

## Review Article

# New Aspects in Thrombosis Research: Possible Role of Mast Cells as Profibrinolytic and Antithrombotic Cells

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## Keywords

Thrombophilia, repair, mast cells, heparin, tPA, fibrinolysis

## Summary

Venous thromboembolism represents a significant cause of morbidity worldwide. The factors that underly thrombophilia are manifold. The concept of Virchow defines the well known triad of stasis, humoral factors, and pathologies of the vascular wall. In the current article, an additional factor, the “accumulation of repair cells” is discussed. This novel concept highlights the mast cell that accumulates around thrombosed vessels and provides a number of important repair molecules including heparin, profibrinolytic tPA, and fibrinogenolytic  $\beta$ -tryptase. Thus, mast cell recruitment and activation may result in local thrombolysis and prevention of coagulation. In line with this concept, mast cell-deficient mice are more susceptible to lethal thrombogenic stimuli compared to normal mice. The factors (cytokines) that trigger mast cell accumulation and release of repair molecules have also been identified – the most important one appears to be stem cell factor (SCF). All in all, our novel concept suggests that the patho-physiology of thrombosis may involve a “physiologic” cell that provides the same repair molecules that are used for treatment of thrombotic disorders by the physician. Whether an altered availability of components of this cellular repair system can predispose for thrombophilia remains to be determined.

## Introduction

Thromboembolic disorders represent a significant cause of morbidity and mortality worldwide. The factors that can predispose for venous thrombosis are manifold. The simple concept of Virchow defines the triad of stasis, humoral factors, and pathologies of the vascular wall (1). However, recent data suggest that apart from this triad, also other additional factors may contribute to the thrombophilic state (2). A new exciting hypothesis is that distinct perivascular cells accumulate and

provide repair molecules to thrombosed vessels. A number of cell types residing in extravascular areas such as the tissue macrophage, have been discussed as repair cells in this regard.

Mast cells (MC) are extravascular cells that express a number of vasoactive substances (histamine, others) and repair molecules such as heparin, trypsin-like proteases, and tissue-type plasminogen activator (tPA) (3-6). These mediators are stored in MC and secreted in a constitutive manner or in response to cell activation. Physiologically, MC are located in perivascular areas often in close apposition to capillaries and postcapillary venules (3, 7). Recent data suggest, that MC increase in number and accumulate in areas of venous thrombosis (8-11). In light of expression and release of repair molecules, these observations have raised the possibility that MC contribute to the pathophysiology of venous thrombosis as an important repair cell. In the current article, this novel concept is introduced and discussed.

## Origin and Distribution of Mast Cells

Mast cells (MC) are multifunctional hemopoietic effector cells. In common with all other hemopoietic cells they derive from multipotent hemopoietic progenitors (12-14). However, in contrast to other blood cells, MC undergo differentiation and maturation in extramedullary organs. Thus, MC progenitors are circulating cells that migrate into tissues (15). A well established concept is that homing, migration and differentiation of MC progenitors are regulated by stem cell factor (SCF) also termed mast cell growth factor (MGF) or KIT ligand (14-16). SCF is a stroma cell-derived cytokine primarily expressed in (and released from) fibroblasts and vascular endothelial cells (17-19). MC as well as mast cell growth factor (SCF) can be detected in most organ systems (3, 7, 17). The lungs and the gastrointestinal tract contain remarkably high numbers of MC (3). Usually, MC are located around blood vessels or in loose connective tissues where they can easily be identified by their metachromatic granules (3, 7).

## Functional Role of Mediators Expressed by Mast Cells

Mast cells are a source of multiple mediators including histamine, heparin, cytokines, prostaglandin-D<sub>2</sub>, and proteolytic enzymes such as tryptase and chymase (3-6). Several of these mediators appear to be involved in the regulation of vascular cells. Other mediators apparently play a role in coagulation and thrombolysis. Likewise,  $\beta$ -tryptase, a MC-specific enzyme, is capable of degrading fibrinogen (20). In addition,  $\beta$ -tryptase activates pro-urokinase within the fibrinolytic system (21). Another MC-specific enzyme, chymase, has been described to inactivate thrombin (22). Heparin, which is selectively stored in MC (23)

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Table 1 Pathophysiologic effects of mast cell-derived mediators

mediator	major pathophysiologic effects
tPA	induction of thrombolysis (fibrinolysis)
heparin	antithrombotic effect (ATIII-cofactor activity) promotes thrombolysis (tPA-cofactor activity) promotes fibrinogenolysis (tryptase-cofactor)
tryptase	induction of fibrinogenolysis activation of pro-urokinase (uPA pathway) angiogenesis (mitogen for endothelial cells) fibrosis (mitogen for fibroblasts)
chymase	antithrombotic effect - inactivates thrombin involved in the processing of endothelin acts as an angiotensin converting enzyme
histamine	induces capillary leak and platelet aggregation as well as activation of endothelial cells
prostaglandin D <sub>2</sub>	induces smooth muscle cell contraction inhibits platelet aggregation
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ATIII, anti-thrombin III	

prevents coagulation by acting as a co-factor of anti-thrombin III (AT-III). However, heparin is also a co-factor of  $\beta$ -tryptase (24) and modulates the activity of tissue type plasminogen activator (tPA), a major regulator of fibrinolysis (25). Recent data suggest that MC themselves can express and release tPA (26). All in all, MC express several important molecules involved in the regulation of fibrinolysis and coagulation. Table 1 shows a summary of respective molecules.

### Mast Cells Express tPA, a Major Regulator of Fibrinolysis

The key-enzyme of fibrinolysis, plasmin, is generated from inactive plasminogen through the catalytic action of two major enzymes, tPA and urinary type plasminogen activator (= uPA = urokinase) (27, 28). Both enzymes play a role in endogenous fibrinolysis. Thus, disruption of the *uPA gene* in mice leads to impaired clot lysis and spontaneous deposition of fibrin (29). The additional lack of a functional *tPA gene* promotes the *uPA*-knock-out phenotype. Thus, mice with a combined deficiency suffer from extensive fibrin-deposition and occurrence of vascular thrombosis (29). The emerging concept is that endogenous

tPA and uPA are involved in the degradation of locally generated fibrin. Human tissue MC appear to produce and secrete tPA in a constitutive manner but do not express uPA (26). However, MC express detectable amounts of uPA receptor (CD87) (30). This is of particular interest since this molecule has been implicated in several repair processes including fibrinolysis and chemotaxis. Notably, urokinase is a potent chemoattractant for human MC (30).

### Mast Cells Lack Plasminogen Activator Inhibitors

In most physiologic cells, the fibrinolytic activities of tPA and uPA are under control of plasminogen activator inhibitors (PAI-1, PAI-2, PAI-3) (31, 32). This holds true for endothelial cells, macrophages, smooth muscle cells, and fibroblasts (Table 2). In contrast, however, resting MC produce tPA without producing PAIs (26) (Table 2). As a result, MC exhibit a unique and strong fibrinolytic potential (26). Likewise, the supernatants of cultured MC are capable of lysing a fibrin clot *in vitro* similar to recombinant tPA (26). Correspondingly, the clot-lysing effect of MC (supernatants or lysates) can be neutralized by an anti-tPA antibody or addition of PAI-1 (26). Activation of MC by SCF or other cytokines is associated with increased release of tPA but not with PAI-expression (26). This observation suggests that even when activated by cytokines, MC exhibit profibrinolytic activity. Under certain conditions, however, activated MC may also produce and release PAI-1. In fact, when exposed to PMA, MC can produce PAI-1 (33). A physiologic inducer of PAI-1 expression in human MC remains to be identified, however. All in all, under various (physiologic) conditions, MC express tPA in the absence of PAIs and therefore may play a role in endogenous fibrinolysis.

### Mast Cells Are a Source of Heparin

In contrast to all other cells in the tissues, MC are a source of heparin (23). Likewise, it can be assumed that "standard heparin" isolated from the porcine gastrointestinal tract is almost exclusively derived from MC. Heparin has potent anticoagulant activity through its action as AT-III co-factor. In addition, however, heparin is a co-factor of tPA and of  $\beta$ -tryptase (24, 25). The emerging concept is that MC produce and store all these repair molecules in their granules and can release these compounds most probably in form of a multimolecular complex. In line with this notion, crude MC supernatant (releasate) contains functionally active tPA, whereas purified MC tPA or recombinant tPA are ineffective with regard to plasminogen activation unless heparin or

Table 2 Fibrinolytic activity and tPA expression in mast cells – comparison with other cell types and role of inhibitory PAI-1

Cell type	expression of		
	fibrinolytic activity	tPA	PAI-1
Mast cells	+	+	-
HMC-1	+	+	-
HUVEC	-	+	+
SMC	-	+	+
Fibroblasts	-	+	+
WBC	-	+	+
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HMC-1 is a human mast cell line derived from a patient with mast cell leukemia; HUVEC, human cultured umbilical vein endothelial cells; SMC, human smooth muscle cells (from coronary arteries); WBC, white blood cells			

fibrin is added to the reaction (26). The concept would imply, that MC-tPA is released into tissues together with heparin (probably in a complex) and thus as an enzyme that directly catalyzes the generation of plasmin even in the absence of fibrin, a major regulator of tPA activity.

### Mast Cells Increase in Venous Thrombosis

A number of previous and more recent studies have shown that MC increase in number in venous thrombosis (6, 8-11, 34, 35). In deep vein thrombosis, MC accumulate around thrombosed vessels often in close vicinity to the vasa vasorum (8). This is an interesting aspect – in fact the vasa vasorum represent most important nutritive vessels and have to stay open during and after thrombosis. In auricular thrombosis, MC redistribute to and accumulate in the upper endocardium (9-11). MC also increase in number and accumulate in prostate vein thrombosis, liver vein thrombosis, or pulmonary embolism (6). In all models, MC express tPA, but do not express PAIs (8-11). These observations raise the possibility that MC act as repair cells in thrombotic processes and thus are involved in the pathophysiology of thrombosis. This novel concept has also been supported by an *in vivo* model. In fact, it has been shown that MC-deficient W/W<sup>v</sup> mice have a significantly increased incidence to develop fatal thromboembolic events after India ink injection compared to normal mice (36). Interestingly, addition of heparin was found to counteract India-ink-induced thrombosis in this model (36). Moreover, MC-reconstitution of W/W<sup>v</sup> mice by bone marrow transplantation from normal mice resulted in a protection from India-ink-induced thrombosis (36). In light of these data it is tempting to speculate that MC may act as repair cells in thromboembolic disease states. However, the precise role of MC in the pathophysiology of thrombosis and especially their contribution to tissue repair and endogenous fibrinolysis, remain to be defined. Also, the exact role of MC-derived repair molecules, namely heparin and tPA, in thromboembolic disorders, remains unknown. Clinical studies are currently under way to address these issues and to further define the role of MC as repair cells in various disease models.

### Role of KIT and KIT Ligand

KIT is a transmembrane tyrosine kinase receptor for SCF. The KIT ligand SCF is a major regulator of MC functions. In fact, SCF induces

differentiation and migration of MC as well as mediator secretion (14-16, 37-40). The SCF receptor (KIT = CD117) is expressed in MC progenitor cells as well as in mature MC (41, 42). Recent data suggest that both SCF and KIT play a role in the repair functions of MC. First, SCF is detectable in thrombin-activated endothelial cells as well as around thrombosed vessels (where endothelial cells are considered to be in an activated state) (9, 18). Thrombin-activated endothelial cells appear to produce and secrete the soluble form of SCF, and to display MC-chemotactic activity (18). Thus, SCF may be involved in the accumulation of MC around thrombosed vessels. Since SCF is also expressed in membrane-bound form in endothelial cells or other stroma cells, the localizing effect of SCF may also be due to adhesion of KIT+ MC to SCF-bearing cells in the tissues (19, 43). However, SCF not only mediates chemotaxis and adhesion in human MC but also mediator secretion (38, 39). Thus, SCF also promotes the release of heparin and tPA (26). Moreover, SCF induces an increase in expression of uPAR (30).

### The Emerging Concept

Based on the observations that MC accumulate at the sites of thrombosis and contain a number of repair molecules, a new concept that represents an extension of the triad of Virchow is proposed. In this concept, activated endothelial cells produce and secrete SCF that induces accumulation and activation of MC. Activated MC in turn provide a number of repair molecules to thrombosed vessels. These repair molecules (tPA, heparin, others) would then counteract thrombosis and help to prevent further thrombus formation. Figure 1 shows a scheme of our novel hypothesis.

### Concluding Remarks

So far, MC have mainly been implicated in the “effector-phase” of allergic and other inflammatory reactions. The possibility that MC, in addition, can fulfil an important repair function in the thromboembolic state, is a novel concept – and a novel hitherto unrecognized function of MC. Clinical studies will clarify whether indeed MC play an important role in endogenous fibrinolysis and whether a defect in the MC-repair system may contribute to the thrombophilic state.

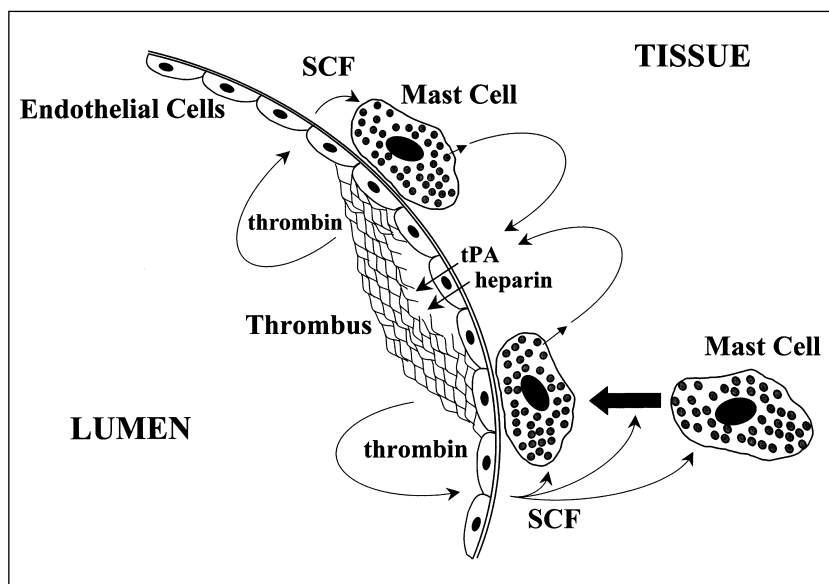


Fig. 1 Regulation of thrombolysis by mast cell-endothelial cell interactions. During an thromboembolic event, thrombin activates endothelial cells to express and release the soluble form of stem cell factor (SCF). SCF induces differentiation and chemotaxis in mast cells thereby leading to a local accumulation of these cells. Moreover, SCF triggers secretion of various mediators including heparin and tPA in mast cells. The released mediators may play a significant role in endogenous thrombolysis

## Appendix

All co-authors contributed equally to the development of the concept, and each of the persons listed as co-author contributed special expertise and input in the fields of mast cell biology (P. V.), endothelial cell research (M. B.), histopathology (H. C. B.), molecular biology (C. S.), mast cell activation (W. R. S.), vascular biology (J. W.), fibrinolysis and biochemistry (B. R. B.), and thrombosis research (K. L.).

## References

- Ratnoff OD. Thrombosis and the hypercoagulable state. *Circulation* 1984; 70: 72-6.
- Blann AD, Lip GY. Virchow's triad revisited: the importance of soluble coagulation factors, the endothelium, and platelets. *Thromb Res* 2001; 101: 321-7.
- Galli SJ. Biology of disease: New insights into "the riddle of the mast cells": microenvironmental regulation of mast cell development and phenotypic heterogeneity. *Lab Invest* 1990; 62: 5-33.
- Schwartz LB. The mast cell. In: Kaplan AP (ed). *Allergy*, volume 1. Edinburgh, Churchill Livingstone 1985; 53-92.
- Lewis RA, Austen KF. Mediation of homeostasis and inflammation by leukotrienes and other mast cell dependent compounds. *Nature* 1981; 293: 103-8.
- Valent P, Sillaber C, Baghestanian M, Bankl HC, Kiener HP, Lechner K, Binder BR. What have mast cells to do with edema formation, the consecutive repair, and fibrinolysis? *Int Arch Allergy Immunol* 1998; 115: 2-8.
- Valent P, Sillaber C, Bettelheim P. The growth and differentiation of mast cells. *Prog Growth Factor Res* 1991; 3: 27-41.
- Bankl HC, Großschmidt K, Pikula B, Bankl H, Lechner K, Valent P. Mast cells are augmented in deep venous thrombosis and express a profibrinolytic phenotype. *Human Pathol* 1999; 30: 188-94.
- Bankl HC, Radaszkiewicz T, Klappacher GW, Glogar D, Sperr WR, Grossschmidt K, Bankl H, Lechner K, Valent P. Increase and redistribution of cardiac mast cells in auricular thrombosis. Possible role of kit ligand. *Circulation* 1995; 91: 275-83.
- Bankl HC, Valent P. Mast cells and mast cell growth factor: possible role in auricular thrombosis. *Biomed Rev* 1995; 4: 29-32.
- Bankl HC, Radaszkiewicz T, Pikula B, Baghestanian M, Mherabi MR, Bankl H, Lechner K, Valent P. Expression of fibrinolytic antigens in redistributed cardiac mast cells in auricular thrombosis. *Human Pathol* 1997; 28: 1283-90.
- Kitamura Y, Yokoyama M, Matsuda H, Ohno T, Mori KJ. Spleen colony-forming cell as common precursor for tissue mast cells and granulocytes. *Nature* 1981; 291: 159-60.
- Agis H, Willheim M, Sperr WR, Wilfing A, Kromer E, Kabrna E, Spanblöchl E, Strobl H, Geissler K, Spittler A, Boltz-Nitulescu G, Lechner K, Valent P. Monocytes do not make mast cells when incubated with recombinant SCF: characterization of the circulating mast cell progenitor as CD34+, c-kit+, Ly-, CD14-, CD17-, colony forming cell. *J Immunol* 1993; 151: 4221-7.
- Kirshenbaum AS, Goff JP, Kessler SW, Mican JM, Zsebo KM, Metcalfe DD. Effect of IL-3 and stem cell factor on the appearance of human basophils and mast cells from CD34+ pluripotent progenitors. *J Immunol* 1992; 148: 772-7.
- Valent P. The Riddle of The Mast Cell: c-kit Ligand as Missing Link? *Immunol Today* 1994; 15: 111-4.
- Valent P, Spanblöchl E, Sperr WR, Sillaber Ch, Agis H, Zsebo K, Geissler K, Bettelheim P, Lechner K. Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor (SCF)/kit ligand (KL) in long term culture. *Blood* 1992; 80: 2237-45.
- Lammie A, Drobnjak M, Gerald W, Saad A, Cote R, Cordon-Cardo C. Expression of c-kit and kit ligand proteins in normal human tissue. *J Histochem Cytochem* 1994; 42: 1417-25.
- Baghestanian M, Hofbauer R, Kress HG, Wojta J, Fabry A, Binder BR, Kaun C, Müller MR, Mehrabi MR, Kapiotis S, Sengoelge G, Ghannadan M, Lechner K, Valent P. Thrombin augments vascular cell-dependent migration of human mast cells: role of MGF. *Thromb Haemost* 1997; 77: 577-84.
- Zsebo KM, Williams DA, Geissler EN, Broudy VC, Martin FH, Atkins HL, Hsu RY, Birkett NC, Okino KH, Murdock DC, et al. Stem cell factor is encoded at the Sl locus of the mouse and is the ligand for the c-kit tyrosine kinase receptor. *Cell* 1990; 83: 213-24.
- Schwartz LB, Badford TR, Littman BH, Wintroub BU. The fibrinogenolytic activity of purified tryptase from human lung mast cells. *J Immunol* 1985; 135: 2762-7.
- Stack MS, Johnson DA. Human mast cell tryptase activates single chain urinary-type plasminogen activator (pro-urokinase). *J Biol Chem* 1994; 269: 9416-9.
- Pejler G, Karlstrom A. Thrombin is inactivated by mast cell secretory granule chymase. *J Biol Chem* 1993; 268: 11817-22.
- Yurt RW, Leid RW, Austen KF, Silbert JE. Native heparin from rat peritoneal mast cells. *J Biol Chem* 1977; 252: 518-21.
- Sakai K, Ren S, Schwartz LB. A novel heparin-dependent processing pathway for human tryptase. Autocatalysis followed by activation with dipeptidyl peptidase I. *J Clin Invest* 1996; 97: 895-6.
- Stein PL, van-Zonneveld AJ, Pannekoek H, Strickland S. Structural domains of human tissue type plasminogen activator that confer stimulation by heparin. *J Biol Chem* 1989; 264: 15441-4.
- Sillaber C, Baghestanian M, Bevec D, Willheim M, Agis H, Kapiotis S, Füreder W, Bankl HC, Kiener H, Speiser W, Binder BR, Lechner K, Valent P. The mast cell as site of tissue type plasminogen activator production and fibrinolysis. *J Immunol* 1999; 162: 1032-41.
- Collen D, Lijnen HR. Basic and clinical aspects of fibrinolysis and thrombolysis. *Blood* 1991; 78: 3114-24.
- Vassalli JD, Sappino AP, Belin D. The plasminogen activator/plasmin system. *J Clin Invest* 1991; 88: 1067-72.
- Carmeliet P, Schoonjans L, Kieckens L, Ream B, Degen J, Bronson R, De Vos R, van den Oord JJ, Collen D, Mulligan RC. Physiological consequences of loss of plasminogen activator gene function in mice. *Nature* 1994; 368: 419-24.
- Sillaber C, Baghestanian M, Hofbauer R, Virgolini I, Bankl HC, Füreder W, Agis H, Willheim M, Leimer M, Scheiner O, Binder BR, Kiener H, Bevec D, Fritsch G, Majdic O, Kress HG, Gadner H, Lechner K, Valent P. Molecular and functional characterization of the urokinase receptor on human mast cells. *J Biol Chem* 1997; 272: 7824-32.
- Kruihof EKO. Plasminogen activator inhibitors – a review. *Enzyme* 1988; 40: 113-21.
- Yamamoto C, Kaji T, Sakamoto M, Kozuka H, Koizumi F. Calcium regulation of tissue type plasminogen activator and plasminogen activator inhibitor-1 release from cultured human vascular endothelial cells. *Thromb Res* 1994; 74: 163-8.
- Cho SH, Tam SW, Demissie-Sanders S, Filler SA, Oh CK. Production of plasminogen activator inhibitor-1 by human mast cells and its possible role in asthma. *J Immunol* 2000; 165: 3154-61.
- Sundberg M. On the mast cells in the human vascular wall. *Acta Pathol Microbiol Immunol Scand Suppl* 1955; 107: 7-81.
- Pomerance A. Peri-arterial mast cells in coronary atheroma and thrombosis. *J Pathol Bacteriol* 1958; 76: 55-70.
- Kitamura Y, Taguchi T, Yokoyama M, Inoue M, Yamatodani A, Asano H, Koyama T, Kanamaru A, Hatanaka K, Wershil BK. Higher susceptibility of mast-cell-deficient W/W<sup>v</sup> mutant mice to brain thromboembolism and mortality caused by intravenous injection of India ink. *Am J Pathol* 1986; 122: 469-80.
- Irani AM, Nilsson G, Miettinen U, Craig SS, Ashman LK, Ishizaka T, Zsebo KM, Schwartz LB. Recombinant human stem cell factor stimulates differentiation of human mast cells from dispersed fetal liver cells. *Blood* 1992; 80: 3009-16.

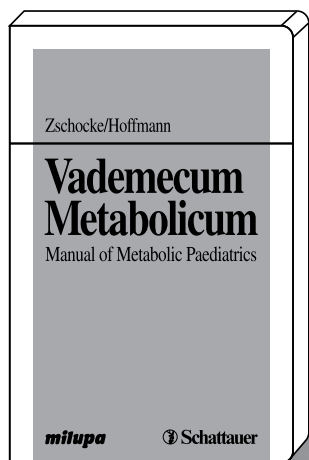
38. Bischoff SC, Dahinden CA. c-kit ligand: A unique potentiator of mediator release by human lung mast cells. *J Exp Med* 1992; 175: 237-44.
39. Sperr WR, Czerwenka K, Mundigler G, Müller MR, Semper H, Klappacher G, Glogar D, Lechner K, Valent P. Specific activation of human mast cells by the ligand for c-kit: comparison between lung-, uterus- and heart mast cells. *Int Arch Allergy Appl Immunol* 1993; 102: 170-5.
40. Nilsson G, Butterfield JH, Nilsson K, Siegbahn A. Stem cell factor is a chemotactic factor for human mast cells. *J Immunol* 1994; 153: 3717-23.
41. Valent P, Bettelheim P. Cell surface structures on human basophils and mast cells: biochemical and functional characterization. *Adv Immunol* 1992; 52: 333-423.
42. Sillaber C, Bevec D, Ashman LK, Butterfield JH, Lechner K, Maurer D, Bettelheim P, Valent P. IL-4 regulates c-kit gene product expression in human myeloid- and mast cell progenitors. *J Immunol* 1991; 147: 4224-8.
43. Adachi S, Tsujimura T, Jippo T, Morimoto M, Isozaki K, Kasugai T, Nomura S, Kitamura Y. Inhibition of attachment between cultured mast cells and fibroblasts by Phorbol 12-Myristate 13-Acetate and stem cell factor. *Exp Hematol* 1995; 23: 58-65.

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