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Review Article

The role of mast cell in tissue morphogenesis. Thymus, duodenum, and mammary gland as examples

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ABSTRACT

Mast cells (MCs) are strategically located at host/environment interfaces like skin, airways, and gastro-intestinal and uro-genital tracts. MCs also populate connective tissues in association with blood and lymphatic vessels and nerves. MCs are absent in avascular tissues, such as mineralized bone, cartilage, and cornea. MCs have various functions and different functional subsets of MCs are encountered in different tissues. However, we do not' know exactly what is the physiological function of MC. Most of these functions are not essential for life, as various MC-deficient strains of mice and rats seems to have normal life spans. In this review article, we have reported and discussed the literature data concerning the role of MCs in tissue morphogenesis, and in particular their role in the development of thymus, duodenum, and mammary gland.

Contents

1. Introduction

MC committed progenitors complete their maturation with concomitant phenotypic diversity after moving into diverse peripheral tissues, and are regulated by local growth factors and cytokines [24]. In the adult mouse, the mucosa of the intestine contains the largest peripheral pool of the committed progenitors [25].

The progenitors give rise to distinct phenotypes, in terms of protease expression after moving in different tissues [58]. Mature MCs do not circulate like cells of hematopoietic lineages and do not dominate a single organ like parenchymal cells.

The regulation of the tissue distribution of MCs requires the stem cell factor (SCF) or c-kit ligand, to elicit the c-kit mediated signal that ensures the expression of dermal and connective tissue constitutive MCs. In 1978, Kitamura et al. characterized W/W^v mice, harboring natural occurring mutations in the W locus encoding c-kit. These mutations reduce signaling through c-kit to about 10% of the normal level and W/W^v mice are profoundly mast cell deficient [36].

MCs are strategically located at host/environment interfaces like skin, airways, and gastro-intestinal and uro-genital tracts. MCs also populate connective tissues in association with blood and lymphatic vessels and nerves. MCs are absent in avascular tissues,

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such as mineralized bone, cartilage, and cornea.

A distinction established in the mouse is that connective tissue mast cells (CTMCs) are constitutive and T independent, while mucosal mast cells (MMCs) are induced and T cell dependent as defined in the intestine and mouse lung. CTMCs are predominantly found in the skin and in peritoneal cavity, and their granules contain heparin and large amounts of histamine and carboxypeptidase A. In contrast, MMCs are localized mainly in the mucosal layer of the gut and lung and their granules contain chondroitin, and relatively less amount of histamine and carboxypeptidase. In the mouse intestine, MCs exists in anatomical distributions that are T-cell independent in the submucosa and T-cell dependent in the epithelium (in athymic nude mice intraepithelial MCs are absent).

Human MCsT, containing tryptase alone, correspond to the rodent MMCs while human MCsTC, containing both tryptase and chymase along with other proteases (carboxypeptidase A and cathepsin G), correspond to the rodent CTMCs. MCsT are prevalent in the alveolar septa of the lung and in the small intestinal mucosa. In human intestinal mucosa, MCs consist of approximately 2–3% of the inflammatory cell infiltrate localized in healthy subjects [3].

In the respiratory system, the greatest concentration of MCs is found in the trachea and large bronchi, just underneath the epithelium, but some MCs are present also within the bronchial epithelium.

MCsTC predominate in the connective tissue areas, such as skin, submucosa of the stomach and intestine, breast parenchyma, myocardium, thymus, lymph nodes, conjunctiva, and synovium [14,28].

In the human skin, MCs are preferentially located in the most superficial layers where up tenfold more MCs are found as compared with the subcutis [63]. MCs are more numerous around hair follicles, sebaceous and sweat glands, and around small vessels. Small MCs are found in the subepithelial portion, their size and granule content increasing towards the subcutis. The human skin is an extramedullary reservoir of MC precursors, which resides in the connective tissue sheath of hair follicles [30].

In the lymph nodes, the MCs are in the capsular and in the septal connective tissue, but few may be seen in the interfollicular reticulum. Otherwise, spleen is relatively poor in MCs and most are localized in the capsule and stroma.

T cell-derived growth factors play an important role in the development and maintenance of human MCsT at mucosal site [29]. The intraepithelial accumulation of MCs in bronchi of patients with asthma, which occurs in association with subepithelial infiltrations of activated eosinophils and Th2 cells suggests that MCs respond to T-cell-derived cytokines *in vivo* [49]. Moreover, In humans with T-cell deficiency intestinal intraepithelial MCs are absent [29].

MCs release in the surrounding microenvironment a broad array of preformed mediators and signaling molecules affecting the functional profile of different resident tissue cells, like fibroblasts, smooth muscle cells, endothelial cells, epithelial cells and nerve fibers [21,45,52,60]. In addition, they synthesize and release both serine- and metallo-proteases (MMPs), which cause extracellular matrix degradation and tissue remodeling [37]. These functional properties put MCs in a central, strategic position to maintain tissue homeostasis [41]. The presence of MCs in connective tissues has been linked to the development of fibrosis through the production of histamine, heparin, tryptase, fibroblast growth factor-2 (FGF-2), tumor necrosis factor alpha (TNFα) and transforming growth factor beta (TGFβ), which stimulate the proliferation of myofibroblasts and fibrosis.

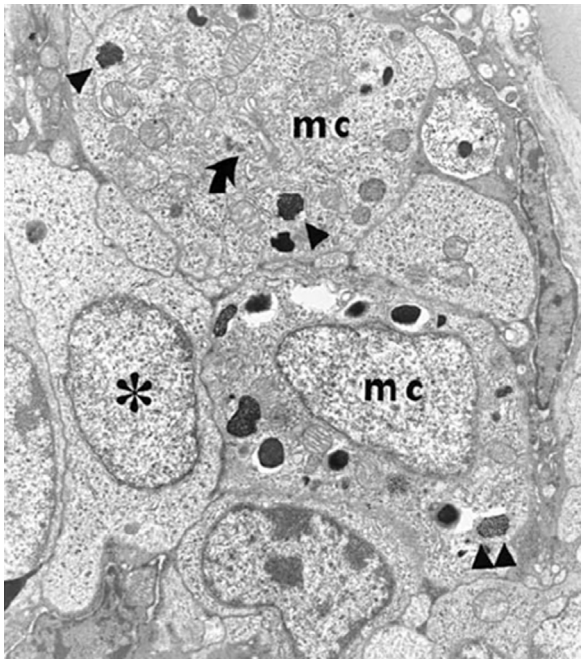

Fig. 1. Ultrastructural features of two mast cells (mc) lie in the medullary parenchyma of chick embryo thymus, close to a thymic epithelial cell (asterisk). One mast cell shows a prominent Golgi apparatus (curved arrow). Granules present either an irregularly scroll-like pattern (single arrowheads) or a punctate texture (double arrowheads).(Reproduced form [13]).

2. Mast cells in thymus

In thymus, MCs localize in the connective tissue of the capsule and interlobular septa, and inside the thymic lobules [35,7]. MCs are either situated in the perivascular spaces [35] or interspersed among lymphoid and stromal cells, particularly close to peptidergic nerves [39,43,64]. Intrathymic MCs have been linked to neuro(endocrine)-immune circuits involving MC-peptidergic nerve contacts [39,43,64] and changes in the number of MCs inside the organ have been reported in a series of experimental conditions related to manipulation of the neuroendocrine axis [1,2].

MCs synthesize and release a large panel of growth factors and cytokine, including interleukin (IL)-1, IL-2, IL-3, IL-4, IL-6, TNFα, granulocyte-monocyte colony stimulating factor (GM-CSF), and nerve growth factor(NGF),which stimulate thymocyte and thymic epithelial cell functions [15,56,57].

In human and chick thymus, MCs were restricted to the medulla and to connective tissue septa and their number increased in adult thymus when compared with foetal thymus (Fig. 1) [13,51]. In the thymoma specimens MCs were closer to each other and to the vessels than in normal thymus. The mean distance from vessels and the mean distance from the nearest cell profile were significantly lower than in normal thymus specimens [51].

3. Mast cells in dudenum

A significant association has been recognized between villous architecture and the number of MCs in the small bowel mucosa. Indeed, high values of total and tryptase-reactive MCs in the lamina propria of human duodenum were associated with normal villous profile while low values were associated with defective or atrophic villi, suggesting participation of MC in the network of cellular and molecular signals regulating villous structure and affecting mucosal morphology [12].