

Chapter 1

Paul Ehrlich's Mastzellen: A Historical Perspective of Relevant Developments in Mast Cell Biology

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Abstract

Following the discovery of mast cells (or mastzellen) by the prolific physician researcher, Paul Ehrlich, many advances have improved our understanding of these cells and their fascinating biology. The discovery of immunoglobulin E and receptors for IgE and IgG on mast cells heralded further in vivo and in vitro studies, using molecular technologies and gene knockout models. Mast cells express an array of inflammatory mediators including tryptase, histamine, cytokines, chemokines, and growth factors. They play a role in many varying disease states, from atopic diseases, parasitic infections, hematological malignancies, and arthritis to osteoporosis. This review will attempt to summarize salient evolving areas in mast cell research over the last few centuries that have led to our current understanding of this pivotal multifunctional cell.

Key words Mast cells, Immunoglobulin E, Cytokine, Gene expression, Host defense, Inflammation, History

1 Ehrlich's "Mastzellen"

Paul Ehrlich (Fig. 1) is credited with the initial discovery of mast cells (Fig. 2) as we know them today. He was born near Breslau, now called Wroclaw Poland, in 1854. He studied to become a medical doctor at the university there and attended universities in Strasbourg, Freiburg, and Leipzig [1]. Ehrlich was greatly influenced by his cousin Karl Weigert, an eminent histopathologist who pioneered the use of aniline dyes for staining bacteria and tissue sections [1]. Weigert had a strong and positive influence throughout Ehrlich's life [2]. As a result, even as a medical student, Ehrlich had an extensive knowledge of structural organic chemistry and a

I would like to dedicate this chapter to my father, Dr. Narayanaswamy Krishnaswamy, M.B.B.S., an immunologist and clinician extraordinaire, who encouraged me to enter academic medicine and who continues to inspire me with his clinical acumen, his wide-armed compassion, and his practical yet gentle wisdom. By Guha Krishnaswamy, M.D.



Fig. 1 Picture of Paul Ehrlich from the Nobel Archives. *Source:* © Nobelstiftelsen

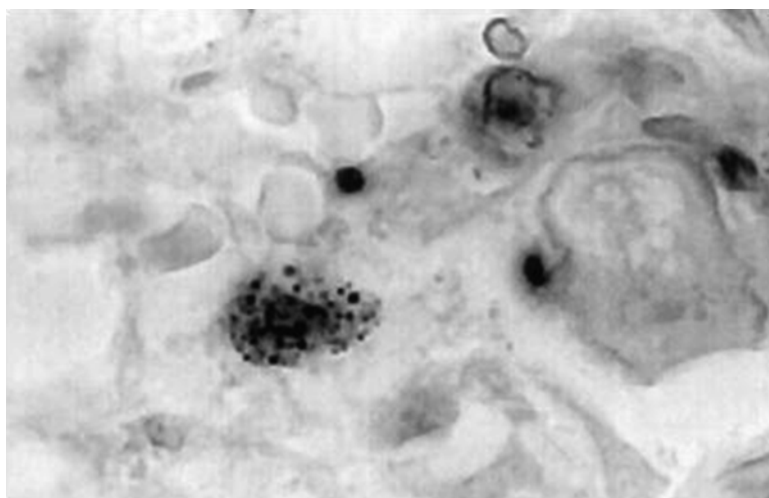


Fig. 2 Mast cell in atheromatous plaque (Courtesy Dr. George Youngberg, M.D., East Tennessee State University)

fascination for dyes as probes of cellular structure [2]. He was quite excited by the idea that organic chemicals can have differential and specific reactions with various tissues and bacteria.

On June 17, 1878, Paul Ehrlich, a 24-year-old medical student at the time, presented his doctoral thesis “Contributions to the theory and practice of histological staining” to the Medical Faculty of Leipzig. The medical student divided his thesis into two halves. In the first part he talked about the chemical basis of many important histological reactions, while in the second he presented a detailed discussion about aniline dyes [1]. The first description of the mast cell comes in the portion of the thesis dedicated to the histological applications of the aniline dyes. He presented his point of view that

“aniline dyes displayed an absolutely characteristic behavior towards protoplasmic deposits of certain cells” which he referred to as “mastzellen,” now known as mast cells. He sought to distinguish these cells from “plasmazellen” cells previously described by Waldeyer [1].

Ehrlich said that these anilophilic cells from, the descriptive point of view, should be most conveniently described as “granular cells of the connective tissue.” From a physiological standpoint, these cells, according to Ehrlich, might represent a “further development of the fixed cells of the connective tissue.” To support his theory, Ehrlich explained that aniline-reactive cells indeed “have a tendency to collect around developing preformed structures in the connective tissue.” He also stated that “granular cells are characterized by an ‘undetermined chemical substance’ in the protoplasm with which the aniline dye reacts to give a typical metachromasia” [1]. To this day, although by no means absolute, mast cells are recognized by the presence of metachromatic granules when fixed and stained with toluidine blue.

Further in his dissertation, Ehrlich provided an accurate description of the microscopic features of mast cells. He described that the typical aspect of these “granular cells” is mostly unstained protoplasm filled with numerous granules of varying size with a nucleus not stainable even in samples that otherwise displayed beautiful nuclear staining. He strived to classify these cells using specific histochemical reactions rather than histology, a forward-looking concept for his time.

A historically interesting aspect is why Ehrlich decided to call these cells the “mastzellen” or mast cell as these were plump-appearing cells (well-fed cells). The name for these new cells was probably derived from the Greek “mast” (or breast) or the German “mastung” (masticate). In today’s research, mast cells are being increasingly recognized for their role in connective tissue remodeling and repair [1]. We now know that their granules contain many proteases and cytokines that are known to exert far-reaching effects on other cell types like the smooth muscle, fibroblasts, and endothelial cells.

Ehrlich also recognized that mast cells sometimes localize far from the blood vessels and express a series of biological functions not related to vascular functions. He also noted that these cells could be found around developing tissues. The close relationship between mast cell and tumor growth stems from this very same idea. Unfortunately, the original text of this remarkable work was destroyed in an air raid on Leipzig in 1943. In the same year, Ehrlich moved to the Charité Hospital in Berlin, where he continued his work and wrote an influential thesis on the oxygen requirement of cells. In January of 1879, the Physiological Society of Berlin reviewed the remarkable paper by Paul Ehrlich wherein he first described the mast cells that he had discovered as a medical student several years earlier. Ehrlich, in these papers, pointed out that mast cells exhibit a great avidity to basic dyes and characteristically altered the shade of the dye [1].

In 1891 along with Westphal, one of his pupils, Ehrlich showed another characteristic feature of mast cell granules in many species, namely their water solubility. Almost 50 years later, Michels wrote that “uncounted pages of useless and misleading research have been a result of failure on the part of many investigators to heed admonition originally given by Ehrlich and Westphal that mast cell granules are soluble in water and that to preserve them, tissues must be fixed in 50 % alcohol and stained in alcoholic thionine [1].”

Ehrlich then studied the special affinity of leucocytes for various dyes. In 1891, he had discovered basophilic granular cells in blood from a patient with myeloid leukemia and was quick to infer with his characteristic insight that, in higher species especially humans, the mast cells are actually leucocytes arising from precursor cells in the bone marrow. He believed that there were two types of mast cells: the first is often located in connective tissue and the second, of bone marrow origin, localized in the peripheral blood. In 1900, Jolly had established the bone marrow origin for the mast cells. Hence, by the time his textbook (*Die Anaemie* by Ehrlich and Lazarus, 1898) was revised in 1909, human mast cell origins were better understood. It is now accepted that mast cells arise from a pluripotent cell in the bone marrow that expresses CD34, *c-kit*, and CD13.

Ehrlich also led the way in observing mast cells in two pathological situations of utmost importance—chronic inflammation and neoplasia. He felt that in both of these situations, the tissue was “over nourished” due to lymph stasis, and hence, there was an accumulation of tissue fluid rich in nutriment. This led the mast cells to convert some of this abundant extracellular fluid to specific intracellular granules [1]. Thus, according to Ehrlich, mast cells served as an “indices for the nutritional status of the connective tissue,” whose activity increased and decreased during periods of hypernutrition and starvation. Ehrlich and his pupil Westphal found that mast cells accumulated in many tumors, more in the periphery of carcinomatous tumors than the substance of the tumor. Besides the discovery of the mast cell, Ehrlich made pioneering contributions to the method of staining the bacillus that causes tuberculosis, to the development of a therapeutic antiserum against diphtheria, and to the concepts of antibodies and chemotherapy. Some typical features of Paul Ehrlich’s colorful personality included his habits of smoking 25 cigars a day, carrying around a pocketful of colored precisely sharpened pencils with which he would write daily instructions to his research team, and his exceptional clinical knowledge and acumen. On the 150th anniversary of his birth, we cannot help but admire the invaluable contribution he made to the science of immunology.

A chronology of developments in mast cell and immediate hypersensitivity research is provided below (Table 1). This includes Paul

Ehrlich's initial description, culminating in immunological, molecular, and genomic technologies that have accelerated our understanding of the mechanisms underlying immediate hypersensitivity and relevant mast cell biology in diverse inflammatory processes.

Table 1
Chronology of developments in immediate hypersensitivity and relevant mast cell research

Year(s)	Major development in the understanding of mast cell biology
3300–3640 (BCE)	Allergic reaction to bee sting in a pharaoh is documented historically
1878	Paul Ehrlich describes mast cells in his doctoral thesis at the University of Leipzig and coins the term “mastzellen” derived from German word “mast” (breast) [1]
1879	Paul Ehrlich describes metachromasia [1]
1891	Water solubility of mast cells demonstrated by Paul Ehrlich [1]
1891	Description of cells with basophilic granules in leukemia by Paul Ehrlich [1]
1898	Paul Ehrlich describes two types of cells with basophilic granules. One localized to tissue (tissue mast cells) and another derived from bone marrow and localized to blood (blood mast cell, basophil, mast leukocyte) [1]
1900	Demonstration of bone marrow origin of mast cells by Jolly [1]
1900	Paul Ehrlich describes antibody formation theory [1]
1902	Description of “anaphylaxis” is made by Paul Portier and Charles Richet [3]
1906	The term “allergy” is coined by Clemens von Pirquet
1907	Histamine is synthesized by Windaus and Vogt [4]
1908	Paul Ehrlich receives the Nobel Prize in Physiology or Medicine along with Ilya Ilyich Mechnikov for discoveries in immunology
1910	Physiological functions of histamine described by Dale and Laidlaw [4]
1913	Nobel Prize awarded to Charles Richet for discovery of “anaphylaxis” [3, 5–7]
1913	Schultz and Dale describe smooth muscle contraction in sensitized animals; Schultz used intestinal muscle, while Dale used uterine muscle of guinea pigs [8–10]
1921	Description of passive transfer of hypersensitivity with serum by Prausnitz, popularly known as the Prausnitz-Kustner reaction (P-K reaction) [11–13]
1948	Description of passive cutaneous anaphylaxis (PCA) by Ovary [10]
1952	Discovery of “histamine” in mast cells by James Riley and Geoffrey West [14]
1961	Ovary demonstrates the release of slow-reacting substance of anaphylaxis (SRS-A) from mast cells when activated by allergen [10]
1961	Mast cells identified in the bronchial tissue in asthma
1973	Putative receptor on mast cells for IgE recognized [15]

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Year(s)	Major development in the understanding of mast cell biology
1979	Slow-reacting substance of anaphylaxis (SRS-A) identified in mast cells as a “leukotriene” [16]
1988	Sir James Black awarded the Nobel Prize for the discovery of histamine (H ₂) receptor antagonist [17]
1967	Kimishige Ishizaka recognizes immunoglobulin E as reagenic antibody [18, 19]
1985	Susumu Tonegawa receives the Nobel Prize for identification of immunoglobulin genes [20–22]
1989	Plaut and Paul show mast cells are capable of secreting multiple lymphokines [23]
1989	Cloning of canine mast cell tryptase is reported [24]
1990	Cloning of human mast cell tryptase is reported [25]
1990	Steel locus kit ligand (KL) is identified as ligand for <i>c-kit</i> and reported to be involved in mast cell proliferation [26, 27]
1990	Cloning of canine mast cell chymase is reported [28]
1991	Cloning of human mast cell chymase is reported [29]
1994	Ability of mast cells to phagocytose bacteria is shown [30]
1994	Murine mast cells are shown to present antigen to T cells [31]
1994–1996	Dominant role for mast cells in the Arthus reaction is demonstrated [31–33]
1996	Mast cells are shown to be important in defense against <i>E. coli</i> infection [34]
2001	Transcriptome of human mast cells is analyzed [35, 36]
2001–2003	Toll-like receptors are described on mast cells [37–39]
2003	Toll-like receptor and high-affinity IgE signaling shown to induce distinct gene profiles in mast cells [40]
2003	Histamine deficiency induced by histidine decarboxylase gene targeting in mice reveals lower mast cell numbers and defective mast cell degranulation [41]
2004	Expression of nitric oxide synthase and nitric oxide in human mast cells demonstrated [42]
2006	Genomic profiling of mast cells and transcriptome analysis show a wide range of inflammatory responses [43, 44]
2009–2010	Molecular involvement of mast cells in diverse gastrointestinal tract diseases such as Crohn’s disease and eosinophilic esophagitis demonstrated [45, 46]
2011	Mast cell targeting shown to hamper development of prostate carcinoma [47]
2012	Siglec-8 expressed in mast cells and eosinophils may be a target for asthma therapy [48]
2012	Mast cells may link eczema to airway reactivity in a mouse model [49]
2012	Pimecrolimus, a calcineurin inhibitor, may be an effective treatment for mast cell-related disease processes [50]

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