

New insights into the origin of mast cells

To the Editor,

Single-cell RNA-sequencing and colony-forming assays suggest that bone marrow hematopoietic stem and progenitor cells traverse through a differentiation landscape before commitment to the mast cell and other cell lineages.¹ However, the bone marrow contribution for the formation of tissue-resident mast cells has been questioned, and the prenatal origin of mast cells was recently uncovered.² Through fate mapping experiments Gentek et al² elegantly demonstrated that mast cells arise during two distinct waves of the embryonic development, one from the yolk sac and the other via the aorta-gonad-mesonephros. Li et al³ now confirms the presence of distinct developmental waves and reveal that each wave contribute in varying degrees to mast cells in different tissues. Here, we discuss these paradigm-shifting studies in the context of mast cell subtypes, and we highlight how the results can change our understanding of the human mast cell-driven disease mastocytosis.

Murine mast cells are generally divided into two distinct subtypes, connective tissue-type mast cells and mucosal mast cells. The connective tissue-type mast cells are constitutively present, whereas the mucosal mast cells are induced in a T cell-dependent manner.⁴ Gentek et al² investigated the appearance of mast cells in the skin, tongue, and peritoneal cavity, three sites harboring connective tissue-type mast cells. Their data demonstrate that mast cells appear in two distinct waves, that is, from the yolk sac and via the aorta-gonad-mesonephros. Li et al³ performed fate mapping experiments to show that there are likely three distinct waves of mast cell differentiation. The early primitive erythromyeloid progenitors appearing in the yolk sac contribute to the first mast cells followed by a second mast cell wave originating from late erythromyeloid progenitors. The definitive hematopoietic wave emerging within the aorta-gonad-mesonephros produces hematopoietic stem cells and gives rise to the third wave of mast cells. Mast cells appearing in the first wave are largely replaced by mast cells in the later waves, with a few exceptions including mast cells in adipose tissue and pleural cavity. Li et al³ further show that mast cells in the gut arise from the third hematopoietic wave to a high extent. The gut is known to harbor mucosal and connective tissue-type mast cells. The observations may therefore favor a scenario in which the third hematopoietic wave contributes to mucosal mast cells, whereas the first and second waves primarily give rise to connective-tissue mast cells. However, future studies will hopefully address this theory in detail.

Gentek et al² questions the bone marrow origin of mast cells in the postnatal setting. However, this topic also needs to be addressed with the two mast cell subtypes in mind. For example, the bone marrow contribution for the appearance of mucosal mast cells in the airways has previously been studied in great detail. Bone marrow mast cell

progenitors are recruited to the inflamed airways through a T cell-dependent mechanism.⁵ Cell maturation into the mucosal subtype follows the transendothelial migration of the mast cell progenitors.⁵ However, while the mucosal mast cells increase in numbers following airway provocation, the connective tissue-type mast cells do not.⁵ This significant detail suggests that the mechanisms for the increase in connective tissue-type and the mucosal mast cells are different.

Gentek et al² demonstrate that the connective tissue-type mast cells in the skin, tongue, and peritoneal cavity can be partially or completely restored in numbers without bone marrow involvement. The experimental setup can explain parts of the lack of bone marrow involvement. Connective tissue-type (peritoneal) mast cells are long-lived radioresistant cells that feedback-inhibit the recruitment and maturation of their progenitors.⁶ A considerable contribution of reconstituted bone marrow progenitors to the connective tissue-type mast cell frequency is therefore not expected following shielded or whole-body irradiation. Not even induced systemic mast cell depletion is sufficient to promote bone marrow progenitors to reconstitute the skin and tongue mast cells.² Notably, this setting is analogous to reconstitution of mast cell deficient mice, which exhibit deregulated mast cell reconstitution demonstrated by abnormally high mast cell numbers in some tissues and low in others.⁷ However, distilled water injection into the peritoneum of mice, which locally depletes mast cells, stimulates the recruitment of bone marrow mast cell progenitors to the affected site.⁶ These mast cell progenitors gradually mature, and the progenitors were verified to originate from transplanted bone marrow. To summarize, much evidence suggests that induced mucosal mast cells are bone marrow-derived in the postnatal setting. Connective tissue-type mast cells have potential to be generated locally without bone marrow involvement, especially during steady-state or near-homeostatic conditions. However, even the connective tissue-type mast cells can be reconstituted by bone marrow progenitors when the stimulus is sufficient.

Whether the developmental origin of mast cells is similar in humans and mice is yet to be investigated. However, our understanding of mast cell-driven diseases, for example mastocytosis, would fundamentally change if the mechanisms were similar. Mastocytosis is a severe disease characterized by increased mast cell numbers, and the symptoms are frequently associated with mast cell activation.⁸ The systemic chronic form typically develops in adults whereas the pediatric mastocytosis is commonly of the cutaneous form that often regresses spontaneously before adulthood.⁹ These observations might in fact be explained by the distinct developmental waves of mast cells described by Gentek et al² and Li et al³. The adult onset mastocytosis could reflect aberrancies in mast cells of the definitive hematopoiesis, cells that accumulate with age.

Pediatric mastocytosis could instead be caused by aberrant mast cells derived from the first wave that are cleared with age. We look forward to see studies addressing this hypothesis.

Altogether, the exciting results by Gentek et al² and Li et al³ are changing our understanding of the development of mast cells in mice. Important questions that now need to be addressed are if the mucosal mast cells have the same developmental origin in the embryo as the connective tissue-type mast cells, and if the conclusions will be similar for the development of human mast cells. The answer to these questions may reveal mechanisms behind mast cell-driven diseases.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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