Ultrastructural Evidence for the Common Origin of Human Mast Cells and Basophils

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Although the functional similarity of basophils and mast cells is widely accepted, their distinctive morphological features have been taken to indicate the existence of two different, albeit functionally complementary, cell systems. The recent demonstration that mast cells as well as basophils originate from the bone marrow raises the possibility that these cells derive from the same precursor. This report provides evidence for this theory by describing a distinctive "intermediate" cell possessing the ultrastructural features typical of both basophils and mast cells. These cells were encountered in three patients with myeloproliferative diseases and may thus be more readily found in states of disturbed myelopoiesis. These observations have given impetus for the first comparative description of the ultrastructure of human basophils, human mast cells, and the newly recognized intermediate cell within a single report.

There are compelling data in support of the concept that mast cells as well as basophils derive from the bone marrow. Though the functional similarity of the two cells has also been recognized widely, it is not certain that they actually originate from the same committed precursor. Both mast cells and basophils possess large metachromatic granules that contain, among other substances, potent vasoactive amines, e.g., histamine and a sulfated mucopolysaccharide likely to be heparin. Both cells bind IgE by means of specific receptors, which, when crosslinked by anti-IgE or a variety of other ligands, cause the cells to degranulate and participate in the immediate hypersensitivity reaction. In most animals, there appears to exist a reciprocal relationship between the level of circulating basophils and the number of mast cells in the tissues. However, except for some differences in enzyme content, such as the presence of peroxidase in basophils and of a proteolytic enzyme in mast cells, it would be difficult to tell the cells apart on morphological grounds in most species examined. In contrast, in healthy man, the appearance of the two cells is highly distinctive. Circulating basophils have a segmented end-stage nucleus with a chromatin pattern like that of other granulocytes, whereas the nuclei of mast cells are round or oval and resemble those of the connective tissue cells among which they reside. Human basophil granules are more water soluble than mast cell granules and required the introduction of aldehyde fixatives and epoxy embedding media for their ultrastructural description. Basophil granules have a particulate appearance, whereas the content of mast cell granules may be amorphous or display crystals, "lamellae," "scrolls," or "whorls." What may represent the definitive ultrastructural analysis of human pulmonary mast cells illustrating all the forms such organelles may assume has been published recently. Despite the disparity in morphology and enzyme content, it seems possible that even in man, basophils and mast cells have the same cellular origin. Such a possibility is not remote if one recalls the diverse morphological and biochemical properties acquired by monocytes when they diapedese into tissues and transform into various cells making up the reticuloendothelial system. Support for the possibility that human basophils and mast cells arise from the same precursor would be provided by the finding of transitional cells, e.g., cells with overlapping morphology under some circumstances. This article presents our observation that in patients with myeloproliferative diseases such transitional cells exist.

MATERIALS AND METHODS
The buffy coat cells of the peripheral blood and bone marrow of two patients with untreated chronic myelogenous leukemia (CML) and one patient with agnogenic myeloid metaplasia collected for unrelated reasons were fixed in 3% phosphate-buffered glutaraldehyde, postfixed in osmium tetroxide, and embedded in Epon 812 as is routine in this laboratory. All three patients had an increase in blood basophils ranging from 3% to 10% of the white blood cell count. On routine smears, these basophils did not appear remarkable. Thin sections cut with an LKB ultrotome were contrasted with uranyl acetate and lead citrate. They were viewed with a Siemens Elmiskop I electron microscope.

RESULTS
A typical blood basophil is shown in Fig. 1A. A detailed description of its ultrastructure has been published before and will not be repeated here. However, particular attention is drawn to the relative uniformity of the granules. Each granule is filled with particles that measure ± 200Å in diameter, appear uniform in size within the same granule (Fig. 1B), but may vary in size in different granules within the same
Fig. 1. (A) Ultrastructure of a mature basophil obtained from the blood of a patient with CML is indistinguishable from its normal counterpart. Note segmentation of the nucleus and abundance of electron-opaque heterochromatin (H) distributed peripherally as in other mature granulocytes. The granules within the demarcated rectangle are seen at higher resolution in Fig. 1B. The granule indicated by the arrow is seen at higher resolution in Fig. 1C (× 18,000). (B) Two typical basophil granules (see text) at high magnification. The unit membrane enclosing the particles is clearly resolved. (N, nucleus; × 72,000.) (C) Granule indicated by the arrow in Fig. 1A shown at higher resolution. Note that the content of this granule is also particulate, but that the particles are much smaller than those in the majority of granules in mature basophils. Granules containing fine particles are more abundant in immature basophils (see arrows in Fig. 1D). (× 102,000.) (D) Basophil myelocyte. The nucleus is not yet segmented. The chromatin distribution is typical for the granulocyte series. There is a mixture of granules, some containing fine (arrows), others coarse particles. In the Golgi region (G), granule formation is still evident (× 10,000).
Fig. 2. (A) The ultrastructure of this typical mast cell should be compared with that of the basophil illustrated in Fig. 1A. Except for a small indentation, the nucleus is oval and exhibits a dispersed chromatin pattern. The heterogeneity in granule structure is apparent even at low magnification. The arrow indicates a granule shown at high resolution in Fig. 2B (× 14,000). (B) Example of a typical mast cell granule showing "scrolls" consisting of several coils of a crystalline or fibrillar structure, as well as parallel lines, which probably represent the scrolls cut along their long axis (× 150,000). (C) A large mast cell granule showing several crystal patterns. The right half consists of parallel lines separated by 150-Å spaces, the left half exhibits a herringbone lattice, while at the bottom the beginning of a scroll pattern is seen (arrow) (× 96,000). (D) Illustration of 3 adjacent mast cell granules in the same mast cell. While granule 1 appears to have a homogeneous content, granule 2 shows condensation in the center; granule 3 exhibits even greater overall density, beginning scroll formation at the top (arrow) and 2 scrolls with 5–7 concentric coils at the bottom (× 78,000).
Fig. 3. (A) Intermediate cell from the marrow of a patient with CML. The chromatin pattern of the nucleus is characteristic of a mature basophil, but the majority of the granules resemble those of mast cells (x 14,000). The demarcated area is seen at higher magnification in Fig. 3B. (B) Higher resolution of the area demarcated by the rectangle in Fig. 3A. Granules 1, 2, and 3 show typical mast cell scrolls, while granule 1 also contains particles typical of basophil granules. Granule 4 exhibits vermiform condensations within an amorphous background material. This kind of condensation is not usually seen in normal basophils or mast cells (x 55,000).

Fig. 4. Example of an abnormal basophil from the blood of a patient with CML. The nucleus suggests a metamyelocyte stage of development, but still has a prominent nucleolus (Nu). Many granules contain fine particles such as those normally seen in less mature cells (Fig. 1C). There are also numerous granules with an abnormal substructure. The one indicated by the arrow (x 13,500) is illustrated at higher resolution in the inset (x 46,000).

cell. For instance, the arrow in Fig. 1A indicates a granule containing smaller particles shown at higher magnification in Fig. 1C. The majority of granules in basophil promyelocytes and myelocytes have this appearance (Fig. 1D). In mature basophil granules, the peripheral row(s) of particles seem to be arranged concentrically with the granule membrane (Fig. 1B). Although the cell illustrated in Fig. 1A is derived from a patient with CML, it is indistinguishable from basophils in the blood of healthy subjects.
Fig. 5. (A and B) Details of cells from the marrow of patients with CML chosen to illustrate that the cells cannot be classified as either basophils or mast cells on the basis of their granules. In normal human blood, the granules labeled 1 are characteristic of basophils, whereas the granules labeled 2 are more characteristic of tissue mast cells. In pathologic conditions, this distinction may be lost, and there may be complete morphological overlap. Also note the unusually large "scroll," which may be located in the same granule as the particles in granule 1 of Fig. 5A (arrow) (x 102,000).

Since mast cells are difficult to find in normal bone marrow, especially when searched for with the electron microscope, the mast cell illustrated in Fig. 2 was obtained from a rectal biopsy specimen. The distinctive features of its nucleus and granules should be contrasted with those of the basophil (Fig. 1A–D). The nucleus is not segmented and displays a dispersed chromatin pattern, while the granules are either homogeneous or exhibit every variation of crystalline array described exhaustively in the literature. To date, such cells have never been seen by us in the circulating blood of healthy subjects. (More than 1000 normal buffy coat specimens have been processed in this laboratory.) On the other hand, in the bone marrow of
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the three patients studied here and in the peripheral blood of one of the patients with CML, the cells were seen to possess a mixture of granules that were characteristic of basophils as well as mast cells (Figs. 3–5). Typical basophil granules with a particulate content as well as the typical mast cell granule exhibiting "whorls" were seen side by side within the same cells (Figs. 3B, 5A and B). In addition to these "transitional" cells, the marrow contained fully developed basophils and mast cells that posed no difficulty in classification. Quantitation of the number of each cell variant present in these specimens was not attempted.

DISCUSSION

The origin of human basophils from precursors located in the bone marrow is beyond dispute. Basophil promyelocytes and myelocytes are morphologically identifiable, and although it is by no means clear at what stage of development histamine or heparin are synthesized, it is generally assumed that granule differentiation parallels the process taking place in other granulocytes. Since few, if any, mast cells are found in normal marrow, it is likely that mast cell precursors leave the medullary cavity in the guise of indistinguishable committed stem cells, much like other granulocyte precursors, which can be isolated with mononuclear cell fractions and shown to differentiate into neutrophil/macrophage and eosinophil colonies when cultured in soft agar. The development of mast cell colonies from peripheral blood "lymphocyte" fractions prepared from rats has been observed in this laboratory. It is not difficult to conceive that the microenvironment prevailing in connective tissue differs from the local influences in the bone marrow and that such factors determine the development of properties that distinguish mast cells from basophils. The present studies do not address the question whether mature basophils can transform into mast cells or vice versa. It is known, however, that the cells that infiltrate tissues during acute reactions, e.g., contact hypersensitivity caused by allergens such as poison ivy, represent bona fide basophils. Whether in pathologic states mast cells return from peripheral tissues to the medullary cavity, or whether the cells develop in situ is not known, nor is it particularly relevant to the issue under consideration. The significance of the observation that, under some circumstances, there exist intermediate cells that cannot be classified as either basophils or mast cells suggests that the cells are not inherently different and that their divergent properties may be induced by environmental stimuli. In myeloproliferative diseases, particularly when there is myeloid metaplasia or aplasia, the connective tissue elements in the marrow are also increased, perhaps locally raising the mast cell stimulating factor(s) to a level not normally present in the marrow. In any case, the increase in the number of mast cells in hypoplastic or regenerative marrows is generally recognized and substantiated by published data. In most of these diseases, there is disorderly maturation and release of cells from the medullary environment. This may also provide the opportunity for a responsive target cell to come under the influence of a multiplicity of factors that may eventuate in the development of the intermediate basophil/mast cell illustrated in this report.

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REFERENCES

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