Recent Advances in Mast Cell Biology

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Mast cells (MCs) are not simple trouble makers in immediate allergic hypersensitivity, but play various important biological roles in host defense as well as tissue remodeling after inflammation such as wound healing and fibrosis. Since heterogeneity exists in human MCs, human skin type MCs should be used for dermatological research. A large number of pure human skin type MCs which satisfy all characteristics of cutaneous MCs have been established from human dispersed skin in the absence of serum under the stimulation of stem cell factor. However, biological roles of human MCs should be investigated in vivo and human MC development in mice after xenotransplantation of human hematopoietic stem cells is confirmed. Both human cutaneous and mucosal type MCs can develop in immunodeficient NOG mice with identical distribution pattern to human body. This model may provide a potential tool for the in vivo investigation of human MC functions. More recently, we have established embryonic stem cell-derived MCs which may suggest a unique embryonic pathway for early development of cutaneous MCs. Further investigations on MC biology should be encouraged to elucidate the mechanism of human skin diseases leading to the development of new drugs in dermatology. (Dermatol Sinica 27: 79-84, 2009)

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INTRODUCTION

Mast cells (MCs) were first described by Dr. Paul Ehrlich more than a century ago. Morphologically, they have metachromatic granules and both preformed and newly generated mediators such as histamine, leukotrienes and prostaglandins. Of course they express FcεR1 which plays an important role in immediate allergic reactions. More importantly, they have proteinases such as tryptase and chymase. Tryptase is a most specific biological marker of human MCs which also plays important biological roles.

MCs are not simple trouble makers in immediate hypersensitivity or itch; however they play various biological roles in host defense and tissue remodeling.1 In this article, recent advances in MC biology are briefly reviewed and some new data from our lab will be presented.

HETEROGENEITY OF HUMAN MCs

Human MCs are originated from hematopoietic stem cells and circulate as immature MCs differentiating into either skin type MCs or mucosal type MCs depending on...
The microenvironments. Skin type MCs have both tryptase and chymase, and thus called MC_{TC} which can be stimulated not only by IgE but also by substance P and compound 48/80. In contrast, mucosal type MCs (MC_{T}) have only tryptase and are stimulated only by IgE (Fig. 1). In skin, over 99% of MCs are MC_{TC}, but in pulmonary alveoli and small intestinal mucosa, most of MCs are MC_{T}.

Most typical example of this heterogeneity can be observed in mastocytosis. In patients with cutaneous mastocytosis (urticaria pigmentosa), remarkably increased number of MCs are found in the lesional skin and most of them are tryptase/chymase double positive MC_{TC}. In patients with systemic mastocytosis, proliferating MCs are chymase negative MC_{T}, though the number of MCs is much smaller than cutaneous mastocytosis. These findings indicate that systemic and cutaneous mastocytosis are different in nature. In cutaneous mastocytosis, transient overproduction of stem cell factor (SCF) results in the local proliferation of MC_{TC} as well as local pigmentation since melanocytes also express SCF receptor (KIT) responding to the stimulation of SCF. This is why spontaneous regression occurs if the local overproduction of SCF is ceased with unknown reasons. In systemic mastocytosis, mutation of KIT is frequently observed leading to the spontaneous proliferation of MC_{T} in various organs resulting in systemic manifestations. One may infer that systemic mastocytosis is induced by “gain of function of kit” and localized albinism (piebaldism) is induced by “loss of function of kit”.

**BIOLOGICAL FUNCTIONS OF HUMAN CUTANEOUS MCs**

Since MCs are distributed regularly around the vessels and at portals of bacterial entry, it is speculated that MCs might work against invaders from outside of the skin for host defense. Also, MCs are increased in number in various skin diseases that show fibrosis such as keloid and scleroderma, which may indicate that MCs play some role in tissue remodeling.

1. **Possible roles of MCs in host defense and post infection urticaria**

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*Fig. 1 Heterogeneity of human mast cells (MCs) in different organs.*

Human MCs are originated from hematopoietic stem cells and circulate as immature MCs differentiating into either skin type MCs or mucosal type MCs depending on the microenvironments. SCF, stem cell factor.
Important roles of MCs in host defense have been confirmed using MC deficient mice. Echtenacher et al. reported in 1996 that survival rate in MC deficient mice is significantly lower than wild type mice if the experimental acute septic peritonitis was induced, which could be recovered by reconstitution of cultured MCS, suggesting the protective role of MCs and MC-derived TNF in acute bacterial infection. This biological role of MCS may explain a part of the pathogenesis of post infection urticaria. IFN-γ induces Toll-like receptor (TLR) expressions on mast cells, and lipopolysaccharide or other products induced by infection activate MC via TLRs leading to the production of TNF (unpublished data). Infections are considered to be major causative mechanisms of urticaria, which can partly be explained through TLR-mediated MC activation.

### 2. Possible roles of MCs in tissue remodeling

Significant increases of MCs in number at the local sites have been described in various human diseases such as asthma, allergic rhinitis, atopic dermatitis (lichenification sites), rheumatoid arthritis, scleroderma and keloid (Fig. 2). How do these MCs contribute to fibrosis? In order to answer this question, we have co-incubated cultured human MCs and human fibroblasts and evaluated the fibroblast proliferation. When fibroblasts are co-cultured with IgE-activated MCs, significant increases both in fibroblast proliferation and collagen production were observed. We have also found that tryptase is an important MC-derived mediator for fibrosis. Fig. 3 shows that tryptase-induced proliferation of fibroblasts can partly be inhibited by the addition of anti-tryptase antibody, indicating that tryptase plays a critical role in fibrosis and that developing the drugs that regulate the tryptase activity might be promising in future. Moreover, MCs generate not only mediators but cytokines and growth factors such as TGF-β1 for fibrosis. MCs are also working for degradation process of fibrotic changes, since production of matrix metalloproteinases 9 (MMP-9) from human MCs

![Fig. 2 Mast cell (MCs) hyperplasia in skin diseases.](image)

Significant increases of MCs in number at the local sites have been described in various skin diseases such as atopic dermatitis (lichenification sites) and keloid.
was detected by RT-PCR, gelatin zymography and immunochemistry. Recently, histamine has been reported to induce MMP-9 expression in keratinocytes and promote collagen type IV degradation in the basement membranes, suggesting that MCs may play an important role in tissue remodeling and chronic inflammation.

As shown in Fig. 4, there are mutual interactions between MCs and fibroblasts in fibrotic process. MCs are stimulated for proliferation and differentiation by SCF generated by fibroblasts, however in turn, MCs produce various mediators, growth factors and proteinases that control fibrosis.

**DEVELOPMENT OF HUMAN CULTURED MCs**

Most of the past researches on MCs have been performed using rodent MCs, however, human MCs should be used for MC research, because human MCs are quite different from rodent MCs and biotechnology has made it possible to produce a large amount of recombinant human SCF. We initially obtained cultured human MCs from cord-blood cells in the presence of SCF, however, these MCs were tryptase positive but chymase negative suggesting that this method established the way to get mucosal type MCs. Every effort has been made to switch human MC\(T\) to MC\(TC\) in vitro by adding IL-4 or NGF but in vain. Finally, a large number of pure skin-type MCs can be obtained from dispersed skin in the presence of SCF under serum-free conditions which satisfied all characteristics of MC\(TC\).

**HUMAN MC PROLIFERATION AFTER XENOTRANSPLANTATION INTO NOG MICE**

Although we have established both cultured human MC\(T\) and MC\(TC\) in vitro, biological roles of MCs should be investigated in vivo. However, experiments using...
human tissues are ethically never allowed. This is why we tried to expand human MC proliferation after xenotransplantation of human CD34⁺ hematopoietic stem cells into NOG (NOD/SCID/gamma null) mice with severe immunodeficiency and IL-2 receptor common γ-chain defect mutation. Complete reconstitution of human lymphocytes from cord blood CD34⁺ cells were reported in peripheral blood, bone marrow and spleen of NOG mice. Human MCs were also developed in NOG mice in skin as well as in other organs suggesting that this model may provide a potential tool for the in vivo investigation of human MC functions (Fig. 5). Recently, we established a unique system to induce direct development of functionally mature tryptase/chymase double positive connective tissue-type mast cells from primate embryonic stem cells. The rapid maturation of embryonic stem-derived MCs suggests a unique embryonic pathway for early development of MCTc, which may be independent from the development pathway of MCT.
CONCLUSION

MCS have long been considered to work only for urticaria in dermatology, however, recent advances in MC biology revealed that MCS contribute to various biological functions such as host defense and tissue remodeling. Most of the past researches on MCS were performed using rodent MCS, however, human MCS should be employed since human MCS are quite different from rodent MCS in nature. Although both human cultured MC\textsuperscript{TC} and MC\textsuperscript{T} are available, biological functions of MCS are preferably investigated \textit{in vivo}, and human MCS were developed in NOG mice providing a novel tool for further researches to elucidate the mechanism of human skin diseases and develop the new drugs in dermatology.

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REFERENCES