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Review

Mast cell ontogeny: An historical overview

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ABSTRACT

Mast cells were first identified by Paul Ehrlich in 1878, when he was still a medical student. Many fundamental aspects of mast cell ontogeny have been elucidated since Ehrlich's first identification. Demonstration of mast cell derivation from bone marrow precursors could be established in 1977 when Kitamura's group first showed reconstitution of mast cells in mast cell-deficient mice by the adaptive transfer of wild type bone marrow and indicated that these cells were of hematopoietic origin. It is now definitively established that development of mast cells in bone marrow occurs along the myeloid pathway. However, several aspects need further clarification. In particular, identification and chemical characterization of growth factors expressing mast cell differentiating properties and the relationship between mast cell and basophils developmental pathways.

1. Introduction

The traditional view is that mast cells arise from mast cell committed precursors in the bone marrow, circulate as agranular cells, then traverse the vascular space and enter the tissues or serosal cavity, where they complete their development, giving rise to specific subsets of mast cells with characteristic profiles of intracellular mediators at distinct sites within the body. They reside close to blood vessels, nerves, and mucosal surfaces, such as respiratory tract and gastrointestinal tract. Mast cells are absent in avascular tissues, including mineral bone, cartilage and cornea [1].

The history of the discovery of mast cell origin is complex and goes down to the early time when these cells were recognized by Ehrlich. It took many decades for scientist to elucidate the main aspects of mast cell ontogeny. Molecular biology and genetics have recently opened new field of research on this important research issue.

2. Early concepts on mast cell origin

Mast cells were first identified by Paul Ehrlich (Fig. 1) in 1878, when he was still a medical student. In his doctoral dissertation, whose title was "Beiträge zur Theorie und Praxis der histologischen Färbung" ("Contribution to the theory and practice of histological dyes"), Ehrlich described a class of aniline-positive cells of the connective tissues endowed with cytoplasmic metachromatic granules ("granulierte Bindgewebezellen") for which he coined the name of "Mastzellen" [2]. He soon faced the issue of their origin. In his opinion, mast cells were connective cells which developed as a result of hyper nutrition. Thus, their aniline-positive metachromatic granules would represent deposits of nutrients. Being the functional role of the newly discovered cells mainly related to a "feeding" or "nourishing" activity, Ehrlich believed that they might derive from tissue pre-existing progenitors, suggesting that they differentiated from fibroblasts [3]. Later, Ehrlich regarded mast cells as "indices of the nutritional state of the connective tissue" [4]. Accordingly, it was feasible to find these cells accumulated in such over-nourished conditions as chronic inflammation, especially when it was aggravated by chronic lymphatic obstruction, and tumors.

In successive memories, Ehrlich described the staining reactions of blood leukocytes on the basis of their specific affinities for various dyes [5,6]. He encountered cells with basophilic, metachromatic granules, and thus came to recognize two types of "Mastzellen". The first, which could be identified and differentiated by its repertoire of coarse basophile granules (γ granulation), lived in the connective tissues and apparently derived from them (tissue "Mastzell"). The second, the counterpart of the neutrophil polymorph and eosinophil leukocyte, contained basophilic granulation of the fine type (δ granulation), its origin was in the bone marrow and its habitat was in the peripheral blood (blood "Mastzell", basophil or mast

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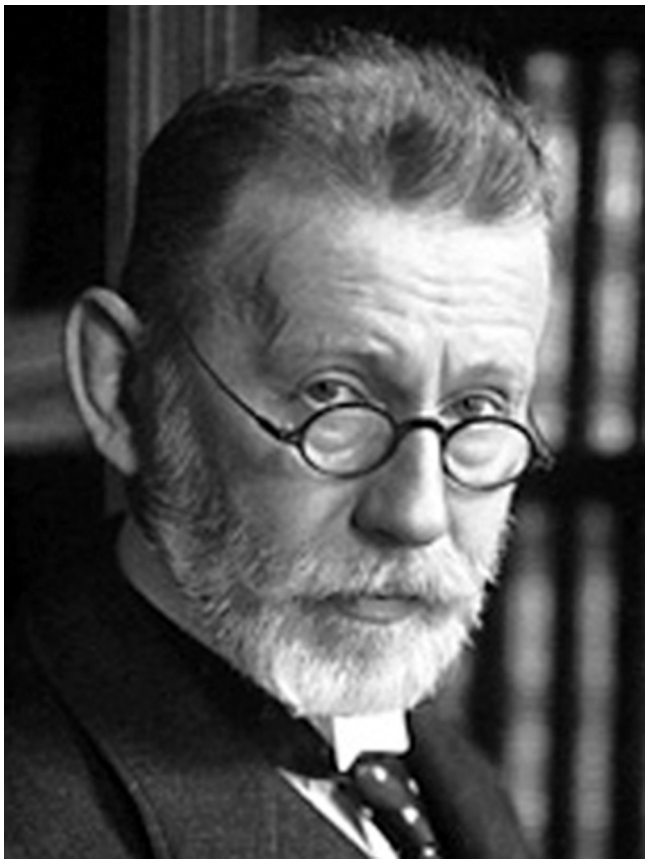

Fig. 1. A portrait of P. Ehrlich.

leukocyte). By the time that his textbook of 1898 came to be revised [6], the evidence for the myeloid origin of the blood mast cells was complete [7].

Sixteen years after Ehrlich's first description of Mastzellen, the English histologist and physiologist William Bate Hardy (Fig. 2) distinguished two types of granular basophile cells, i.e., the "coarsely granular basophile cells" and the "splanchnic basophile cells", which both belonged to the population of "wandering cells" (the modern leukocytes) [8,9]. These tissue-homing cells corresponded to the subsets of connective tissue-type and mucosal mast cells, respectively, which would be described seventy years later by Enerbäck in rodents [10,11] (Fig. 3). Among the coarsely granular basophile cells, he also differentiated those cells which populated the serosal cavities – the so-called coelomic coarsely granular basophile cells – from the common coarsely granular basophile cells which were localized in the connective tissues. Hardy's view of basophile cell function was partly in line with Ehrlich's concept of a nutritional role for these cells. He believed that these cells might be somehow involved in the up-take and storage of substances as a result of hypernutrition. However, he also explored other experimental areas, such as the potential contribution of granular basophile cells to phagocytosis of pathogens and the participation of these cells to defence mechanisms during infections (for further historical data, see reference [12]).

For several decades after Ehrlich's discovery, the study of mast cell origin stood on pure conjectural bases being investigations supported by almost exclusively histological procedures. The scientific debate mainly focussed on the difference between mast cell and basophil developmental pathways. It was argued that mast cells and basophils, although very similar from a pure histological and histochemical ground, differed both in habitat and in parentage, at least in higher organisms. The derivation of mast cells was related

Fig. 2. A portrait of W. Bate Hardy.

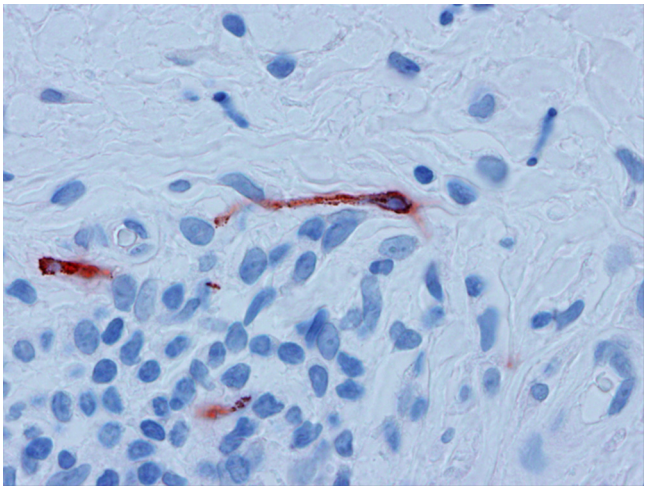

Fig. 3. A typical elongated mast cell stained with an antibody anti-tryptase. Original magnification ×160.