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Review

Inflammatory and Immune Reactions Associated with Stratum Corneum and Neutrophils in Sterile Pustular Dermatoses

TADASHI TERUI

Department of Dermatology, Tohoku University School of Medicine, Sendai 980-8574

TERUI, T. *Inflammatory and Immune Reactions Associated with Stratum Corneum and Neutrophils in Sterile Pustular Dermatoses.* Tohoku J. Exp. Med., 2000, **190** (4), 239-248 —— In this review we present our own experimental findings as well as those from the literature related to the pathomechanisms for the inflammatory changes in psoriasis and its related diseases. A growing body of evidence has indicated that T cell-mediated immunity plays an important role in triggering and maintenance of psoriatic lesions. It has been revealed that lymphokines produced by activated T cells in psoriatic lesions have a strong influence on the proliferation of the epidermis. Characteristic neutrophil accumulation under the stratum corneum can be observed in the highly inflamed areas of psoriatic lesions. These neutrophils are chemotactically attracted and activated there by synergistic action of chemokines, IL-8 and Gro-α released by stimulated keratinocytes, and particularly by C5a/C5a des arg produced via the alternative complement pathway activation. We demonstrated that the infiltrating neutrophils adhere to iC3b-opsonized corneocytes to produce active oxygen and probably lysosomal enzymes. From a close relationship observed between neutrophil accumulation and high mitotic ratio of the lesional epidermis, we think that these stimulated neutrophils influence the growth and differentiation of epidermal keratinocytes. Aberrant expression of HLA-DR on neutrophils suggests their activation of infiltrating T cells in the presence of bacterial superantigen. These T cells in turn influence the transepidermal neutrophil migration through the effect of their cytokines on the keratinocyte production of proinflammatory mediators including IL-8 and C3. In this review we discuss the pivotal roles played by stratum corneum and neutrophils in several skin diseases, where neutrophils accumulate beneath the stratum corneum in a sterile condition ———— psoriasis; neutrophils; T cells; keratinocytes; cytokines

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Address for reprints: Tadashi Terui, M.D., Department of Dermatology, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

e-mail: terui@mail.cc.tohoku.ac.jp

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Psoriasis is a T cell-mediated immune dermatosis

Psoriasis is a common chronic inflammatory disorder of the skin in western countries. Clinically, typical psoriasis is characterized by the presence of sharply demarcated erythematous papules and plaques that are covered by silvery scaling. Although psoriasis was once regarded as a dermatosis caused by benign epidermal hyperproliferation, there have been many reports published, which focused on the inflammatory changes. Initially attention centered on humoral immunity, but later, shifted to cellular immunity related to T cells. Based on the results of several studies, there is now sufficient evidence for T cell involvement in the development and maintenance of psoriatic lesions. For example, in bone marrow transplants, those cells of the immune system may cause the appearance or disappearance of psoriasis (Eedy et al. 1990; Gardembas-Pain et al. 1990). Furthermore, several immunosuppressive agents targeting T cells were found to induce the improvement of psoriasis (Ellis et al. 1986, 1991; Weinshenker et al. 1989; Nicolas et al. 1991; Poizot-Martin et al. 1991; Gottlieb et al. 1995). These clinical findings indicate that psoriasis is a T cell-mediated immune dermatosis.

Psoriatic keratinocytes appear to be modulated by T-cell lymphokines in vivo because they begin to express class II major histocompatibility complex (MHC) and protein IP-10, molecules uniquely induced on the surface of keratinocytes by interferon (IFN)-γ (Morhenn et al. 1982; Terui et al. 1987; Gottlieb et al. 1988). Indeed, IFN-γ mRNA is detected in psoriatic epidermis (Barker et al. 1991b). Later studies confirmed that T cell clones isolated from psoriatic lesions could produce IFN-γ (Prinz et al. 1994; Schlaak et al. 1994; Szabo et al. 1998). In addition, other proinflammatory cytokines such as IL-1β, IL-6, IL-8, growth-related oncogene α (GRO-α), and transforming growth factor (TGF)-α have also been reported to be increased in psoriatic plaques (Schröder and Christophers 1986; Fincham et al. 1988; Elder et al. 1989; Grossman et al. 1989; Takematsu and Tagami 1993; Bonifati et al. 1994; Debets et al. 1995; Gillitzer et al. 1996; Kulke et al. 1996; Lundqvist and Egelrud 1997). These cytokines are thought to be produced by activated keratinocytes as well as by infiltrating macrophages and T cells.

In such T cell-mediated psoriatic lesions, neutrophils characteristically accumulate not only under the stratum corneum, culminating in the formation of Munro's microabscesses, but also are observed at different levels of the stratum corneum in the developed or maturated lesions as a result of their preceding cyclic transepidermal migration (Ragaz and Ackerman 1979). It has been demonstrated that neutrophils have an influence on the recruitment and function of T cells, i.e., T cell-mediated delayed hypersensitivity responses (Kudo et al. 1993; Chertov et al. 1996). Actually, similar neutrophil accumulation can also be seen in T cell-mediated chronic joint lesions of rheumatoid arthritis (Kock et al. 1995; De Gendt et al. 1996). These observations suggest that neutrophils also play an

important role in the T cell-mediated immune responses rather than just accumulate there passively. However, the underlying mechanism is not fully understood yet. The results of our study may be useful for deciphering it.

Neutrophil infiltration and chemotactic factors

Cyclic transepidermal migration of neutrophils towards the stratum corneum, a hallmark of the psoriasiform tissue reaction, suggests that the concentration of neutrophil chemotactic factors should be highest at the subcorneal portion and that these substances are possibly trapped in the stratum corneum. In fact, these substances extracted from psoriatic scales enhance the adhesion, phagocytosis, and respiratory burst of neutrophils in the lesional stratum corneum (Tagami et al. 1987). Further studies demonstrated that the concentration of C5a/C5a des arg is increased variably in psoriatic scales (Takematsu et al. 1986; Bergh et al. 1993), whereas Interleukin (IL)-8 concentration is persistently high (Schröder and Christophers 1986; Fincham et al. 1988; Takematsu and Tagami 1993), irrespective of the presence or absence of neutrophil accumulation in the lesional epidermis (Takematsu and Tagami 1993) (Fig. 1). The latter finding in chronically inflamed lesions, even without Munro's microabscess, suggests that IL-8 is probably released by proliferating keratinocytes in psoriatic skin lesions and that it may be responsible for accumulation of T lymphocytes as well as neutrophils (Larsen et al. 1989; Barker et al. 1991a). Furthermore, our colleagues (Takematsu and Tagami 1993) demonstrated, by comparison of the concentrations of these chemokines in scale extracts with neutrophil chemotactic activity that C5a/C5a des arg levels correlate well with the chemotactic activity of the scale extracts. This suggests its pathogenic role in the induction of cyclic transepidermal neutro-

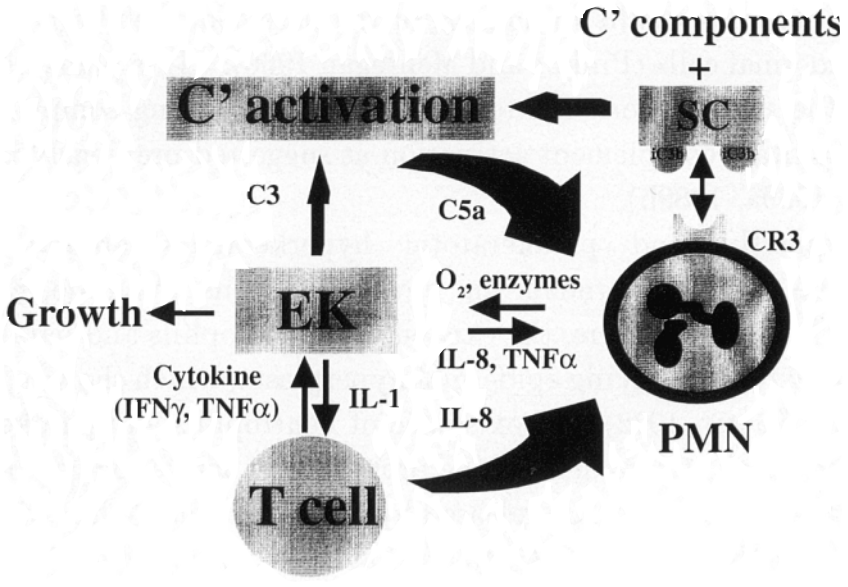

Fig. 1. A neutrophil-associated inflammation-boosting loop inducing acute inflammation at localized areas within chronic plaque lesions. SC, stratum corneum; EK, epidermal keratinocyte; PMN, polymorphonuclear leukocytes.

phil chemotaxis. It also seems to agree with the fact that the inflammatory changes in psoriatic lesions are not uniform even in the same lesions (Soltani and Van Scott 1972).

Evidence for complement activation in psoriasis

Marley et al. (1982) detected complement abnormalities that were related to activation of the alternative complement pathway in patients with active psoriasis. They found low serum properdin (P) concentrations in 12 of 20 patients with psoriasis and their normalization as patients showed a clinical improvement by the treatment (Rosenberg et al. 1990). Ohkohchi et al. (1989) also detected high levels of the control proteins of alternative pathway, H and I, in psoriasis patients compared to control subjects.

It has not been known how the aberrant complement activation occurs. We carried out several experiments to investigate the mechanism, focusing on the close relationship between the stratum corneum and neutrophils. We have reported that the stratum corneum obtained from plantar callus of normal subjects effectively activates complement in vitro via the alternative pathway to generate chemotactic C5a anaphylatoxin (Terui et al. 1989a, 1989b) (Fig. 1). To facilitate activation of the alternative complement pathway, its two essential components, C3 and factor B, are produced in the skin by keratinocytes (Basset-Seguin et al. 1990). Furthermore, we recently demonstrated that such C3 is more effectively produced by differentiated keratinocytes and that T-cell-derived cytokines such as IFN-γ and TNFα synergistically enhance the generation of C3 from these cells (Terui et al. 1997) (Fig. 1).

The exact mechanisms that lead to complement activation in psoriatic skin lesions, however, remain to be elucidated. Exocytosis of inflammatory cells into the lesional epidermis results in damage of the basement membrane zone and the overlying epidermal cells (Pinkus and Mehregan 1966). It is plausible that direct exposure of the stratum corneum to tissue fluids containing complement components may facilitate complement activation as suggested previously by our group (Terui et al. 1989a, 1989b).

We frequently find parakeratotic hyperkeratosis around neutrophils infiltrating the stratum corneum in psoriatic lesions (Van de Kerchief and Lammers 1987). Furthermore, the existence of neutrophils and parakeratosis are also consistent with underlying epidermal hyperplasia, which shows a high mitotic rate (Cox and Watson 1972). Coexistence of neutrophils and parakeratosis is in part explained by the tissue-destructive properties of active oxygen intermediates and proteolytic enzymes that are released by activated neutrophils attached to the stratum corneum (Kato et al. 1990, 1991) that are opsonized by iC3b through the alternative complement activation (Terui et al. 1995) as well as by the cytotoxic effects of terminal complement complex (Fleming et al. 1996) (Fig. 1).

A neutrophil-associated inflammation-boosting loop inducing acute inflammation within the chronic plaque

It has been demonstrated that activated T cells in psoriatic skin lesions produce lymphokines that induce not only epidermal cell proliferation but also secretion of cytokines such as IL-1 and IL-8 by psoriatic epidermal keratinocytes, which in turn augment the activation-state of T cells. This T cell-mediated inflammation-sustaining loop provides a good explanation of the development and the persistence of psoriatic epidermal hyperplasia associated with "chronic" inflammation. However, there exist sites of "acute" inflammation unevenly within the "chronic" inflammatory areas. As stated above, the lack of uniformity of the "acute" inflammation seems to correspond well with variable levels of C5a/C5a des arg demonstrable in the lesional stratum corneum, but not with the persistently high levels of chemokines even in that of chronically inflamed sites (Takematsu et al. 1986).

In general, the primary function of neutrophils in the immune responses appears to be the phagocytic clearance of foreign pathogens and release of inflammatory mediators including cytokines (Lopez et al. 1986; Jack and Fearon 1988; Cicco et al. 1990; Dubravec et al. 1990; Shirafuji et al. 1990; Bazzoni et al. 1991; Lord et al. 1991). They also constitutively express various surface proteins, including Fc receptors, CR1, CR3, and MHC class I molecules (Matsumoto et al. 1987; Petroni et al. 1988; Neuman et al. 1992). Antigen presentation to T cells is mostly accomplished by professional antigen presenting cells, such as macrophages, Langerhans cells, and dendritic cells. However, several other non-professional types of cells also present antigens to $CD4^+$ T cells when MHC class II molecules are induced. It has been shown that human neutrophils can be induced to express HLA-DR both in vitro (Gosselin et al. 1993; Smith et al. 1995; Fanger et al. 1997) and in vivo (Mudzinski et al. 1995; Reinisch et al. 1996). Neutrophils expressing HLA-DR by their treatment with granulocyte macrophage-colony stimulating factor (GM-CSF) and IFN-γ were found to fail to support activation of tetanus toxin-specific T cells probably due to lack of expression of accessory molecules, B7-1 and B7-2 (Fanger et al. 1997). However, a recent study confirmed that neutrophils are capable of directly activating T cells under certain conditions where T cells can be activated by neutrophils expressing HLA-DR by GM-CSF and/or IFN-γ in the presence of bacterial superantigens (Fanger et al. 1997). Our preliminary data demonstrated that neutrophils in the psoriatic lesions were indeed HLA-DR positive. This suggests that $HLA\text{-}DR^+$ neutrophils may augment the activation-state of T cells in the psoriatic lesional skin (Fig. 2).

We would like to propose a neutrophil-associated inflammation-boosting loop that may well explain the localized "acute" inflammatory changes scattered throughout chronic psoriatic plaques as well as those in acutely inflamed lesions

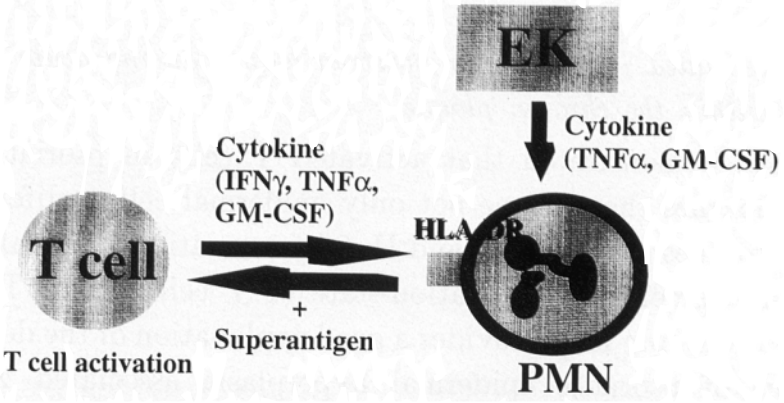

Fig. 2. Interaction between T cells and neutrophils. HLA-DR positive neutrophils may augment the activation state of T cells in psoriasis.

of pustular psoriasis (Figs. 1 and 2). From the observations mentioned above, it is likely that accumulation of neutrophils may not be simply a passive event in psoriatic lesions but may actively influence T cells by further enhancing their activation state. Subsequently, lymphokines released by such T cells stimulate epidermal keratinocytes to produce IL-8 and C3 that facilitates complement activation as well as neutrophil accumulation. Those neutrophils located in the stratum corneum may influence keratinocytes to induce disturbances of epidermal keratinization and underlying hyperproliferation. They also express HLA-DR under the influence of IFN-γ and GM-CSF in turn to potentiate T cells. Even in the tuberculin test, the classic type of T cell-mediated delayed hypersensitivity reactions, neutrophil infiltration has been noted (Kuramoto and Tagami 1989). Neutrophils can appear at extremely inflamed portions of T cell-mediated immune reactions (Kock et al. 1995; De Gendt et al. 1996). Thus, neutrophils infiltrating into the lesional skin may play a pivotal role in the eliciting the acute inflammatory responses in classic psoriatic lesions.

Conclusion

Neutrophils seem to play an important role in the formation of "acute" inflammatory changes in psoriasis, while "chronic" inflammation is well explained by a T cell-associated inflammation-sustaining loop. As discussed in this review, neutrophils are capable of potentiating the T cell-associated inflammation-sustaining loop by activating both epidermal keratinocytes and T cells through the production of cytokines, active oxygen intermediates, and proteolytic enzymes, and their expression of HLA-DR on their surfaces. Thus, we propose a neutrophil-associated inflammation-boosting loop as an inducer of "acute" inflammation with focal infiltration of neutrophils in psoriatic lesions. We would like to emphasize that the interaction of neutrophils and the stratum corneum through complement activation have strong influence on this loop.

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References

1) Barker, J.N.W.N., Jones, M.L., Mitra, R.S., Crockett-Torabe, E., Fantone, J.C., Kunkel, S.L., Warren, J.S., Dixit, V.M. & Nickoloff, B.J. (1991a) Modulation of keratinocyte-derived interleukin-8 which is chemotactic for neutrophils and T lymphocytes. *Am. J. Pathol.*, **139**, 869–876.
2) Barker, J.N., Karabin, G.D., Stoof, T.J., Sarma, V.J., Dixit, V.M. & Nickoloff, B.J. (1991b) Detection of interferon-gamma mRNA in psoriatic epidermis by polymerase chain reaction. *J. Dermatol. Sci.*, **2**, 106–111.
3) Basset-Seguin, N., Caughman, W. & Yancey, K.B. (1990) A-431 cells and human keratinocytes synthesize and secrete the third component of complement. *J. Invest. Dermatol.*, **95**, 621–625.
4) Bazzoni, F., Cassatella, M.A., Rossi, M., Ceska, M., Dewald, B. & Baggiolini, M. (1991) Phagocytosing neutrophils produce and release high amounts of the neutrophil-activating peptide 1/interleukin 8. *J. Exp. Med.*, **173**, 771–774.
5) Bergh, K., Iversen, O.-J. & Lysvand, H. (1993) Surprisingly high levels of anaphylatoxin C5a des Arg are extractable from psoriatic scales. *Arch. Dermatol. Res.*, **285**, 131–134.
6) Bonifati, C., Ameglio, F., Carducci, M., Sacerdoti, G., Pietravalle, M. & Fazio, M. (1994) Interleukin-1-beta, interleukin-6, and interferon-gamma in suction blister fluids of involved and uninvolved skin and in sera of psoriatic patients. *Acta Derm. Venereol. (Stockh)*, Suppl. **186**, 23–24.
7) Chertov, O., Michiel, D.F., Xu, L., Wang, J.M., Tani,. K., Murphy, W.J., Longo, D.L., Taub, D.D. & Oppenheim, J.J. (1996) Identification of defensin-1, defensin-2, and CAP34/azurocidin as T-cell chemoattractant proteins released from interleukin-8-stimulated neutrophils. *J. Biol. Chem.*, **271**, 2935–2940.
8) Cicco, N.A., Lindemann, A., Content, J., Vandenbussche, P., Lubbert, M., Gauss, J., Mertelsmann, R. & Hermann, F. (1990) Inducible production of interleukin-6 by human polymorphonuclear neutrophils: role of granulocyte-macrophage colony-stimulating factor and tumor necrosis factor-α. *Blood*, **75**, 2049–2052.
9) Cox, A.J. & Watson, W. (1972) Histological variation in lesions of psoriasis. *Arch. Dermatol.*, **106**, 503–506.
10) Debets, R., Hengman, J.P.J.J., Troost, R.J.J., Benner, R. & Prens, E.P. (1995) Enhanced production of biologically active interleukin-1β and interleukin-1β by psoriatic epidermal cells ex vivo: Evidence of increased cytosolic interleukin-1β levels and facilitated interleukin-1 release. *Eur. J. Immunol.*, **25**, 1624–1630.
11) De Gendt, C.M., de Clerck, L.S., Bridts, C.H., Van Osselaer, N. & Stevens, E.J. (1996) Relationship between inerleukin-8 and neutrophil adhesion molecules in rheumatoid arthritis. *Rheumatol. Int.*, **16**, 169–173.
12) Dubravec, D.B., Spriggs, D.R., Mannick, J.A. & Rodrick, M.L. (1990) Circulating human peripheral blood granulocytes synthesize and secrete tumor necrosis factor α. *Proc. Natl. Acad. Sci. USA*, **87**, 6758–6761.
13) Eedy, D.J., Burrows, D., Bridges, J.M. & Jones, F.G.C. (1990) Clearance of severe psoriasis after allogeneic bone marrow transplantation. *BMJ*, **300**, 908.
14) Elder, J.T., Fisher, G.J., Lindquist, P.B., Bennett, G.L., Pittelkow, M.R., Coffey, R.J., Jr., Ellingsworth, L., Derynck, R. & Voorhees, J.J. (1989) Overexpression of trans-

forming growth factor α in psoriatic epidermis. *Science*, **243**, 811–814.
15) Ellis, C.N., Gorsulowsky, D.C., Hamilton, T.A., Billings, J.K., Brown, M.D., Headington, J.T., Cooper, K.D., Baadsgaard, O., Duell, E.A., Annesley, T.M., Turcotte, J.G. & Voorhees, J.J. (1986) Cyclosporin improves psoriasis in a double-blind study. *JAMA*, **256**, 3110–3116.
16) Ellis, C.N., Fradin, M.S., Messana, J.M., Brown, M.D., Siegel, M.T., Hartley, A.H., Rocher, L.L., Wheeler, S., Hamilton, T.A., Parish, T.G., Ellis-Madu, M., Duell, E., Annesle, T.M., Cooper, K.D. & Voorhees, J.J. (1991) Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N. Engl. J. Med.*, **324**, 277–284.
17) Fanger, N.A., Liu, C., Guyre, P.M., Wardwell, K., O'Neil, J., Guo, T.L., Christian, T. P., Mudzinski, S.P. & Gosselin, E.J. (1997) Activation of human T cells by major histocompatibility complex class II expressing neutrophils: Proliferation in the presence of superantigen, but not tetanus toxoid. *Blood*, **89**, 4128–4135.
18) Fincham, N.J., Camp, R.D., Gearing, A.J., Bird, C.R. & Cunningham, F.M. (1988) Neutrophil chemoattractant and IL-1-like activity in samples from psoriatic skin lesions. Further characterization. *J. Immunol.*, **140**, 4294–4299.
19) Fleming, C.J., Holme E.R. & Mackie R.M. (1996) Systemic complement activation in psoriasis vulgaris. *Clin. Exp. Dermatol.*, **21**, 415–418.
20) Gardembas-Pain, M., Ifrash, N., Foussard, C., Boasson, M., Saint Andre, J.P. & Verret, J.L. (1990) Psoriasis after allogeneic bone marrow transplantation. *Arch. Dermatol.*, **126**, 1523.
21) Gillitzer, R., Ritter, U., Spandau, U., Goebeler, M. & Brocker, E.-B. (1996) Differential expression of GRO-α and IL-8 mRNA in psoriasis: A model for neutrophil migration and accumulation in vivo. *J. Invest. Dermatol.*, **107**, 778–782.
22) Gosselin, E.J., Wardwell, K., Rigby, W.F. & Guyre, P.M. (1993) Induction of MHC class II on human polymorphonuclear neutrophils by granulocyte/macrophage colony-stimulating factor, IFN-γ, and IL-3. *J. Immunol.*, **151**, 1482–1490.
23) Grossman, R.M., Krueger, J., Yourish, D., Granelli-Piperno, A., Murphy, D.P., May, L. T., Kupper, T.S., Shegal, P.B. & Gottlieb, A.B. (1989) Interleukin 6 is expressed in high levels in psoriatic skin and stimulates proliferation of cultured keratinocytes. *Proc. Natl. Acad. Sci. USA*, **86**, 6367–6371.
24) Gottlieb, A.B., Luster, A.D., Posnett, D.N. & Carter, D.M. (1988) Detection of a gamma interferon-induced protein IP-10 in psoriatic plaques. *J. Exp. Med.*, **168**, 941–948.
25) Gottlieb, S.L., Gilleaudeau, P., Johnson, R., Estes, L., Woodworth, T.G., Gottlieb, A. B. & Krueger, J.G. (1995) Response of psoriasis to a lymphocyte-selective toxin (DAB389IL-2) suggests a primary immune, but not keratinocytes, pathogenic basis. *Nature Med.*, **1**, 442–447.
26) Jack, R.M. & Fearon, D.T. (1988) Selective synthesis of mRNA and proteins by human peripheral blood neutrophils. *J. Immunol.*, **140**, 4286–4293.
27) Kato, T., Iizawa, O., Terui, T. & Tagami, H. (1990) Lucigenin-dependent chemiluminescence in neutrophils stimulated with stratum corneum sheet. *Arch. Dermatol. Res.*, **282**, 208–209.
28) Kato, T., Hara, M., Iizawa, O., Terui, T. & Tagami, H. (1991) Interaction between human neutrophils and corneocytes: corneocyte-induced respiratory burst of neutrophils assessed by chemiluminescence. *Inflammation*, **25**, 213–221.
29) Kock, A.E., Kunkel, S.L., Shah, M.R., Hosaka, S., Halloran, M.M., Haines, G.K., Burdick, M.D., Pope, R.M. & Strieter, R.M. (1995) Growth-related gene product alpha. A chemotactic cytokine for neutrophils in rheumatoid arthritis. *J. Immunol.*, **155**, 3660–3666.
30) Kudo, C., Yamashita, T., Araki, A., Terashita, M., Watanabe, T., Atsumi, M., Tamura, M. & Sendo, F. (1993) Modulation of in vivo immune responses by selective depletion of neutrophils using monoclonal antibody, RP-3. *J. Immunol.*, **150**, 3728–3738.

31) Kulke, R., Todt-Pingel, I., Rademacher, D., Rowert, J., Schröder, J.-M. & Christophers, E. (1996) Co-localized overexpression of GRO-α and IL-8 mRNA is restricted to the suprapapillary layers of psoriatic lesions. *J. Invest. Dermatol.*, **106**, 526–530.
32) Kuramoto, Y. & Tagami, H. (1989) Histopathologic pattern analysis of human intracutaneous tuberculin reaction. *Am. J. Dermatopathol.*, **11**, 329–337.
33) Larsen, C.G., Anderson, A.O., Appella, E., Oppenheim, J.J. & Matsushima, K. (1989) The neutrophil-activating protein (NAP-1) is also chemotactic for T lymphocytes. *Science*, **243**, 1464–1466.
34) Lopez, A.F., Williamson, D.J., Gamble, J.R., Begley, C.G., Harlan, J.M., Klebanoff, S. J., Walterdorph, A., Wong, G., Clark, S.C. & Vadas, M.A. (1986) Recombinant human granulocyte-macrophage colony-stimulating factor stimulate in vitro mature human neutrophil and eosinophil functions, surface receptor expression, and survival. *J. Clin. Invest.*, **78**, 1220–1228.
35) Lord, P.C., Wilmoth, L.M., Mizel, S.B. & McCall, C.E. (1991) Expression of interleukin-1 α and β genes by human polymorphonuclear leukocytes. *J. Clin. Invest.*, **87**, 1312–1321.
36) Lundqvist, E.N. & Egelrud, T. (1997) Biologically active, alternatively processed interleukin-1β in psoriatic scales. *Eur. J. Immunol.*, **27**, 2165–2171.
37) Marley, W.M., Belew, P.W., Rosenberg, E.M., Urmson, J.R., Stitzel, A.E. & Spitzer, R. E. (1982) Abnormalities in the alternative pathway of complement in psoriasis. *Clin. Exp. Dermatol.*, **7**, 387–396.
38) Matsumoto, S., Takei, M., Moriyama, M. & Imanishi, H. (1987) Enhancement of Ia-like antigen expression by interferon-γ in polymorphonuclear leukocytes. *Chem. Pharm. Bull.*, **34**, 436–439.
39) Morhenn, V.B., Abel, E.A. & Mahle, G. (1982) Expression of HLA-DR antigen in skin from patients with psoriasis. *J. Invest. Dermatol.*, **78**, 165–168.
40) Mudzinski, S.P., Christian, T.P., Guo, E., Cirenza, E., Hazlett, K.R. & Gosselin, E.J. (1995) Expression of HLA-DR (major histocompatibility complex II) on neutrophils from patients treated with granulocytes-macrophage colony-stimulating factor for mobilization of stem cells [letter]. *Blood*, **86**, 2452–2453.
41) Neuman, E., Huleatt, J.W., Vargas, H., Rupp, E.E. & Jack, R.M. (1992) Regulation of MHC class I synthesis and expression by human neutrophils. *J. Immunol.*, **148**, 3520–3527.
42) Nicolas, J.-F., Chamchick, N., Thivolet, J., Wijdenes, J., Morel, P. & Revillard, J.P. (1991) CD4 antibody treatment of severe psoriasis [letter]. *Lancet*, **338**, 321.
43) Ohkohchi, K., Torinuki, W. & Tagami, H. (1989) Plasma concentrations of complement-modulating proteins (C1 inhibitor, C4 binding protein, factor H and factor I) inflammatory dermatoses wit special reference to psoriasis. *Dermatologica*, Suppl. 1, **179**, 30–34.
44) Petroni, K.C., Shen, L. & Guyre, P.M. (1988) Modulation of human polymorphonuclear leukocyte IgG Fc receptors and Fc receptor-mediated functions by IFN-γ and glucocorticoids. *J. Immunol.*, **140**, 3467–3472.
45) Pinkus, H. & Mehregan, A.H. (1966) The primary histologic lesion of seborrheic dermatitis and psoriasis. *J. Invest. Dermatol.*, **46**, 109–116.
46) Poizot-Martin, I., Dhiver, C., Mawas, C., Olive, D. & Gastaut, J.A. (1991) Are CD4 antibodies and peptide T new treatments for psoriasis? [letter]. *Lancet*, **337**, 1477.
47) Prinz, J.C., Grob, B., Vollmer, S., Trommler, P., Strobel, I., Meurer, M. & Plewig, G. (1994) T cell clones from psoriasis skin lesions can promote proliferation in vitro via secreted products. *Eur. J. Immunol.*, **24**, 593–598.
48) Ragaz, A. & Ackerman, A.B. (1979) Evolution, maturation, and regression of lesions of psoriasis. *Am. J. Dermatopathol.*, **1**, 199–214.
49) Reinisch, W., Tillinger, W., Lichtenberger, C., Gangl, A., Willheim, M., Scheiner, O. & Steger, G. (1996) In vivo induction of HLA-DR on human neutrophils in patients

treated with interferon-α [letter]. *Blood*, **87**, 3068.
50) Rosenberg, E.W., Noah, P.W., Wyatt, R.J., Jones, R.M. & Kolb, W.P. (1990) Complement activation in psoriasis. *Clin. Exp. Dermatol.*, **15**: 16–20.
51) Schlaak, J.F., Buslau, M., Jochum, W., Hermann, E., Girndt, M., Gallati, H., Buschenfelde, K.-H. & Fleischer, B. (1994) T cells involved in psoriasis vulgaris belong to the Th1 subset. *J. Invest. Dermatol.*, **102**, 145–149.
52) Schröder, J.-M. & Christophers, E. (1986) Identification of C5a des arg and an anionic neutrophil-activating peptide (ANAP) in psoriatic scales. *J. Invest. Dermatol.*, **87**, 53–58.
53) Soltani, K. & Van Scott, E.J. (1972) Patterns of sequence of tissue changes in incipient and evolving lesions of psoriasis. *Arch. Dermatol.*, **106**, 484–490.
54) Shirafuji, N., Matsuda, S., Ogura, H., Tani, K., Kodo, H., Ozawa, K., Nagata, S., Asano, S. & Takaku, F. (1990) Granulocyte colony-stimulating factor stimulates human mature neutrophilic granulocytes to produce interferon-α. *Blood*, **75**, 17–19.
55) Smith, W.B., Guida, L., Sun, Q., Korpelainen, E.I., van den Heuvel, C., Gillis, D., Hawrylowicz, C.M., Vadas, M.A. & Lopez, A.F. (1995) Neutrophils activated by granulocyte-macrophage colony-stimulating factor express receptors for interleukin-3 which mediate class II expression. *Blood*, **86**, 3938–3944.
56) Szabo, S.K., Hammerberg, C., Yoshida, Y., Bata-Csorgo, Z. & Cooper, K.D. (1998) Identification and quantitation of interferon-γ producing T cells in psoriatic lesions: localization to both $CD4^+$ and $CD8^+$ subsets. *J. Invest. Dermatol.*, **111**, 1072–1078.
57) Tagami, H., Iwatsuki, K. & Takematsu, H. (1987) Psoriasis and leukocyte chemotaxis. *J. Invest. Dermatol.*, **88**, 18S–23S.
58) Takematsu, H., Ohkohchi, K. & Tagami, H. (1986) Demonstration of anaphylatoxins C3a, C4a and C5a in the scales of psoriasis and inflammatory pustular dermatoses. *Br. J. Dermatol.*, **114**, 1–6.
59) Takematsu, H. & Tagami, H. (1993) Quantitation of chemotactic peptides (C5a anaphylatoxin and IL-8) in psoriatic lesional skin. *Arch. Dermatol.*, **129**, 74–80.
60) Terui, T., Aiba, S., Kato, T., Tanaka, T. & Tagami, H. (1987) HLA-DR antigen expression on keratinocytes in highly inflamed parts of psoriatic lesions. *Br. J. Dermatol.*, **116**, 87–93.
61) Terui, T., Rokugo, M., Kato, T. & Tagami, H. (1989a) Analysis of the proinflammatory property of epidermal cyst contents: Chemotactic C5a anaphylatoxin generation. *Arch. Dermatol. Res.*, **281**, 331–34.
62) Terui, T., Kato, T. & Tagami, H. (1989b) Stratum corneum activation of complement through the antibody-independent alternative pathway. *J. Invest. Dermatol.*, **92**, 593–597.
63) Terui, T, Zhen, Y.-X., Kato, T. & Tagami, H. (1995) Mechanism of human polymorphonuclear leukocyte adhesion to serum-treated corneocytes. *J. Invest. Dermatol.*, **104**, 297–301.
64) Terui, T., Ishii, K., Ozawa, M., Tabata, N., Kato, T. & Tagami, H. (1997) C3 production of cultured human epidermal keratinocytes is enhanced by IFNγ and TNFα through different pathways. *J. Invest. Dermatol.*, **108**, 62–67.
65) Van de Kerchief, P.C.M. & Lammers, A.M. (1987) Intraepidermal accumulation of polymorphonuclear leukocytes in chronic stable plaque psoriasis. *Dermatologica*, **174**, 224–227.
66) Weinshenker, B.G., Bass, B.H., Eber, G.C. & Rice, G.P.A. (1989) Remission of psoriatic lesions with muromonab-CD3 (Orthoclone OKT3) treatment. *J. Am. Acad. Dermatol.*, **20**, 1132–1133.