time point.](http://www.jimmunol.org/)
seen in the jejunal lamina propria or submucosa, even though most jejunal MCs resided in these sites at weeks 2–4. In rats infected with the tapeworm *Hymenolepis diminuta*, the number of apoptotic MCs in the jejunum never exceeds 3% (25). Thus, our failure to see large numbers of apoptotic MCs in the jejunum of the *T. spiralis*-infected BALB/c mouse does not appear to be a consequence of the animal or parasite used in these studies.

The fact that most MCs and eosinophils in the small intestine were not apoptotic or necrotic could be a consequence of their rapid engulfment and destruction by jejunal macrophages. Macrophages that had engulfed an eosinophil and/or lymphocyte were occasionally found in the jejunum. However, our failure to detect large numbers of macrophages in the lamina propria or submucosa of the jejunum with remnants of eosinophil or MC granule constituents suggested that during the recovery phase of the helminth infection most senescent jejunal eosinophils and MCs are able to escape engulfment by jejunal macrophages. The phagocytosis of apoptotic neutrophils and eosinophils by macrophages is mediated by CD36, thrombospondin, and the αvβ3 integrin (53, 54). The αvβ3 integrin recognizes vitronectin and fibrinogen. Inasmuch as both vitronectin and fibrinogen inhibit the macrophage-mediated apoptosis of senescent neutrophils in vitro, it is possible that senescent MCs and eosinophils escape apoptosis in the jejunum because of increased deposition of vitronectin and/or fibrinogen at this site. Alternately, the jejunal MCs and eosinophils might not express one of the ligands for the apoptotic regulatory proteins.

The failure to detect appreciable numbers of apoptotic jejunal MCs and eosinophils at wk 4, coupled with the previous observation that MCs migrate in the various strata of the intestine during the infection (14), raised the possibility that most senescent MCs and eosinophils translocate from the jejunum to another tissue site. During the recovery phase of helminth infection, the draining lymph nodes contained large numbers of eosinophils but, surprisingly, very few MCs (Fig. 4). At day 11 in the infection, the spleen and lymph nodes contained 3– and >100-fold more eosinophils, respectively, than the corresponding tissue in a noninfected mouse (Fig. 6). The additional finding that many of the eosinophils in the lymph nodes were undergoing apoptosis and were being engulfed

**FIGURE 8.** Enzyme cytochemistry and immunohistochemistry of splenic MCs in BALB/c mice infected with *T. spiralis* for 1 (a and b) and 4 (c–e) wk. Shown at each time point are data from serial-sectioned tissue (a–b and c–d). Very few MCs are present in the spleen of noninfected mice (data not shown) and in the mice exposed to *T. spiralis* for 1 wk (a and b). These chloroacetate esterase⁺ MCs (a; arrow) do not express mMCP-9 (b). Increased numbers of chloroacetate esterase⁺ MCs are present in the sinusoids at wk 4 during the resolution phase of the intestinal mastocytosis (c). Nearly all of these MCs express mMCP-9 (d), and many express mMCP-2 (e). Those rare MCs in the lymphoid germinal centers (arrow) are the only population that do not express this chymase. Many of the MCs in the spleen during the recovery phase of helminth infection contain segmented nuclei (e).
by macrophages (Fig. 4) now indicates that draining lymph nodes are graveyards for most of the senescent eosinophils that leave the jejunum.

The failure to see comparable numbers of MCs in the draining lymph nodes and the failure to see macrophages that had engulfed apoptotic MCs (Fig. 4) suggest that the MCs that leave the jejunum lack the necessary complement of adhesion receptors to be physically retained in the draining lymph nodes. Alternately, they must depart by a different route. Large numbers of V3 MCs (43) and bone marrow-derived MCs (55) are found in the sinuses of the spleen after their i.v. administration into BALB/c and C57BL/6-Kit+/mice, respectively. Although these findings indicate that certain populations of MCs prefer to translocate to the spleen and/or liver from the peripheral blood, we sought evidence that viable MCs could emigrate from a tissue, enter the blood stream, and eventually translocate to the spleen. To address this issue, v-abl-immortalized V3 MCs were adoptively transferred i.p. into normal, noninfected BALB/c mice. Some of these transformed MCs were able to leave the peritoneal cavity and make their way to the spleen (Fig. 5). The inability of V3 MCs to translocate to the liver when injected i.p. suggests that these MCs probably alter their surface homing receptors as they move from the peritoneal cavity to the peripheral blood.

Based on the V3 MC data and the reports of others (56–58) that the spleen is the major filtration organ for circulating erythrocytes and other hematopoietic cells, the MCs in the spleen were quantitated (Fig. 6) and phenotyped (Figs. 7 and 8) during the different phases of helminth-induced mastocytosis. MCs were sparse in number in the spleen of noninfected BALB/c mice. Although the MCs in the spleen of noninfected BALB/c mice express many mMCPs (43), these cells do not express mMCP-9 (36). As assessed by the chloroacetate esterase cytochemistry procedure, the number of MCs in the spleen of T. spiralis-infected mice at wk 4 were >10-fold higher than the number in the spleen of noninfected animals (Fig. 6). More importantly, essentially all of these splenic MCs expressed mMCP-2 and mMCP-9 (Fig. 8).

Based on the observations that only a few MCs in the jejunum of helminth-infected mice were extruded into the lumen (Fig. 3), that only a few MCs in the jejunum were undergoing apoptosis (Fig. 3), that mMCP-9 MCs increased in number in the spleen of helminth-infected mice when their numbers decreased in the jejunum (Fig. 6), and that the splenic MCs were not proliferating (Figs. 7 and 8), we conclude that most of the MCs found in the spleen during the recovery phase of the infection probably originated in the small intestine. The occasional finding of a mMCP-2/mMCP-9 MC in the lumen of the blood vessels in contiguity with splenic sinuses (Fig. 9) is compatible with this conclusion. Although apoptosis of lymphocytes occurs primarily in the central and mantle zones of the lymphoid follicles in the medulla, senescent erythrocytes undergo destruction in the cortex. This site is lined by cells of the mononuclear phagocytic system. Inasmuch as the mMCP-9 MCs in the spleen 4 wk after helminth infection preferentially reside in the sinuses of the cortex, senescent MCs and erythrocytes probably use comparable mechanisms to localize to this organ. It is possible that excess jejunal MCs are preferentially targeted to the spleen simply because the normal clearance mechanism is overwhelmed in this region of the intestine. However, targeting of the jejunal MCs to the spleen would ensure that any mMCP that is nonspecifically released from the dying cell is rapidly trapped and destroyed by this macrophage-rich organ.

At no time during the helminth infection do the MCs in the large intestine express mMCP-9. Because essentially all of the MCs in the spleen during the recovery phase of the infection express mMCP-9 (Fig. 8b), it is unlikely that a high proportion of the apoptotic MCs in the large intestine eventually translocate to the spleen. Although the ultimate fate of this MC population remains to be determined, MCs occasionally can be seen in the lumen during the recovery phase of the infection (Fig. 3a). Thus, it is possible that this population tends to directly exfoliate into the lumen. The reason why most of the amplified MCs residing in the large intestine do not translocate to the spleen is unknown, but it might be an indirect consequence of the regulatory factors released from the functionally distinct intraepithelial T cells that reside in the large and small intestines (59).

Metachromatic/high-affinity IgE receptor cells, which have been classified as basophils primarily because of their segmented nuclei, have been found in the peripheral blood (60) and spleen (61) of helminth-infected mice, as well as in the spleen of mice receiving goat anti-mouse IgD (62). Although MCs generally have nonsegmented nuclei, in vivo- and in vitro-differentiated MCs with segmented nuclei have been found occasionally in the mouse (45). The discovery of mMCP-2/mMCP-9 MCs with segmented nuclei in the large intestine, jejunum, blood, and spleen of the BALB/c mouse during the recovery phase of a T. spiralis infection now suggests that the cells that have been classified as basophils in some of the above studies are actually senescent, T cell-dependent MCs in transit.

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References


