Psoriasis: the plot thickens ...

MICHAEL P. SCHÖN¹ AND THOMAS RUZICKA²

¹Department of Dermatology, Otto von Guericke University, Leipzigerstrasse 44, 39120 Magdeburg, Germany. (Michael.Schoen@Medizin.Uni-Magdeburg.DE) ²Department of Dermatology, Heinrich-Heine-University, Moorenstrasse 5, 40225 Düsseldorf, Germany

Few diseases illustrate the central role of chemokines in tissue-specific leukocyte recruitment as vividly as psoriasis, one of the most common chronic inflammatory skin disorders. Psoriasis is primarily a T cell-mediated autoimmune disease¹. In addition, there is a prominent infiltration of neutrophils within the dermis that is focused within epidermal microabscesses, mast cells within the dermis and diffusely distributed macrophages. Because its complex tissue alterations require careful orchestration of sequential and highly specific leukocyte functions, psoriasis may serve as a model disease for studying the intertwined interactions of immigrating immune cells with resident epithelial and mesenchymal cells. The microenvironmental regulation of these pathogenic events, however, remains unknown. An exciting new concept is now emerging that highlights a pivotal role of chemokines in trafficking, adhesion, subtype-specific influx and compartmentalization of leukocytes in the psoriatic disease process² (Fig. 1).

As the chemokines TARC and MDC are expressed by the cutaneous vasculature and their receptor, CCR4, is expressed by some circulating CLA⁺ memory T cells, these chemokines presumably contribute to the preferential recruitment of skin-homing memory T cells *via* stimulation of integrin-ICAM-1 adhesive interactions³. CTACK (CCL27), a ligand for the orphan chemokine receptor GPR-2 (CCR10), is constitutively expressed by epidermal keratinocytes but can be increased by TNF- α and IL-1 β ⁴. Because CCR10 is expressed by T cells and skin-derived Langerhans cells, CTACK appears to contribute to epidermal localization of these cells⁴. In addition, MIP-3 α (CCL20) colocalizes in psoriatic epidermis with epidermal T cells and skin-homing CLA⁺ T lymphocytes express high amounts of the MIP-3 α receptor, CCR6⁵. Psoriatic CLA⁺ T cells respond to lower concentrations of MIP-3 α , as compared to T cells from normal donors. In addition, MIP-3 α can be induced on keratinocytes by proinflammatory cytokines involved in the pathogenesis of psoriasis⁵.

The CXC-chemokine, MIG, is expressed

exclusively on a spatially restricted subpopulation of endothelial cells and macrophages within the papillary dermis directly underneath the hyperplastic psoriatic epidermis⁶. As MIG is a T cell-attracting chemokine, it may contribute to epidermal T cell localization, possibly *via* TGF- β -induced expression of

the α_E (CD103) β_7 integrin. Given that MIG can be induced in macrophages and dermal microvascular endothelial cells by T cell-derived IFN- γ , a microenvironmental T cell-associated inflammation-boosting loop may contribute to the histopathological changes of psoriatic skin. This process may be augmented by the CC lymphocyte chemoattractant RANTES, which is up-regulated within psoriatic epidermis but not other inflammatory skin disorders⁷. Another loop exists with respect to the CC chemokine MCP-1, the expression of which is increased in psoriatic epidermis. MCP-1 induces its own production by monocytes (autocrine loop) and stimulates fibroblast expression of TGF- β ¹⁸, a cytokine thought to contribute to epidermal T cell localization *via* induction of the integrin $\alpha_E\beta_7$ (K. Pauls and M. P. Schön, unpublished data). In addition, both MCP-1 and RANTES may attract mast cells to psoriatic skin⁷. Because the CXC chemokine, I-TAC, can be induced by IFN- γ on keratinocytes and endothelial cells⁹, it is conceivable that I-TAC also contributes to cutaneous T cell local-

ization in psoriasis.

The formation of epidermal neutrophil accumulations, called Munro's microabscesses, is a hallmark feature of psoriasis¹. Interestingly, there is a high content of neutrophil-attracting chemokines including IL-8 and GRO- α within psoriatic scales¹⁰, the product of the excessive keratinization within the psoriatic plaques. This results in a "vicious cycle" of neutrophil attraction and further tissue damage mediated by neutrophils themselves as well as other mechanisms. In addition, IL-8 down-regulates epidermal expression of the IL-10 receptor, which results in a loss of negative immunoregulatory stimuli in psoriatic lesions. Keratinocyte hyperproliferation in psoriatic skin also appears to be induced, at least in part, by IL-8 and GRO- α because their receptor, CXCR2, is overexpressed in psoriatic, but not normal, skin¹⁰.

Overall, recent advances in chemokine research have contributed tremendously to our understanding of the immunopathogenesis of psoriasis and, possibly, opened a new era of specific therapeutic interventions.

1. Christophers, E. *Int. Arch. Allergy Immunol.* **110**, 199–206 (1996).
2. Zlotnik, A., Morales, J. & Hedrick, J. A. *Crit. Rev. Immunol.* **19**, 1–47 (1999).
3. Campbell, J. I. et al. *Nature* **400**, 776–780 (1999).
4. Homey, B. et al. *J. Immunol.* **164**, 3465–3470 (2000).
5. Homey, B. et al. *J. Immunol.* **164**, 6621–6632 (2000).
6. Goebeler, M. et al. *J. Pathol.* **184**, 89–95 (1998).
7. Raychaudhuri, S. P. et al. *Acta Derm. Venereol.* **79**, 9–11 (1999).
8. Yamamoto, T., Eckes, B., Mauch, C., Hartmann, K. & Krieg, T. *J. Immunol.* **164**, 6174–6179 (2000).
9. Mazanet, M. M., Neote, K. & Hughes, C. C. W. *J. Immunol.* **164**, 5383–5388 (2000).
10. Kulke, R. et al. *J. Invest. Dermatol.* **110**, 90–94 (1998).

Figure 1. Synopsis of selected chemokine actions in psoriatic lesions.