Mast Cell Adhesion to Extracellular Matrix: Local Effects of Acute Phase Reactants

R.	Rami	Hershkoviz ^{a,b}
L.	Liana	Preciado-Patt ^c
O.	Ofer	Lider ^d
M.	Mati	Fridkin ^c
Y.A.	Yoseph A.	Mekori ^{a,b}

^aAllergy-Clinical Immunology Unit, Department of Medicine, Meir General Hospital, Kfar-Saba, ^bSackler School of Medicine, Tel-Aviv University, Tel-Aviv, and Departments of ^cOrganic Chemistry and ^dImmunology, Weizmann Institute of Science, Rehovot, Israel

Key Words

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Correspondence to: Prof. Yoseph A. Mekori, MD, Chairman, Department of Medicine B, Meir General Hospital, 44281 Kfar-Saba (Israel), Tel. 972 9 900515, Fax 972 9 423218, E-Mail ymekori@netvision.net.il

Mast cells are known to accumulate in various inflammatory processes, some of which are known to be associated with increased local and systemic levels of acute phase reactants such as SAA [1, 2]. Moreover, mast cell accumulation has also been noticed in and around areas with amyloid deposition [3, 4]. Little is known, however, about the mechanism(s) by which mast cells (or their precursors) are recruited to these inflammatory sites. As has been shown for other immunocompetent cells [5], interactions with extracellular matrix (ECM) components appear to be important for the migration and location of mast cells in tissues. Indeed, adhesion of mast cells to fibronectin and laminin has been reported after mast cell activation with phorbol myristate acetate (PMA), calcium ionophore or antigen-mediated FcεRI cross-linking [6, 7]. However, none of these stimuli would appear to be responsible for adhesion of mast cells to ECM in normal physiologic conditions or situations where mast cell activation does not occur. The c-kit ligand, stem cell factor, which is produced by stromal cells and appears in either soluble or membrane-bound form, was found to induce resting mast cell adhesion to fibronectin and thus has been proposed as a major factor responsible for adhesion of mast cells to connective tissue matrix under normal physiologic conditions [8]. In contrast, a number of cyto-kines have been reported not to promote mast cell adhesion to ECM components including PDGF, IFN-γ, TNF-α, GM-

CSF, IL-1, IL-2, IL-3, IL-4 and endothelial cell growth factors [9].

We have examined the possibility that acute-phase proteins such as SAA, which increase significantly during acute phase responses, might affect mast cell adhesion to ECM and thereby control their recruitment and accumulation in inflammatory sites. It has recently been shown that SAA interacts with ECM components and thereby acts as a chemoattractant and regulator of

immune cell migration [10-12]. Based on these observations, we examined the effect of SAA on mast cell adhesion to ECM, an essential step in cellular transmigration. We could first demonstrate strong specific binding of recombinant human SAA (rSAA) to murine mast cells using flow cytometry. Moreover, radio-labeled rSAA was found to bind in a saturable manner to mast cells, reaching a binding affinity in the range of 10⁸ K_D. When immobilized by preincubation with ECM or laminin, both rSAA and the amyloidotic protein AA (amino acid residues 1-76) which contains an RGD-related adhesion motif [12], but not the C-terminal portion of SAA (amino acid residues 77-104), induced the adhesion of murine or human resting mast cells to ECM or laminin, respectively. SAA and AA, in either soluble or immobilized forms, did not activate mast cells to release mediators. Mast cell adhesion to immobilized ECM-SAA complexes appeared to occur through an integrin recognition, as adhesion was cal-

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cium dependent and could be blocked by either an RGD-containing peptide or by anti-CD29 mAb. Genistein also inhibited adhesion, indicating that tyrosine kinase activity was involved. Therefore, ECM appears to serve as a temporary anchorage site for SAA and AA, a condition which enables these molecules to exert their proadhesive/proinflammatory effects locally in the inflammatory site. The adhesion induced by ECM-bound SAA thus appears to be one of the mechanisms by which the tissue microenvironment governs mast cell distribution and promotes their accumulation in inflammation.

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296

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