Upregulation of RANTES in Psoriatic Keratinocytes: A Possible Pathogenic Mechanism for Psoriasis

SIBA P. RAYCHAUDHURI1, WEN-YUE JIANG1, EUGENE M. FARBER1, THOMAS J. SCHALL2, MICHAEL R. RUFF3 and CANDACE B. PERT3

1Psoriasis Research Institute, Palo Alto, CA, USA, 2ChemoCentryx, San Carlos, CA, U.S.A. and 3Georgetown University Medical Center, Department of Physiology and Biophysics, School of Medicine, Washington, DC, U.S.A.

In recent years increased activity of chemokines such as IL-8, GRO-α and MCP-1 have been identified in the keratinocytes of psoriatic lesions (1–4). IL-8 and GRO-α belong to the α sub-family (C–C class) and MCP-1 is a β chemokine (C–C class). The present study was undertaken to investigate the activity of another β chemokine, RANTES (C–C class). Increased activity of RANTES has been reported in various inflammatory conditions, such as rheumatoid arthritis (5), delayed-type hypersensitivity (6) and transplant rejection (7).

MATERIALS AND METHODS

Tissue preparation

Skin biopsies were obtained from chronic psoriatic plaque lesions (n=8), and five biopsies each from non-lesional psoriatic skin, lichen planus, eczematous dermatitis (three numular eczema, two contact dermatitis) and five biopsies each from non-lesional psoriatic skin, lichen planus, eczematous dermatitis. Snap-frozen samples were cut into 7 mm cryosections. The sections were first incubated for 20 h with 6 mg/ml monoclonal anti-RANTES mouse IgG (DNAX, Palo Alto, CA). Standard immunohistochemistry techniques were applied. RANTES was detected only in the keratinocytes of psoriatic tissue. IL-8 and GRO-α belong to a subfamily (C–C class) and MCP-1 is a β chemokine. In this study, we investigated RANTES, which is a β chemokine (C–C class); RANTES has been found to be associated with various cell-mediated hypersensitive disorders. We obtained eight skin biopsies from chronic psoriatic plaques, and five biopsies each from non-lesional psoriatic skin, lichen planus, eczematous dermatitis and skin from healthy controls. Snap-frozen samples were cut into 7 μm cryosections and stained with 6 mg/ml of monoclonal anti-RANTES mouse IgG (DNAX, Palo Alto, CA). Standard immunohistochemistry techniques were applied. RANTES was detected only in the keratinocytes. The number of keratinocytes in per mm² of epidermis stained for RANTES were 116.79 ± 98.42 in psoriatic tissues compared to 32.00 ± 46.05 (p < 0.05), 6.39 ± 5.95 (p < 0.01), 2.64 ± 1.15 (p < 0.01) and 3.53 ± 5.26 (p < 0.01), respectively, in the non-lesional, lichen planus, eczematous lesions and normal skin. This is the first study to report that the keratinocytes of psoriatic tissue express high levels of RANTES compared to the controls. IL-8 and related molecules (C–C class) are predominantly chemotactic for neutrophils and MCP-1 is a strong chemotactic factor for monocytes. In contrast, RANTES is chemotactic for memory T cells and activated naive T cells. Increased amounts of RANTES as reported here provide an explanation for migration of the activated T cells to the epidermis of the psoriatic lesions. In addition, RANTES activates T cells. These results suggest that RANTES may have a significant role in the inflammatory process of psoriasis. Our findings further substantiate a regulatory role for keratinocytes in the inflammatory process of psoriasis. Key words: β chemokine; chemotaxis; cutaneous inflammation.

(Accepted May 22, 1998.)


Eugene M. Farber MD, Psoriasis Research Institute 600, Town and Country Village, Palo Alto, CA 94301, U.S.A.

Psoriasis is a chronic inflammatory skin disease of unknown etiology. Histopathological features of psoriasis are epidermal hyperplasia accompanied by inflammatory infiltrates and vascular proliferation. Intraepidermal collections of neutrophils and lymphocytes are two of the unique features of the inflammatory process of psoriasis. Migration of leukocytes from the dermis to the epidermis suggests a role for chemotactic agents.
which were slightly colored or where the positivity was doubtful were ignored. Tissues were examined for the presence of positively stained cells. RANTES was detected only in the keratinocytes. In psoriatic tissues keratinocytes expressed high levels of RANTES throughout all levels of epidermis except in stratum corneum (Fig. 1). The number of cells positive for RANTES in per square mm of epidermis was calculated by dividing the total number of RANTES positive cells by the surface area. Surface area of the epidermis was determined with the help of a reticle/grid (10 × 10 mm with 1 mm² boxes; Microscoptics, Inc., Milford, MI) placed in the eye piece. The data are described in Table I. The number of keratinocytes in per mm² of epidermis stained for RANTES was 116.79 ± 98.42 in psoriatic tissues compared with 32.00 ± 46.05 (p < 0.05), 6.39 ± 3.59 (p < 0.01), 2.64 ± 1.15 (p < 0.01) and 3.53 ± 5.26 (p < 0.01) in non-lesional skin, lichen planus, eczematous lesions and normal skin, respectively. RANTES expression in the non-lesional psoriatic keratinocytes was relatively higher compared to the normal control skin, eczematous lesions and lichen planus lesions but did not reach statistical significance (p > 0.121, p > 0.446 and p > 0.141, respectively). Statistical analysis: Data in respect to cell counts are presented as mean ± SD (Table I); for statistical analysis, the t-test was applied.

**DISCUSSION**

This is the first study to report that keratinocytes of psoriatic lesions express high levels of RANTES compared to the controls (Figs. 1–3). Chemokines are produced by a variety of cells and their production is regulated by various proinflammatory cytokines. RANTES is secreted by activated T lymphocytes,

<table>
<thead>
<tr>
<th>Biopsies</th>
<th>No.</th>
<th>RANTES+ KC/mm (mean ± SD)</th>
<th>RANTES+ KC/mm² (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>8</td>
<td>17.05 ± 14.37</td>
<td>116.79 ± 98.42</td>
</tr>
<tr>
<td>Psoriasis-non-lesional</td>
<td>5</td>
<td>1.25 ± 1.80</td>
<td>32.00 ± 46.05</td>
</tr>
<tr>
<td>Lichen planus</td>
<td>5</td>
<td>0.56 ± 0.31</td>
<td>6.39 ± 3.59</td>
</tr>
<tr>
<td>Eczema</td>
<td>5</td>
<td>2.64 ± 1.15</td>
<td>35.17 ± 15.34</td>
</tr>
<tr>
<td>Normal</td>
<td>5</td>
<td>0.12 ± 0.18</td>
<td>3.53 ± 5.26</td>
</tr>
</tbody>
</table>

*Acta Derm Venereol (Stockh)* 79
keratinocytes, fibroblasts and epithelial cells subsequent to stimulation with TNF-α and IFN-α (8–11). Additional studies are required to determine whether the increased levels of RANTES in psoriatic keratinocytes is a secondary or a primary event.

IL-8 and related molecules (CXC class) are predominantly chemotactic for neutrophils (7, 12, 13) and MCP-1/MCAF (monocyte chemotactic and activating factor) is predominantly a chemotactic protein for monocytes. Intradermal injection of IL-8 does not cause an accumulation of lymphocytes (14). RANTES is chemotactic for resting CD4+ memory T cells, and activated naïve and memory T cells (13). Increased activity of RANTES as reported in this study provides an explanation for the epidermotropism of activated T cells (15–17) in psoriatic tissue. In addition, RANTES activates T lymphocytes (7). Thus RANTES may have a significant role in the pathogenesis of psoriasis.

REFERENCES
10. Li J, Ireland GW, Farthing PM, Thornhill MH. Epidermal and oral keratinocytes are induced to produce RANTES and IL-8 by cytokine stimulation. J Invest Dermatol 1996; 106: 661–666.