

One of the first reviews on chemokines appeared in 1989 as a Perspective in *The Journal* (1). The paper was solicited by the late Ira Goldstein, a pioneer in the field of leukocyte biology, and was written with the belief that the discovery of IL-8, which insiders liked to call NAP-1 (for neutrophil activating protein-1), was a big step toward the understanding of neutrophil recruitment. What we wrote is still largely valid, but our Perspective was short-sighted as we did not expect the number and variety of chemokines to grow so much so fast. The fact that the chemokine superfamily today comprises more than 30 members indicates by itself that these proteins are important in biology and pathology. At least seven CXC chemokines, including IL-8, are active on neutrophils and share the receptors. For several CC chemokines, overlapping activities on monocytes, lymphocytes, basophils, and eosinophils have been described (2), and additional CC chemokines are in the process of being characterized. The high number of related species is unusual even in the cytokine field, and the redundancy of the chemokine system is in danger of confusing and boring everybody.

Why an editorial on eotaxin, then? The remarkable feature of eotaxin is its apparent selectivity for eosinophil leukocytes. Eotaxin was discovered in 1993 by T.J. Williams and colleagues following a classical protocol. In a model of allergic lung inflammation of the guinea pig they found that the fluid recovered by bronchoalveolar lavage induced the local accumulation of eosinophils when injected into the skin. Since the recruitment was selective it was worth looking for the attractant which was purified and shown to represent a new CC chemokine and was fittingly called eotaxin (3, 4). A homologous chemokine with chemotactic activity for eosinophils was later described in mice (5). The article by Ponath and colleagues in this issue of *The Journal* shows that human beings have eotaxin too (6). Human eotaxin was cloned using a mouse cDNA probe. The mature protein shares > 60% sequence identity with its homologues in guinea pigs and mice. The sequence is also highly related to that of the human monocyte chemotactic proteins (MCP-1, MCP-2, and MCP-3), but much less to that of RANTES.

Human eosinophils express receptors for eotaxin, which also recognize MCP-3 and RANTES, as indicated by binding studies and cross-desensitization experiments. However, eotaxin binds with higher affinity and does not appear to interact efficiently with the other known chemokine receptors. This may explain why eotaxin after local injection in vivo exclusively attracts eosinophils (4–6). In rodents, eotaxin expression was observed in models of allergic inflammation and conditions characterized by eosinophil accumulation (4, 5), and it was shown in guinea pigs that the effect of eotaxin is enhanced by systemic administration of IL-5 which induces eosinophilia and primes eosinophils to respond to chemokines (7). The potential role of eotaxin in allergic and eosinophilic inflammation

is also suggested by Ponath et al. (6) who found expression of this chemokine in tissue cells (epithelium, fibroblasts, and smooth muscle cells) and immigrant leukocytes (including eosinophils) in the areas of eosinophil accumulation on immunohistochemically stained sections prepared from a human nasal polyp.

After the observation that neutrophils are activated and attracted by CXC but not CC chemokines, we all expected CC chemokines to be selective as well (2). The expectations, as usual, were satisfied by early publications suggesting, for instance, that RANTES and MIP-1 α were selective for T lymphocytes and that MCP-1 was selective for monocytes (for review see reference 2). However, further studies showed that the monocyte chemotactic proteins are excellent attractants for lymphocytes (8), that basophils respond to MCP-1, MCP-3, RANTES, and MIP-1 α , and that the same chemokines, except for MCP-1, also stimulate eosinophils (for review see reference 9). The present evidence for the specific action of human eotaxin revives the selectivity issue and suggests that other CC chemokines with a predilection for a given leukocyte or lymphocyte may be found in the coming years.

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References

1. Baggiolini, M., A. Walz, and S.L. Kunkel. 1989. Neutrophil-activating peptide-1/interleukin-8, a novel cytokine that activates neutrophils. *J. Clin. Invest.* 84:1045–1049.
2. Baggiolini, M., B. Dewald, and B. Moser. 1994. Interleukin-8 and related chemotactic cytokines: CXC and CC chemokines. *Adv. Immunol.* 55:97–179.
3. Griffiths-Johnson, D.A., P.D. Collins, A.G. Rossi, P.J. Jose, and T.J. Williams. 1993. The chemokine, eotaxin, activates guinea-pig eosinophils *in vitro* and causes their accumulation into the lung *in vivo*. *Biochem. Biophys. Res. Commun.* 197:1167–1172.
4. Jose, P.J., D.A. Griffiths-Johnson, P.D. Collins, D.T. Walsh, R. Moqbel, N.F. Totty, O. Truong, J.J. Hsuan, and T.J. Williams. 1994. Eotaxin: a potent eosinophil chemoattractant cytokine detected in a guinea pig model of allergic airways inflammation. *J. Exp. Med.* 179:881–887.
5. Rothenberg, M.E., A.D. Luster, and P. Leder. 1995. Murine eotaxin: an eosinophil chemoattractant inducible in endothelial cells and in interleukin 4-induced tumor suppression. *Proc. Natl. Acad. Sci. USA.* 92:8960–8964.
6. Ponath, P.D., S. Qin, D.J. Rindler, I. Clark-Lewis, J. Wang, N. Kassam, H. Smith, X. Shi, J.-A. Gonzalo, W. Newman, J.-C. Gutierrez-Ramos, and C.R. Mackay. 1996. Cloning of the human eosinophil chemoattractant, eotaxin. Expression, receptor binding and functional properties provide a mechanism for the selective recruitment of eosinophils. *J. Clin. Invest.* 97:604–612.
7. Collins, P.D., S. Marleau, D.A. Griffiths-Johnson, P.J. Jose, and T.J. Williams. 1995. Cooperation between interleukin-5 and the chemokine eotaxin to induce eosinophil accumulation in vivo. *J. Exp. Med.* 182:1169–1174.
8. Loetscher, P., M. Seitz, I. Clark-Lewis, M. Baggiolini, and B. Moser. 1994. The monocyte chemotactic proteins, MCP-1, MCP-2 and MCP-3, are major attractants for human CD4⁺ and CD8⁺ T lymphocytes. *FASEB (Fed. Am. Soc. Exp. Biol.) J.* 8:1055–1060.
9. Baggiolini, M., and C.A. Dahinden. 1994. CC chemokines in allergic inflammation. *Immunol. Today.* 15:127–133.