

Somatostatin, Dendritic Cells and Peptide T in Psoriasis. A Clinical, Immunohistochemical and Functional Study

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The occurrence of psoriasis is due to an interaction between a genetically predisposed individual and environmental influences, but the exact cause of the disease remains unknown. Several types of therapy can induce a temporary remission, but there is no known permanent cure. Many patients are obliged to attend day-care centers several times a week. Systemic treatment is given only to the most serious cases because of its side effects. Thus, there is a great need for more research about the pathogenic mechanisms of this disease in order to develop new effective medications without severe adverse effects and which are easy for the patient to handle.

Peptide T

Peptide T is a synthetic octapeptide designed to block the CD4 receptor and originally intended as medication for HIV-infections. In 1987, Wetterberg et al. reported an improvement in coexisting psoriasis in one patient, who was treated with peptide T for AIDS. After peptide T had been given to 3 HIV-negative cases of psoriasis



Dr Toomas Talme (*middle*) defended his thesis in on November 3rd, 2000, at Huddinge University Hospital. Faculty Opponent was Professor Klas Nordlind, Department of Dermatology, Karolinska Hospital, Stockholm (*left*), and Chairman was Professor Jan Marcusson, Haukeland University Hospital, Bergen (*right*).

with promising results, we performed an open phase 1 study, where 9 patients with chronic plaque psoriasis were treated with peptide T during 4 weeks (I). During the study, 5 patients showed an improvement in their PASI score of at least 50%. Notably, 2 patients with chronic psoriasis for several years, were free from lesions for more than 6 months after the peptide T therapy. We also followed the activity of psoriasis by histological scoring and assessing epidermal thickness on serial biopsies taken from one selected lesion (II). These methods permitted a more unbiased assessment of healing in this small, open, clinical study, since they were done on blind-coded specimen. Four weeks after discontinuing of peptide T, all the patients who had improved clinically also showed a significant reduction in

their epidermal thickness and histologic score.

Psoriasis is characterized by a clustering of activated T-cells in the skin lesions. The presence of these cells is believed to be one of the features that controls psoriasis since treatments that inhibit T-cell activation (e.g. cyclosporine and tacrolimus) cause the lesions to resolve. Peptide T has been demonstrated to bind to CD4. Substances which target various surface proteins that are needed for the interaction between T-lymphocytes and antigen-presenting cells and abolish subsequent T-cell activation provide a novel rational approach for the treatment of psoriasis. Advanced clinical trials with such substances are currently in progress. In the case of peptide T, there is, of course, a need

for larger controlled clinical studies before we know whether it can be used to treat psoriasis.

Somatostatin expression in dendritic cells

Neuropeptides have biological actions on cells involved in the psoriasis process. It has been hypothesized that stressful events and local trauma cause the release of neuropeptides, such as substance P from sensory nerves in the skin which, in turn, may initiate the development of psoriasis lesions in predisposed individuals. Somatostatin immunoreactive nerve fibers and cells with dendritic morphology are found in human skin. Somatostatin has also been used in several open-label trials as infusional therapy for psoriasis.

Immunohistochemical evaluation of serial biopsies from psoriasis lesions during peptide T treatment revealed major changes in a population of dendritic cells immunoreactive for somatostatin (III). Our findings raised the question whether the somatostatin-positive cells are also affected by other established treatments for psoriasis. Serial biopsies were therefore taken from psoriasis lesions during topical treatment with clobetasol propionate (a potent corticosteroid) and calcipotriol (vitamin D₃) (IV). They showed a significant reduction in the number of somatostatin-positive cells in the dermis during healing induced by both therapies. This reduction occurred earlier in the clobetasol-treated group than in those treated with calcipotriol.

To characterize the somatostatin-positive dendritic cells in psoriatic skin further, we studied the colocalization of somatostatin and other antigens reported to be expressed by dermal dendritic cells and macrophages. In an immunohistochemical double-labeling study, we found no co-expression of somatostatin and FXIIIa, CD1a, CD35, CD45RB, CD45RO, CD68 or S-100, but a small subgroup of these cells co-expressed HLA-DR (V).

The somatostatin-positive cells seem to represent a specific population of dendritic cells, which differ from Langerhans' cells, FXIIIa-positive dendritic cells and Merkel cells (IV, V). They are found in greater numbers in psoriasis lesions than in normal skin of patients with psoriasis and healthy subjects (IV, V). The exact role of somatostatin-positive cells in psoriasis is not known, but they may affect various functions of immunocompetent cells involved in psoriasis. Somatostatin has been shown to inhibit lymphocyte proliferation, antibody production and cytokine production. Nerve-induced vasodilatation and release of substance P are also inhibited by somatostatin. A subgroup of somatostatin-positive cells found in the psoriatic epidermis co-expresses HLA-DR, which suggests that these cells are able to process and present antigens to T-cells.

Somatostatin receptor expression and function in T-cells

Most somatostatin-positive dendritic cells in psoriasis are found in the pap-

illary and upper reticular dermis where they are surrounded by lymphocytic infiltrates. Since somatostatin is able to modulate responses of the immune system, it is conceivable that the somatostatin-containing dendritic cells in psoriatic skin can regulate the function of T-lymphocytes located in the same compartment. Somatostatin exerts its effects by binding to five distinct receptors (SSTR1-5), which have recently been cloned. By using RT-PCR, we have mapped the mRNA expression of the five different somatostatin receptors in normal blood T-lymphocytes, in eight human leukemic T-cell lines and in a normal human T-cell clone (AF24) (VI). The normal T-cells expressed mRNA for SSTR1 and SSTR5 while the leukemic cell lines did not have SSTR1 and 5. The leukemic T-cell lines showed a strong expression of SSTR2, while normal T-cells had poor SSTR2 expression at the mRNA level. SSTR3 and 4 were generally present in all the normal and leukemic T-cells examined. Normal T-lymphocytes and all the T-cell lines studied were negative with respect to somatostatin mRNA expression. Although T-cells can respond to somatostatin, they do not seem to produce the neuropeptide themselves.

Controlled lymphocyte motility is a vital feature of the immune system and lymphocytes undergo a continuous transition between an intravascular and an extravascular state. Extracellular matrix components, such as fibronectin, collagen type IV and laminin, are present in basement membranes, perivascular connective tissue and connective tissue in inter-

stitial compartments of various organs. After extravasation, interactions with these components play a crucial role in the ability of T-lymphocytes to migrate into tissues, such as the skin, and localize in specific areas. To further clarify the function of the somatostatin receptors in this context, we studied the effect of subtype specific signaling on T-cell adhesion, using somatostatin analogs specific for various receptors (VI). We found that somatostatin analogs specific for SSTR2 and/or SSTR3 enhanced adhesion of T-cells to FN and, to a certain extent, to CIV and LAM.

Treatments, which interfere with the recruitment of skin-homing lymphocytes by inhibiting cell adhesion, and can prevent T-lymphocytes trafficking into the skin, should be useful as

therapy for inflammatory skin disorders. The present study indicates that somatostatin may be a major regulator of the capacity of T-lymphocytes to adhere to ECM components. Our findings suggest that different SSTR subtypes may be useful targets for therapy in disorders involving T-cells. The development of selective SSTR receptor antagonists should provide more information in this regard.

List of original publications

- I. Marcusson JA, Talme T, Wetterberg L, Johansson O. Peptide T - a new treatment for psoriasis? A study of nine patients. *Acta Derm Venereol* 1991; 71: 479-483.
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- VI. Talme T, Ivanoff J, Hägglund M, Ivanoff A, Joost van Neerven RJ, Sundqvist KG. Somatostatin receptor (SSTR) expression and function in normal and leukemic T-cells. Evidence for selective effects on adhesion to extra-cellular matrix components via SSTR2 and/or 3. *Clin Exp Immunol* (accepted).