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A review on structure and function of mast cells

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ABSTRACT

Mast cells, among the largest of fixed connective tissue cells, are ovoid in shape with a diameter about 20 to 30 µm. They possess a centrally placed nucleus and numerous membrane-bounded granules in their cytoplasm. These granules are greatly variable in size and shape. These granules contain acid mucopolysaccharides which stain metachromatically with toluidine blue, among other basic dyes. There are differences in the cytochemistry of mast cells between species, areas within the same animal and even neighboring cells. Mast cells develop from bone marrow precursors and migrate through blood steam to terminate in the connective tissues all over the body. There are two types of mast cells: (1) Connective tissue mast cells which are larger, less mobile, and have more granules and more lifespan; and (2) Mucosal mast cells which are smaller, more mobile, contain chondroitin sulfate, and live in the submucosa of respiratory and alimentary tract. What mast cells do for a living is not entirely clear, but all attention had been focused mainly on its immunological role. In addition to heparin, histamine and neutral proteases, their granules contain β-glucuronidase, hexoaminidase and aryl sulfatase. These enzymes have no roles in immune responses, so normal mast cells may have low level secretory activity that affects the continual turnover of the ground substance of connective tissue. Mast cells are sensitive guards for immune system detecting the entry of foreign proteins and initiating a local inflammatory response. Their activation results in prompt release of potent mediators followed by slower generation of cytokines that serve to recruit other cell types that participate in the body's defense. This response is usually local and relatively mild, but the immune system of allergic individuals may overreact to a second exposure to one of these antigens resulting in tissue damage and symptoms ranging from mild discomfort to serious anaphylaxis.

1. Introduction

Mast cells were first described around 1878 by a medical student who developed a passion for newly available aniline dyes which were being tested on tissue by his older cousin Carl Weigert, a very famous pathologist at that time. The young man soon noticed that some leukocytes stain with basic dyes as do the mast cells (he called them basophils). Others stain with acidic dyes such as eosin (he called them eosinophils), and still others stain with neither (he called them neutrophils). The medical student was Paul Ehrlich, who later shared the Nobel Prize with Metchnikolf in 1908 (Guido and Isabelle, 1994).

In 1901 Prince Albert of Monaco, who was interested in marine biology, set to sea on the princess Alice II to work out the mechanism of poisoning by the Portuguese man-of-war, a stinging jelly fish that can be nuisance on Mediterranean beaches at that time. The ship was equipped with labs for animal experiments. Paul Portier was the resident scientist. To supervise the experiments, Prince Albert invited a senior scholar, Charles Richet (1850-1935), who was also a writer and an eminent physiologist. As the ship cruised along, a number of dogs, ducks, pigeons, and frogs were injected with jellyfish extracts, the only finding worthy of note was that the animals tended to “fall asleep" perhaps by a neurotoxic effect. After the voyage Richet continued the experiments on dogs using sea anemones which cost less. Would their poison have the same narcotic effect as that of the Portuguese man-of-war jellyfish? Richet tried several doses and again, for economic reasons, he used the same dogs for more than one injection. So "dog" Neptune", for example, received three non-lethal doses on the day's first, third and twenty seventh. The first two doses had no apparent harmful effect, but soon after the third dose the dog

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suddenly keeled over, convulsed, vomited and died after 25 minutes (Portier and Richet, 1902).

Portier and Richet were utterly amazed having anticipated, if anything, an immunizing (prophylactic) effect of repeated doses. "Dog Neptune" and others after him-seemed to show the reverse effect. Grouping for a Greek word to mean "reversed protection" they settled on anaphylaxis. After 12 years, Richet was awarded the Nobel Prize for having opened a new field of immunology. Actually anaphylaxis had been seen by others before him but nobody had generalized from it. Neither Richet nor Portier lived long enough to learn its basic mechanism (Guido and Isabelle, 1994).

After Ehrlich's work, interest in mast cells faded away for decades for simple reason that their granules were almost invisible with routine haematoxylin and eosin stain. In 1930s after appropriate fixation the granules stained with most basic dyes, and were found to contain the anticoagulant heparin: a highly acidic sulfated glycosaminoglycan.

Mast cells are extremely heterogeneous with respect to structure, mediators content, granules proteoglycan and, most importantly, response to drugs (Glauert et al., 1978; Austen, 1984; Golstein, 1987; Ha and Reed, 1987; Serafin and Austen, 1987). Mast cells are the largest of the fixed cells of the connective tissue cells (fixed connective tissue cells are fibroblasts, adipose cells, mast cells, and pericytes). They are long-lived population that have developed and remain in place within the connective tissue (Fawcett, 1993).

The presence of numerous basophilic granules is the identifying characteristic of mast cells (Gartner and Hiatt, 1997). Gartner and Hiatt (1997) reported that these membrane-bound granules ranged in size from 0.3 to 0.8 μm. As these granules contain heparin, they stain metachromatically with toluidine blue. They are able to change the color of the dye from blue to magenta.

2. Development and distribution of mast cells

Although mast cells live in the tissues and basophils live in the blood, they are very similar in structure and function as both have conspicuous metachromatic granules, which contain histamine and other mediators of inflammation. Both have surface receptors for immunoglobulin. They both arise from bone marrow precursors. It was once believed that mast cells were derived from mesenchymal cells, as do the other three types of fixed connective tissue cells. It was also believed that mast cells were basophils that had left bloodstream to perform their tasks in the connective tissues. These similarities prompted the speculation that the mast cells of connective tissue might arise from blood basophils (Gordon et al., 1990). It is now well known that basophils and mast cells are completely different cell types and have different and separate precursors (Matsuda et al., 1990).

Mast cells precursors probably originate in the bone marrow, circulate in the blood for a short time, and then enter the connective tissue where they differentiate into mast cells and acquire their-characteristic cytoplasmic granules. These cells have a lifespan of less than a few months and occasionally undergo cell division (Heckbert et al., 1990).

While basophile are smaller and usually have a bilobed nucleus. They are only found in the blood and, like other granular leukocytes, they have a lifespan of only a few days and they are incapable of proliferation.

Precursors of mast cells that are still unidentified are believed to circulate in the blood briefly and only acquire their granules during their subsequent differentiation in the connective tissue (Matsuda et al., 1990).

Mast cells are sparsely distributed throughout the connective tissue proper but are more numerous along the course of small blood vessels especially venules , and beneath the epithelium of the respiratory and gastrointestinal tracts, where antigens are likely to gain access to the underlying tissues. They are sensitive sentinels for immune system detecting the entry of foreign proteins and initiating a local inflammatory response. Their activation results in the prompt release of potent mediators stored in their granules followed by a slower degeneration of cytokines that serve to recruit other cell types that participate in the body's defense mechanisms (Morrow et al., 1991; Lominadze et al., 2005).

3. Types of mast cells

Two major types of mast cells have been identified: the connective tissue mast cells (TC) and the mucosal mast cells (MC). The connective tissue mast cells are larger, less mobile and have more granules. So they have more heparin, histamine and other mediators. They also have longer lifespan than those of mucosal mast cells (Duke et al., 1983). The connective tissue mast cells contain mostly heparin in their granules whereas those located in the alimentary tract mucosa contain chondroitin sulfate instead of heparin (Gartner and Hiatt, 1997). The reason for the existence of the two diverse populations of mast cells is not clearly understood.

4. Structure of mast cells

Mast cells are among the largest of fixed connective tissue cells: about 20-30 μm in diameter. They are large ovoid cells with relatively small ovoid centrally placed nuclei and numerous cytoplasmic basophilic granules. Mast cells granules are soluble in water like those of basophilic leukocytes and, therefore, not very obvious in most routinely prepared haematoxylin and eosin stained sections.

The granules stain metachromatically with toluidine blue as they contain the sulfated glucosaminoglycan heparin. They also contain histamine, neutral proteases, tryptase, chyamase and

an eosinophil chemotactic factor. The membrane-bounded granules range in size from 0.3 to 0.8 µm (Figs. 1, 2 and 3). These granules display great variations in their ultrastructure (even within the same cells) as well as in their size and form (Austen, 1984) (Fig. 4). At high magnification, Matsuda et al. (1990) also found great differences in the granules ultrastructure from cell to cell and indeed within the same cell.

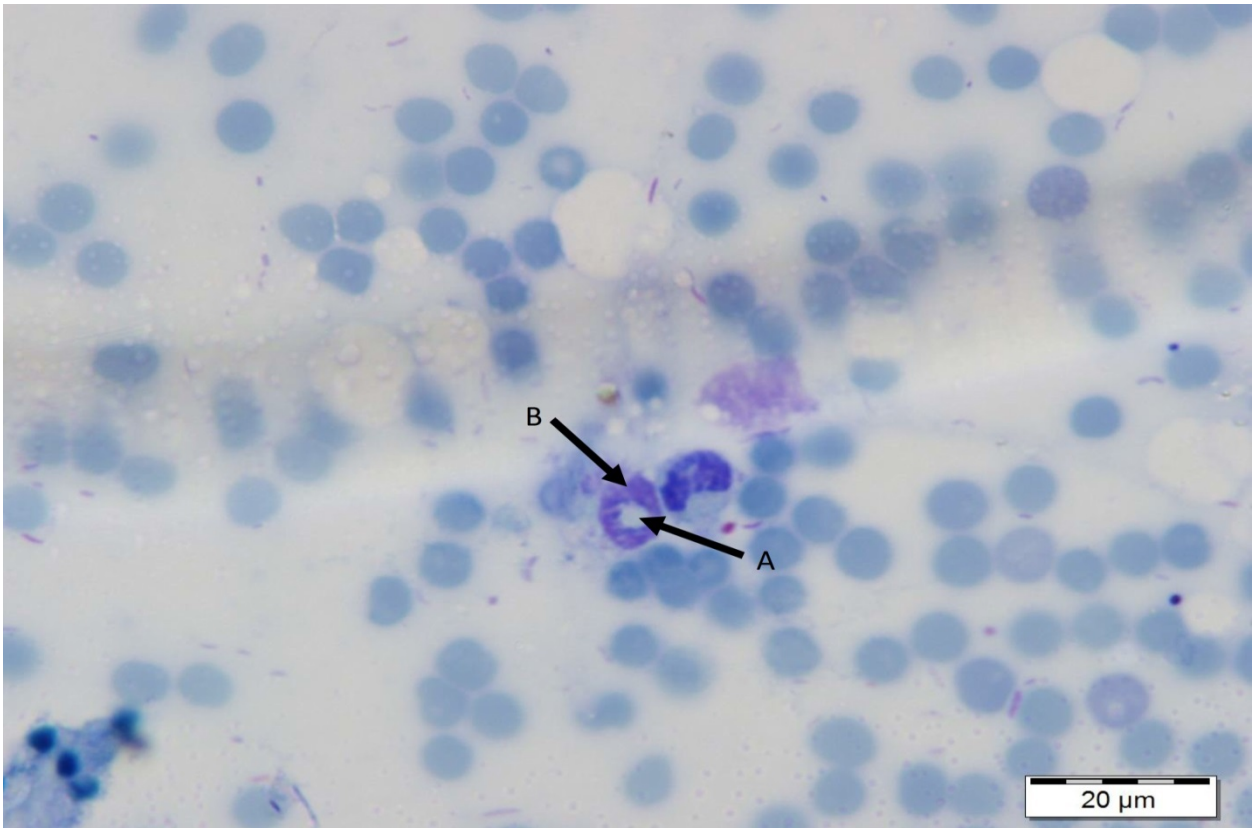

Fig. 1: Mast cell in mesentery of rat. A. nucleus; B. cytoplasmic granules. Toluidine blue, scale bar 20 = µm

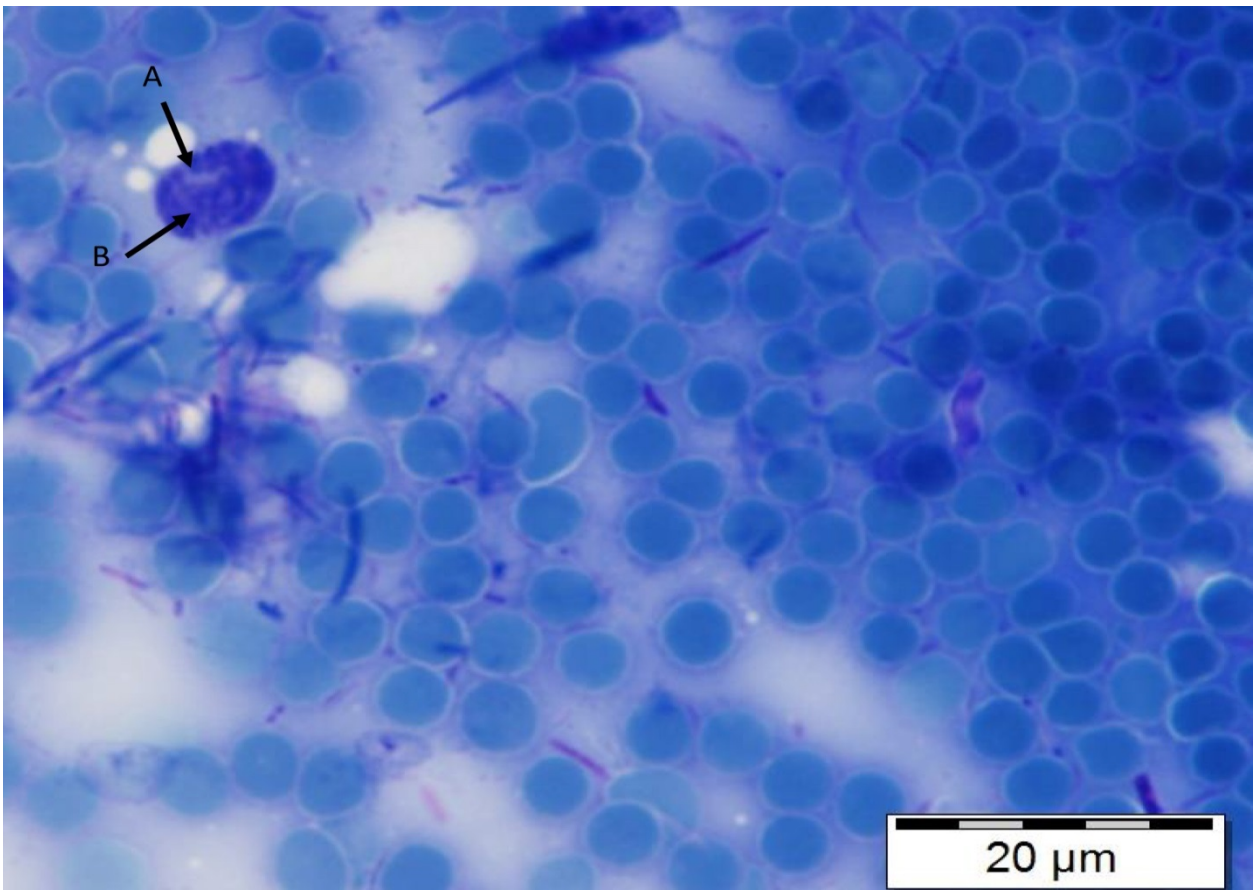

Fig. 2: Mast cell in mesentery of rat. A. nucleus; B. cytoplasmic granules. Toluidine blue, scale bar 20 = µm

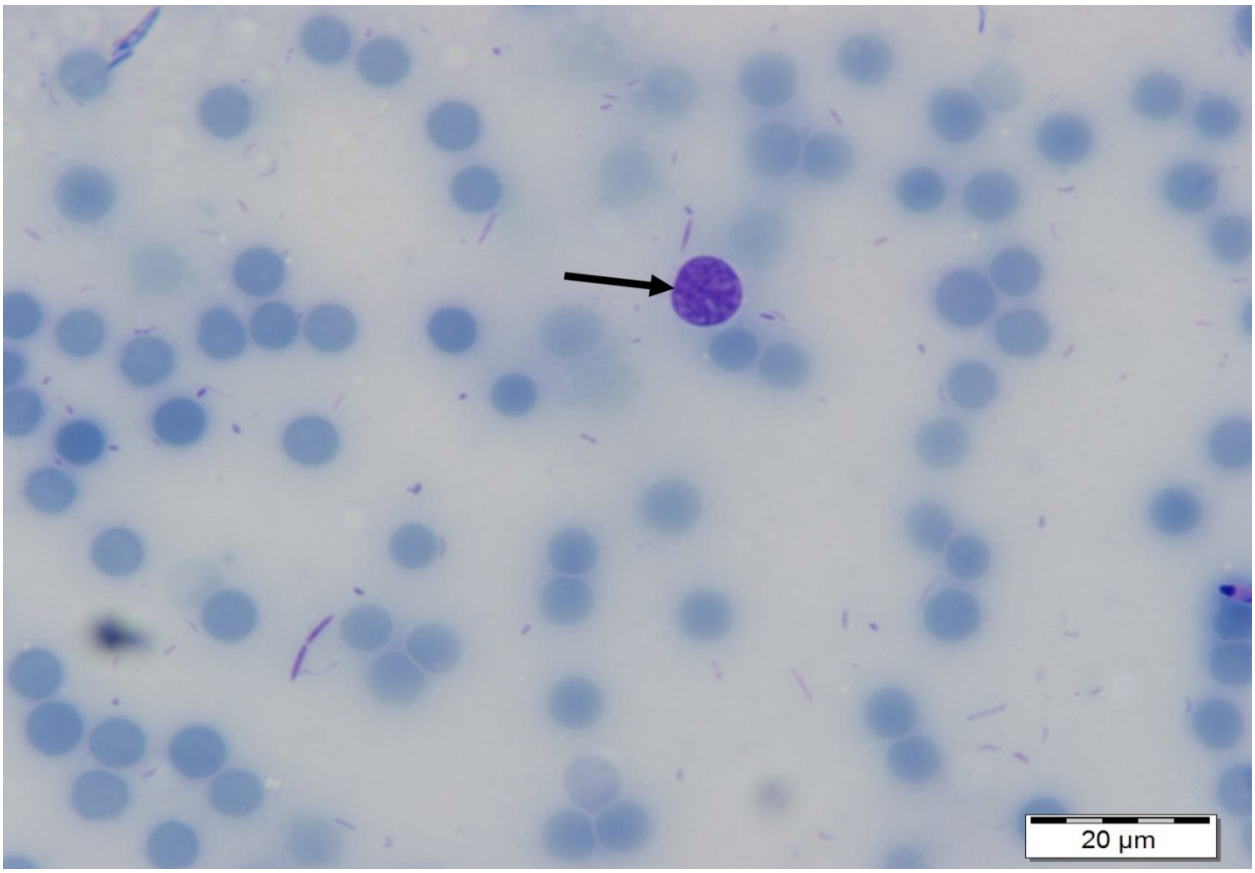

Fig. 3: Mast cell (arrow) in mesentery of rat. Toluidine blue, scale bar 20 = µm

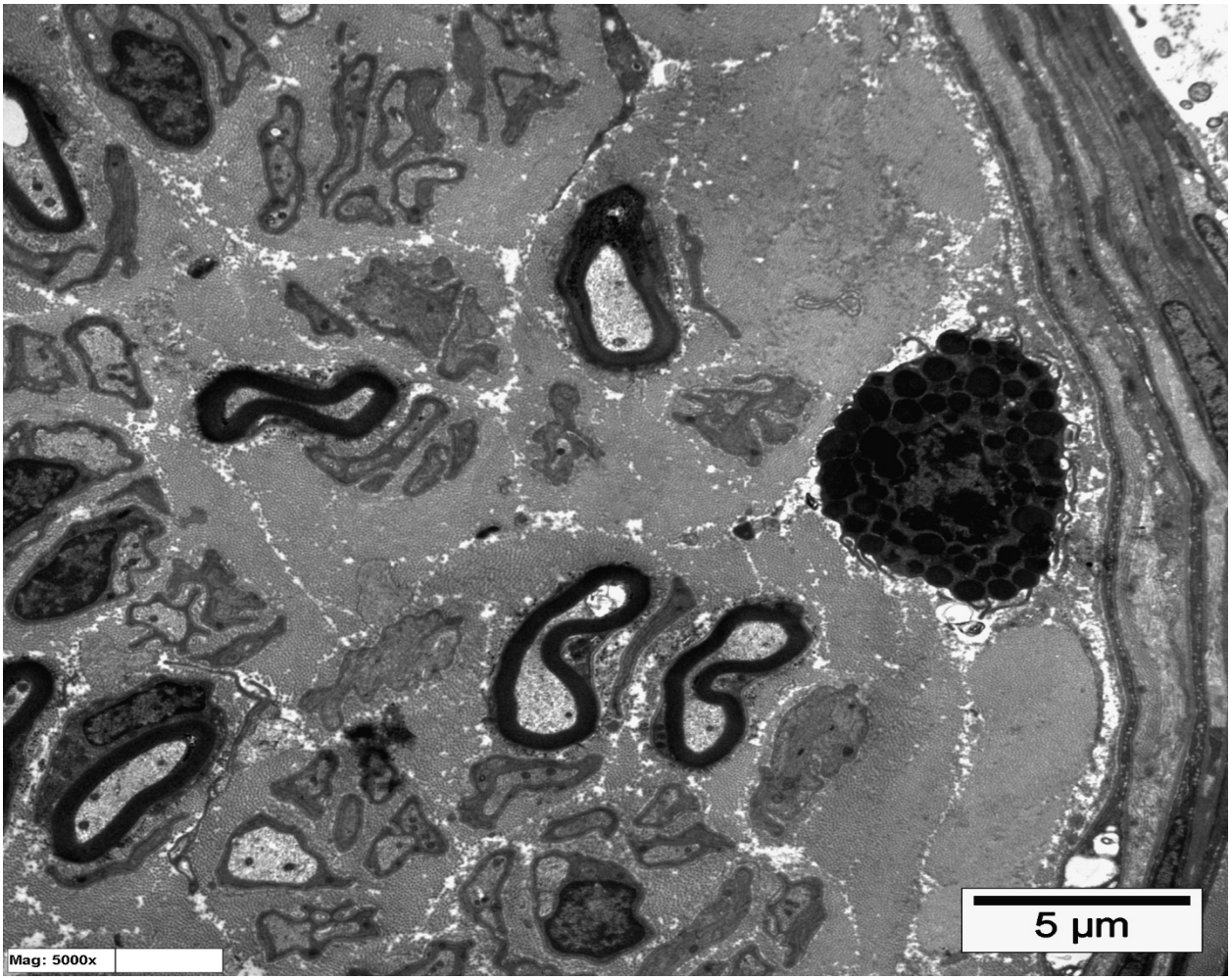

Fig. 4: Electron micrograph of a human mast cell. The granules are quite variable in size. Scale bar 5 = µm.

In electron micrographs, mast cell has a small ovoid or rounded centrally placed nucleus, with unremarkable cytoplasm because it contains a moderate amount of free ribosomes, sparse number of rough endoplasmic reticulum (RER), several mitochondria and relatively well-developed small Golgi complex.

Fawcett (1993) reported that there were considerable interspecies variations in the structure of the granules. In the rat they were homogeneous and electron dense. In the human the granules were quite variable in size and more irregular in outline than those of rodents. Some contained short cylindrical scroll-like inclusion within a finely granular matrix (Figs. 4 and 5). In cross section, Fawcett (1993) found that these inclusions were made up of concentric lamellae which had the dimension of lipid bilayers. In other cells, the granules had a dense matrix surrounding a pale central region, which was occupied by a lattice of parallel linear densities. No one in the available literature could explain the significance of these great variations in the structure of the mast cells granules.

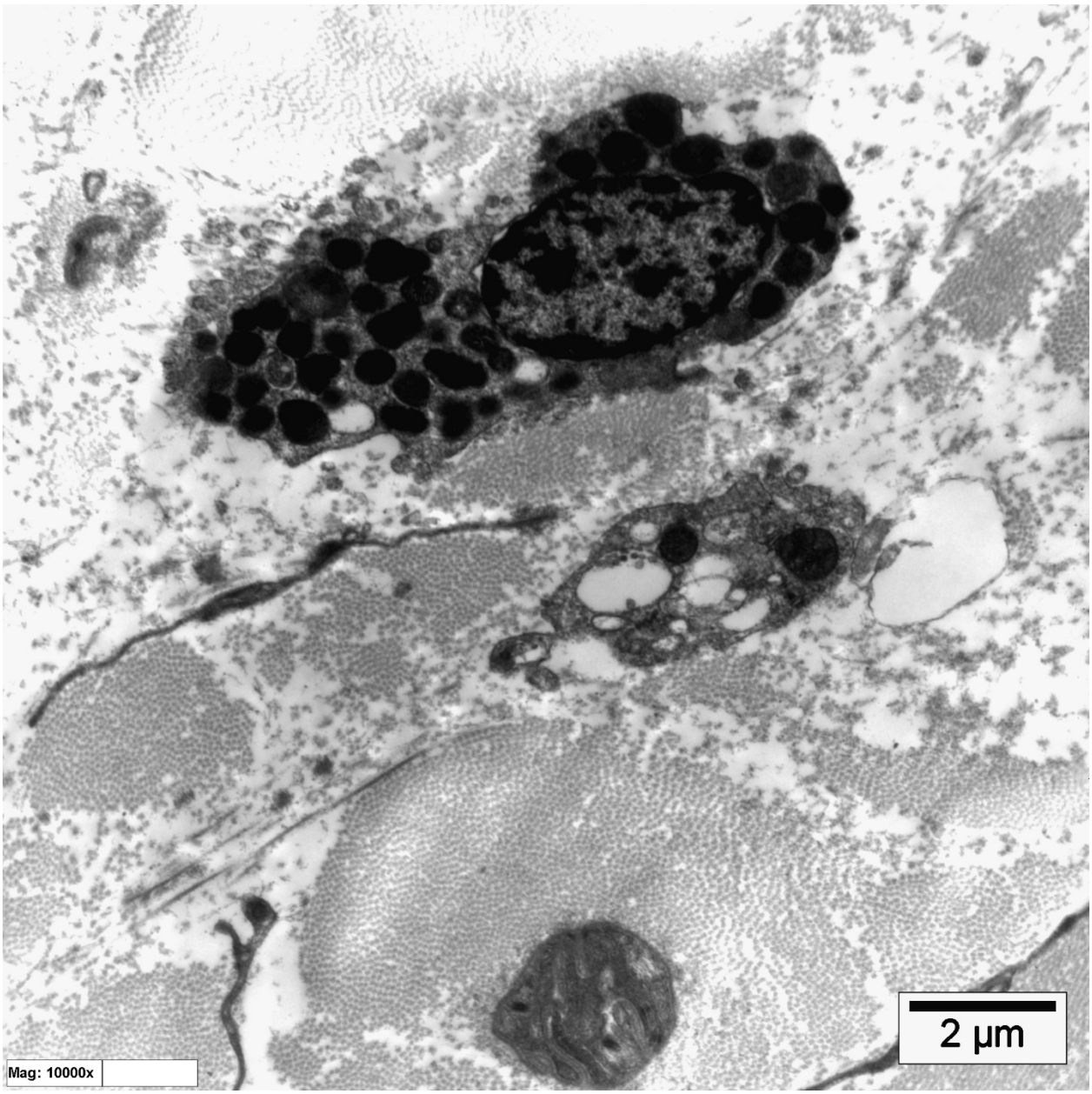

Fig. 5: Electron micrograph of a human mast cell. The granules are quite variable in size. Some contain short cylindrical scroll-like inclusion within a finely granular matrix. Scale bar = 2 µm

5. Mast cells activation and degranulation

The stimulus most commonly evoking degranulation is the presence of any foreign substance (antigen) to which the individual has been sensitized by an immune response to a previous exposure to the same antigen.

Degranulation of mast cells can be induced for experimental purposes by a number of nonspecific agents including polymyxin-B polyrin compound 48/80 and certain snake venoms (Dvorak et al.,

1985; Faurschou and Borregaard, 2003; Veugelers et al., 2004).

Mast cells possess cell-surface Fc receptors for immunoglobulin E (IgE). They function in the immune system by initiating an inflammatory response known as the immediate hypersensitivity reaction (anaphylactic reaction). This response commonly is induced by foreign proteins (antigens) such as bee venom, pollen, and certain drugs.

The first exposure to any of these antigens elicits formation of (IgE) antibodies, which bind to the Fc receptors of the plasmalemma of mast cells thereby sensitizing these cells. Upon re-exposure to the same antigen, the antigen binds to the (IgE) on the mast cell surface causing cross-linking of the bound (IgE) antibodies and clustering of the receptors. Cross-linking and clustering activate membrane-bound receptor coupling factors, which in turn initiate at least two independent processes, the release of primary and secondary mediators (Abbas et al., 1994).

The release of primary mediators is affected by activation of adenylate cyclase, the enzyme responsible for the conversion of adenosine triphosphate into cAMP. This increase in cAMP activates release of Ca^{2+} from intracellular storage sites. The resulting increase in cytosolic Ca^{2+} causes the secretory granules to fuse with each other as well as with the cell membrane. These processes lead to degranulation, and the release of the granules contents, namely histamine, heparin proteases, aryl sulfatase, eosinophil chemotactic factor, and neutrophil chemotactic factor. These constitute primary mediators (Barnes, 1992).

Cross-linking of the membrane-bound (IgE) also activates phospholipase A_2, which acts on membrane phospholipids to form arachidonic acid. Arachidonic acid is converted into secondary mediator's leukotrienes C_4 and D_4 and prostaglandin D_2. It is important to remember that these secondary mediators are not stored in the mast cell granules but are manufactured and immediately released (Table 1).

Table 1: Type, source, and action of mediators released by mast cells

Substance	Source	Type	Action
1. Histamine	Granules	Primary	Increases vascular permeability vasodilatation, smooth muscle contraction of bronchi, increase mucus production.
2. Heparin	Granules	Primary	Anticoagulant
3. Aryl sulphatase	Granules	Primary	Inactivates leukotriene C, thus limiting the inflammatory response
4. Chondroitin sulphate	Granules	Primary	Function not understood
5. Neutral sulphate	Granules	Primary	Protein cleavage to activate complement, increasing inflammatory response.
6. Eosinophil chemotactic factor	Granule	Primary	Attracts eosinophils to site of inflammation
7. Neutrophil chemotactic factor	Granule	Primary	Attracts neutrophils to site of inflammation.
8. Leukotrienes C_4 and D_4	Membrane Lipid	Secondary	Vasodilator increases vascular permeability, bronchial smooth muscle contract.
9. Prostaglandin D_2	Membrane Lipid	Secondary	Causes contraction of bronchial smooth muscle, increases mucus secretion.

The primary and secondary mediators released by mast cells during immediate hypersensitivity reaction initiate the inflammatory response, activate the body defense system by attracting leukocytes to the site of inflammation, and modulate the degree of inflammation. The response is usually local and relatively mild by the immune system but in allergic individuals it may overreact resulting in tissue damage and symptoms ranging from mild discomfort to very serious anaphylaxis.

The contents of mast cell granules are released by an unusual process that has been termed compound exocytosis. Instead of each granule fusing separately with the plasmalemma, a series of granules may fuse with one another and with one opening onto the surface thus creating a membrane limited channel (tube) that extends deep into the cytoplasm. The cells are able to survive this massive degranulation and recover to form new granules (Bowen and Bowen, 1990).

Within seconds after the stimulus to degranulate, histamine is released resulting in vascular leakage, which causes local swelling in many places mainly skin and larynx. Also it leads to drop in the blood pressure, and constriction of the bronchi and other smooth muscle. At the same time the mast cells put the phospholipids in its membranes to work, producing three sets of mediators: leukotrienes, prostaglandins and platelets activating factor (PAF). Prostaglandin D_2 and leukotriene C_4 are powerful bronchoconstrictors and the latter makes the spasm worse by stimulating the secretion of mucus. Thus the victim has plenty of reasons for suffering from air hunger, although the greatest threat of suffocation (in anaphylaxis) comes from edema of the larynx.

5. Discussion and clinical correlations

The details of degranulation vary, but the overall results are that the membranes surrounding the granules fuse to form tubes and the contents of the granules extruded (Lopez et al., 1989). In rats the whole processes takes about two minutes, but in humans it spreads over 15-40 minutes (Heckbert et al., 1990).

How long it takes for an individual mast cell to replace its granules is not clear. Hall et al. (1979) and Yamasaki and Saito (2005) found that all the mast cells in the peritoneum of a rat can be destroyed (not just degranulated) by an interperitoneal injection of distilled water. This procedure appears drastic but surprisingly well tolerated by the other peritoneal cells. A new set of mast cells reappears over six weeks from the injection, most probably supplied by bone marrow precursors.

For an anaphylactic response to occur, whether it is local (as in hay fever) or generalized as in anaphylactic shock, the antigenic material must have the property of inducing antibodies of the IgE class from plasma cells. In most mammals, IgE antibodies bind to the surfaces of mast cells. To understand this procedure we liken the shape of immunoglobulin molecules to lobesters, an IgE molecule binds to the surface of mast cell at Fc receptor zone by its tail and the claws float freely ready to bind antigen. This type of binding is called cytophilic (cell-friendly). When the specific antigen to these antibodies comes along and binds to their outstretched claws, it triggers degranulation of mast cell, to do so; it must be at least divalent so that it can bind two adjacent molecules of IgE together.

What mast cells do for a living is not entirely clear. Although investigative attentions had been focused mainly on the immunological role of mast cells, they may have other functions. In addition to heparin, histamine, and neutral proteases, their granules contain B-glucuronidase, hexosaminidase and aryl sulfatase. These enzymes would seem to have no role in the immune responses, but it is possible that they may degrade some of the glycosaminglycans of the extracellular matrix. Therefore, it has been suggested that, under normal conditions, mast cells may have low level of secretory activity that contributes to the continual turnover of the ground substance of connective tissue.

6. When do mast cells become trouble makers?

Among the several classes of immunoglobulin secreted by plasma cells, IgE is unique in not entering the circulation. Molecules of IgE, of varying antigenic specificity, bind to Fc receptors on mast cells. These cells are then primed to respond immediately when any of these antigens renter the body. The response is usually local and relatively mild, but the immune system of allergic individuals may overreact to a second exposure to one of these antigens, resulting in tissue damage and symptoms ranging from mild discomfort to serious anaphylaxis.

Allergic individuals tend to produce antibodies of the IgE class against pollens, dust and a host of other allergens. Upon re-exposure, these antigens bind to, and cross-link IgE molecules on the surface of mast cells triggering their degranulation and liberation of histamine, leukotrienes, and prostaglandins, which are responsible for the patient's unpleasant symptoms.

Victims of hay fever attacks suffer from effects of histamine being released by the mast cells of the nasal mucosa, causing localized edema from increased permeability of the small blood vessels. The swelling of the nasal mucosa results in feeling “stuffed up" and hinders breathings.

Victims of asthma attacks suffer from difficulty in breathing as a result of bronchospasm caused mainly by leukotrienes and to a less extent by histamine.

In essence mast cells are great, but their functions are still rather mysterious. Perhaps they should be seen as triggers for acute inflammatory response, a function for which they are perfectly equipped.

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