

EDITORIAL

Mast cell matrix interactions

Cell adhesion processes are regarded as mechanisms that translate basic genetic information into the complex three-dimensional patterns of cells in tissues [1]. Thus, the localization of mast cells, which congregate around nerves, blood vessels and lymphatic vessels in a consistent fashion [2], should be regulated by specific membrane receptor ligand interactions. The receptors determine the specificity of cell–cell and cell–extracellular matrix (ECM) recognition. Adhesion of mast cells to components of connective tissue is thought to be important for the recruitment of mast cell progenitors from the circulation into tissue and the subsequent development, distribution, retention, survival, priming and activation of the mature mast cells [3]. In this editorial review, the specific receptors on mast cells will be initially discussed. Secondly, the regulation of integrin binding and mast cell function by the adhesion molecules will be reviewed. Finally, the roles of adhesion mechanisms of mast cells in the generation of tissue architecture will be considered.

Mast cell adhesion receptors

The functional units of cell adhesion are typically multi-protein complexes comprised of three general classes of proteins: the cell adhesion molecules/adhesion receptors, the ECM proteins and the cytoplasmic plaque/peripheral membrane proteins. The receptors include members of the integrin, cadherin, immunoglobulin, selectin and proteoglycan superfamilies. Among them, the integrins are best investigated as the receptors of mast cells. Surface expression of adhesion molecules on murine and human mast cells are well described in several excellent reviews [2–4]. The integrin molecules $\beta 1$ (CD29), $\alpha 4$ (CD49d), $\alpha 5$ (CD49e), αv (CD51) and $\beta 3$ (CD61) are expressed on the surface of mast cells dispersed from human lung, uterine and skin [2–5]. The natural ligands of CD49d/CD29 (very late antigen-4; VLA-4), CD49e/CD29 (VLA-5) and CD51/CD61 (vitronectin receptor; VNR) are fibronectin (FN) and vascular cell adhesion molecule (VCAM)-1; FN; and VN, FN, thrombospondin and fibrinogen, respectively. Mast cells dispersed from skin also express CD49c/CD29 (VLA-3) [5]. The natural ligand of VLA-3 is laminin, collagen I and FN. With regard to nonintegrin adhesion molecules, human mast cells are reported to express intercellular adhesion molecule (ICAM)-1 (CD54), ICAM-2 (CD50), leukosialin (CD43), leucocyte function associated antigen-1 (LFA-1), LFA-3 and c-kit [2–4,6]. Using human fetal liver-derived mast

cells; it has been reported that surface expression of CD29 and CD49d were detected on cells from day 0–4 weeks of culture [7]. However, surface expression of CD49e, CD51 and CD61 along with c-kit was apparent by 4 weeks of culture, whereas expression of each at day 0 was low to undetectable [7]. Recently, it has been reported that the high-granularity, 6-week-old population from cord blood mononuclear cells express $\beta 3$ integrin as well as c-kit/CD13/Fc ϵ RI α , whereas the low-granularity, 6-week-old population (c-kit+/CD13+/Fc ϵ RI+), which are viewed as providing a population of high granularity, are $\beta 3$ negative [8]. Thus, the mast cell adhesion receptors recognize and interact with either other cell adhesion receptor on neighbouring cells such as fibroblasts and endothelial cells, or with proteins of the ECM such as FN and VN. However, the distributions of VN at tissue sites that are both abundant (dermis) and sparse (kidney) in mast cells [7], suggesting that mast cell trafficking may require multiple factors. In Crohn's disease, a striking accumulation of mast cells was observed to be colocalized with patches of laminin in the hypertrophied and fibrotic muscularis propria, but not with FN or VN [9]. These findings suggest that human mast cells may localize differently with regard to components of connective tissue, depend on the disease states.

Regulation of cell adhesion

Adhesiveness of integrins is upregulated rapidly by a number of molecules, including growth factors, cytokines, chemokines and other cell surface receptors through a mechanism termed inside-out signalling. In murine mast cells, c-kit regulates cell-matrix adhesion by phosphatidylinositol 3 kinase and phospholipase C- γ 1 pathways [10]. The inside-out signalling pathways are thought to alter integrin by diffusion/clustering. It has been reported that affinity of VLA-5 for FN was rapidly increased in bone marrow-derived mast cells by antigen cross-linking of Fc ϵ RI through phosphatidylinositol 3-kinase [11]. Furthermore, IL-4 increased the expression of ICAM-1 and LFA-1 on human cord blood-derived mast cells, but not VLA family or VCAM-1 [6].

Regulation of mast cell function

Adhesion results in activation of intracellular signals that not only evoke new cellular responses, but also modulate the response of cells to other stimuli. The signal transduction by

adhesion molecules will not be described here in detail: the reader is referred to several excellent reviews for further information on this topic [12–15]. There is abundant evidence that adhesion molecules participate in a large variety of signal transduction events important for regulating cell adhesion and cell motility, cell growth, apoptosis and specific gene regulation [12–15]. However, it is useful to distinguish between two types of signalling events: signals that control local cytoplasmic processes and signals that influence cell growth and differentiation [1]. Indeed it has been reported that adhesion molecules regulate both local cytoplasmic processes (secretion, alterations of the cytoskeleton) and cell growth and differentiation in mast cells [16–18]. IgE-dependent degranulation is enhanced by adhesion of the rat basophilic-leukaemia cell lines (RBL-2H3) to immobilized FN [16]. Cell adherence and Fc ϵ RI aggregation synergistically regulate tyrosine phosphorylation of paxillin, pp105–115, and pp125FAK [3]. The tyrosine kinase Lyn, appears to be required for FN-mediated RBL-2H3 cell motility and filamentous actin assembly was reported [17]. In addition to the effect on activation, mast cell adhesion has been reported to enhance proliferation in IL-3-dependent bone marrow-derived mast cells [18]. Synergy between cell adhesion-mediated and growth factor-triggered signals may be a significant mechanism for regulating various cellular responses.

Conclusions

Adhesion mechanisms are intimately related to the processes of cell motility and cell migration, and proliferation. Regulation of tissue morphogenesis requires complex interaction between the adhesion receptors, the cytoskeleton and the networks of signalling pathway. Adhesion molecules mediated adhesion to other cells or the ECM proteins serve as a powerful costimulus for mast cell and the neighbouring cell activation. Tryptase is reported to be a fibrogenic factor, which stimulates fibroblast collagen mRNA synthesis [19]. In this issue, Berton *et al.* [20] clearly demonstrated that mast cell extract was able to decrease the contraction of the collagen lattices, to stimulate total protein and collagen synthesis in fibroblasts, and to increase the expression and activation of gelatinase A/MMP-2 in fibroblasts. This is the further evidence of mast cell–fibroblast interaction, which may regulate tissue morphogenesis.

References

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