

Editorial

Integrin expression by eosinophils

H.-U. Simon

SIAF, University of Zurich, Davos, Switzerland

H.-U. Simon
Swiss Institute of Allergy and Asthma Research (SIAF)
University of Zurich
Obere Strasse 22
CH-7270 Davos
Switzerland

Accepted for publication 29 February 2000

In many allergic diseases, eosinophils are believed to contribute to the inflammatory process. Adhesion molecules such as integrins play a key role in cell–cell and cell–extracellular matrix interactions. Such interactions are essential for proliferation and differentiation of eosinophils (but also other inflammatory cells) in the bone marrow (1), their migration into the blood (2), their recruitment into tissues (3, 4), and their activation at inflammatory sites (5). Therefore, it is important to study the expression and function of eosinophil adhesion molecules under physiologic and pathologic conditions.

Integrins are heterodimeric transmembrane glycoproteins composed of α and β subunits (6). More than 20 heterodimers have been described so far. Integrins have been implicated in the pathogenesis of asthma and other chronic eosinophilic inflammations. For example, $\beta 1$ integrins ($\alpha 4\beta 1$: very late antigen-4) have been considered to be important for selective recruitment of eosinophils and lymphocytes to inflammatory sites (3, 4). In contrast, $\beta 2$ integrins (CD11a-c/CD18) are expressed on all leukocytes, and mediate firm adhesion to vascular endothelium and extracellular matrix proteins (e.g., fibronectin, collagen).

In this issue of *Allergy*, Lundahl et al. observe that $\beta 7$ integrin surface protein expression is induced during eosinophil differentiation (7). The increase of $\beta 7$ surface expression was blocked by cycloheximide, suggesting that the newly observed phenomenon was not simply the consequence of redistribution of preformed $\beta 7$ integrins. In agreement with previous work (8), $\beta 7$ appeared to associate with $\alpha 4$ to form an

$\alpha 4\beta 7$ heterodimer. Since $\alpha 4$ and $\beta 1$ integrin levels were slightly decreased in these *in vitro* differentiation assays, it seems that $\alpha 4$ associates less with $\beta 1$ in mature than immature eosinophils.

The functional consequences of less $\alpha 4\beta 1$ and more $\alpha 4\beta 7$ on mature eosinophils are unclear. Both heterodimers serve as ligands for fibronectin, as demonstrated by the study of Lundahl et al. (7). On the other hand, it is likely that $\alpha 4\beta 1$ and $\alpha 4\beta 7$ have different cellular functions. For instance, vascular cell adhesion molecule-1 is a ligand for $\alpha 4\beta 1$, but binds $\alpha 4\beta 7$ only weakly (9, 10). In contrast, mucosal addressin cell adhesion molecule-1 binds $\alpha 4\beta 7$, but not $\alpha 4\beta 1$ (11, 12). This suggests that the differentiation of eosinophils is associated with new properties important for cell–cell and cell–extracellular matrix interactions. Increased $\beta 7$ integrin expression might be important for at least one step of eosinophil migration from bone marrow to other tissues. However, the importance of eosinophil $\beta 7$ integrins under physiologic and pathologic conditions *in vivo* remains to be determined.

Besides neutralization or knockout studies to gain insights into the function of a molecule, it is equally important to investigate the structural requirements of that function. Truncation of the cytoplasmic domain of $\beta 7$ decreases binding to endothelial cells, suggesting that intracellular molecular interactions are important for regulation of integrin avidity. Indeed, there is evidence that activation of cytokine receptors can increase the avidity of integrins, a mechanism that may allow selective activation of these adhesion receptors on certain cells only (13). Further insights

into the molecular interactions between eosinophil integrins and their ligands may provide new therapeutic approaches in chronic allergic disorders.

Acknowledgments

Work in my laboratory is supported by the Swiss National Science Foundation (grant no. 32-58916.99), the EMDO Foundation Zurich, the Saurer Foundation Zurich, and the OPO Foundation Zurich.

References

- OGAWA M. Differentiation and proliferation of hematopoietic stem cells. *Blood* 1993;**81**:2844–2853.
- PALFRAMAN RT, COLLINS PD, SEVERS NJ, ROTHERY S, WILLIAMS TJ, RANKIN SM. Mechanisms of acute eosinophil mobilization from the bone marrow stimulated by interleukin 5. The role of specific adhesion molecules and phosphatidylinositol 3-kinase. *J Exp Med* 1998;**188**:1621–1632.
- SCHLEIMER RP, STERBINSKY SA, KAISER J, et al. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium. Association with expression of VCAM-1. *J Immunol* 1992;**148**:1086–1092.
- MOSER R, FEHR J, BRUIJNZEEL PLB. IL-4 controls the selective endothelium-driven transmigration of eosinophils from allergic individuals. *J Immunol* 1992;**149**:1432–1438.
- KATO M, ABRAHAM RT, OKADA S, KITA H. Ligation of the $\beta 2$ integrin triggers activation and degranulation of human eosinophils. *Am J Respir Cell Mol Biol* 1998;**18**:675–686.
- HYNES RO. Integrins: versatility, modulation and signaling in cell adhesion. *Cell* 1992;**69**:11–25.
- LUNDAHL J, SEHMI R, HAYES L, HOWIE K, DENBURG JA. Selective upregulation of a functional $\beta 7$ integrin on differentiating eosinophils. *Allergy* 2000;**55**:865–872.
- WALSH GM, SYMON FA, LAZAROVITS AI, WARDLAW AJ. Integrin $\alpha 4\beta 7$ mediates human eosinophil interaction with MAdCAM-1, VCAM-1 and fibronectin. *Immunology* 1996;**89**:112–119.
- RÜEGG C, POSTIGO AA, SIKORSKI EE, BUTCHER EC, PYTELA R, ERLE DJ. Role of integrin $\alpha 4\beta 7/\alpha 4\beta 7$ in lymphocyte adherence to fibronectin and VCAM-1 and in homotypic cell clustering. *J Cell Biol* 1992;**117**:179–189.
- CHAN BMC, ELICES MJ, MURPHY E, HEMLER ME. Adhesion to vascular cell adhesion molecule 1 and fibronectin: comparison of $\alpha 4\beta 1$ (VLA-4) and $\alpha 4\beta 7$ on the human B cell line JY. *J Biol Chem* 1992;**267**:8366–8370.
- HU MCT, CROWE DT, WEISSMAN IJ, HOLZMANN B. Cloning and expression of mouse integrin $\beta p(\beta 7)$: a functional role in Peyer's patch-specific lymphocyte homing. *Proc Natl Acad Sci U S A* 1992;**89**:8254–8258.
- BERLIN C, BERG EL, BRISKIN MJ, et al. $\alpha 4\beta 7$ integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell* 1993;**74**:185–195.
- PAUL SUNG KL, YANG L, ELICES M, JIN G, SRIRAMARAO P, BROIDE DH. Granulocyte-macrophage colony-stimulating factor regulates the functional adhesive state of very late antigen-4 expressed by eosinophils. *J Immunol* 1997;**158**:919–927.