Mast cells are a heterogeneous group of tissue-dwelling cells with roles in conditions as diverse as allergy, parasite infestation, inflammation, angiogenesis, and tissue remodeling. The cells were named Mastzellen in 1876 by Paul Ehrlich because they looked stuffed (German „gemästet“, „Mast“) and he believed that the intracellular granules, which appeared purple in color when stained with aniline blue dyes, contained phagocytosed materials or nutrients [1]. This change in color, or metachromasia, we now know to represent the interaction of the dyes with the highly acidic heparin contained within mast cell granules.

The life of the human mast cells begins in the bone marrow as a pluripotent stem cell which enters the bloodstream early on in its development (Fig. 30.1). Studies of culturing mast cells from cord blood suggest that the precursors are a CD34+/CD38+/HLA-DR– population of cells [2]. In vivo in mastocytosis, immature mast cells have been recognized as mononuclear cells that both express mRNA for SCF and have SCF receptors (SCFR, CD 117) on their cell membranes [3]. From the blood the precursors migrate into the tissues where, under the influence of local microenvironmental factors, they undergo their final phases of differentiation and maturation into recognizable mast cells complete with cytoplasmic granules and receptors for IgE. Again, studies of culturing mast cells from cord blood suggest that stem cell factor (SCF) and IL-6 are important for mast cell maturation [2, 4]. It is pertinent at this stage to distinguish mast cells from basophils, which were originally thought to be circulating mast cells, but are actually related more closely to eosinophils, developing in the bone marrow from granulocyte precursors and entering the circulation only when fully mature [5].

Mast cells are distinguished immunocytochemically by their neutral protease content, the MC₇ phenotype containing only tryptase and the MC₅C phenotype containing both tryptase and chymase [6]. Initially, these respective subtypes were suggested to be the equivalents of the „mucosal“ and „connective tissue“ previously described in experimental animals. However, it is now realized that variable amounts of both mast cell subtypes are present within any given tissue, their relative abundance changing with disease. For example, in allergy MC₇, which appear to be „immune system-related“ mast cells with a primarily role in host defense, increase in numbers at mucosal surfaces and allergic foci. Conversely, increased numbers of MC₅C, which appear to be „nonimmune system-related“ mast cells with functions in angiogenesis and tissue remodeling rather than immunological protection, are associated with fibrosis. However, it should be remembered that both phenotypes express FcεRI and may, therefore, participate fully in IgE-dependent allergic reactions.
Mast cells are relatively abundant in human skin, being found in the greatest density in the papillary dermis and the superficial dermal zone immediately below the dermal-epidermal junction [7]. They are concentrated particularly around dermal nerve endings and blood vessels [8, 9] and are, therefore, ideally situated to influence the function of both. Normal skin contains around 7,000 mast cells per mm³ [10, 11] which equates to a histamine content of 12 – 20 ng/mg tissue [12, 13].

Skin mast cell numbers increase dramatically in several diseases. For example, the histamine content of the skin in Behçet’s disease is reported to be twice that of normal skin [13] while mast cell numbers are 10-fold higher in urticarial lesional skin [14] and are even higher in urticaria pigmentosa [15]. In a study using antibodies to tryptase and chymase, the number of mast cells in the superficial dermis of mastocytosis lesions was 40,985 ± 21,772 /mm³ (mean ± SD) compared with 7347 ± 2973 /mm³ in normal skin. Furthermore, the cells in skin lesions of mastocytosis were exclusively MC²-Tc [10]. Mast cell hyperplasia is also associated with skin tumors such as basal cell carcinoma [16] and melanoma [17, 18].

Although histamine has been found in significant amounts in the epidermis [19, 20], mast cells are rarely observed in this layer in normal skin. Whether this indicates histamine synthesis by keratinocytes, as indicated by murine studies [21], or the ability of keratinocytes to take up histamine is not clear.

### 30.1 Mast Cell Activation

Mast cells may be activated by both immunological and nonimmunological mechanisms (Fig. 30.2). To facilitate immunological activation, human mast cells have $10^4$ to $10^5$ high affinity (Ka ~ $10^5$/M) receptors (FcεRI) for immunoglobulin E (IgE) on the plasma-membrane [22, 23]. Mast cell FcεRI is composed of four subunits, an IgE-binding α-chain, a β-chain, and two γ-chains [24]. The presence of the signal-amplifying β-chain [25] in the heterotrimeric αβγγ mast cell and basophil receptor complex distinguishes it from the αγγ heterotrimeric receptor of dendritic cells and monocytes [23]. Cross linkage of these receptors by multivalent allergen stimulates phosphorylation of immunoreceptor tyrosine activation motifs (ITAMs) [23] and initiation of the biochemical cascade which leads to the release of both preformed and newly generated mediators.

Nonimmunological activation, which appears to be unique among human mast cells, may be initiated in two ways, by complement fractions and by basic secretagogues. Human skin mast cells alone express on the plasma membrane CD88, the receptor for the anaphylatoxin C5a, allowing them to be activated in complement-mediated disease [26, 27]. Also, skin mast cells alone respond to a variety of basic nonimmunological secretagogues, including neuropeptides, compound 48/80, and drugs such as morphine, codeine, and muscle relaxants [28, 29]. These agents stimulate a common activation site on the mast cell membrane which is associated with a pertussis toxin-sensitive G protein [30, 31]. The ability of human skin mast cells, but not those from other tissues, to respond to anaphylatoxins and basic nonimmunological secretagogues explains the flushing reactions observed in sensitive individuals in the absence of overt rhinorrhea or bronchoconstriction. Such responses may also be involved in physical urticarias.

In vitro studies of human isolated skin mast cells have shown distinct differences between immunological and nonimmunological mast cell activation. IgE-dependent activation is relatively slow, taking around 5–6 min to reach completion, and requires the presence of extracellular calcium. It is a “complete” stimulus in that it causes release of preformed mediators and initiates the synthesis of the eicosanoids prostaglandin D₂ and leukotriene C₄. In contrast, stimulation of mast cells with basic secretagogues and C5a causes a much more rapid release of histamine, being complete within 30 sec. This release mechanism in which G protein activation leads to subsequent activation of phospholipase C to increase in intracellular inositol triphosphate levels, proceeds in the absence of extracellular calcium,