Neuroimmunologic Aspects of Psoriasis

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Psoriasis is a multifactorial disease with genetic and environmental interactions. Some of the unique features of psoriasis still do not have scientific explanations. Psoriasis may appear at any age,[1,2] often develops at a site of trauma,[3,4] and is symmetrically distributed on the body. Various exogenous and endogenous factors, such as stress, streptococcal infection, xerosis, and certain drugs, play a key role in the natural history of psoriasis.[3-5]

Cytokines, chemokines, growth factors, adhesion molecules, neuropeptides, and T-cell receptors act in integrated ways to create unique inflammatory and proliferative processes typical of psoriasis. In this article, we will present the role of neurogenic inflammation in the pathogenesis of psoriasis.

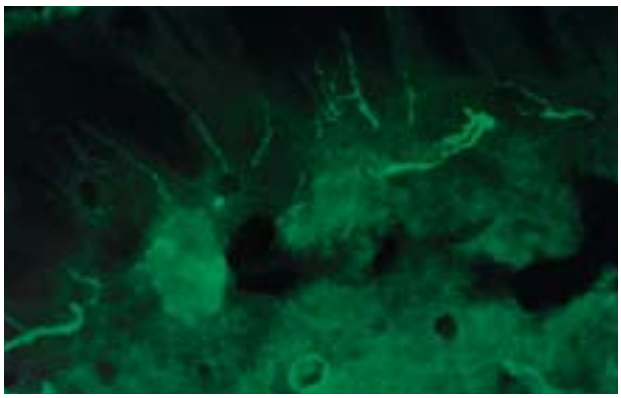

FIGURE 1. Psoriasis biopsy stained with NGF receptor antibody shows multiple NGF-R positive nerve fibers in the papillary dermis (magnification, ×200).

Psychoneuroimmunology, Neurogenic Inflammation and Psoriasis

In several studies of large groups of patients, it has been observed that stress plays an important role in the onset and exacerbations of psoriasis. In a survey of 5600 psoriasis patients, 33% reported that the onset was associated with stressful events.[5] Fava et al[6] correlated the appearance or exacerbation of psoriasis with stress in 80% of their patients, and Gaston et al[7] reported a statistically significant relationship between adverse life events and severity of psoriasis. Studies have shown that anxiety, depression, marital or financial problems, and "near-death" experiences trigger the onset or increased severity of psoriasis. Our recent data from the Psoriasis Research Institute revealed that 45.2% (295 of 652) patients recalled appearance of new lesions when they were worried.

How stress influences the inflammatory and proliferative processes of psoriasis is not clearly understood. Psychoneuroimmunology is revealing the cellular and molecular events involved with emotional stress and the pathogenesis of an inflammatory reaction. The bidirectional communication between the nervous system and the immune system is mediated by the endocrine system. The regulatory role of the nervous system on an inflammatory process is now well established.[8,9]

Among the cardinal features of psoriasis, in addition to stress as a trigger, are symmetry, exacerbations and remissions, and exogenous and endogenous Köbner phenomenon. Correlating the clinical observation that stress exacerbates psoriasis and the symmetric distribution, we proposed a role for neuropeptides in its pathogenesis.[10] Our theory proposes that the release of substance P (SP) and other neuropeptides from unmyelinated terminations of sensory nerve fibers in the skin causes local neurogenic inflammatory responses that trigger psoriasis in a genetically predisposed person.

To elucidate the role that cutaneous nerves and neuropeptides play in the pathogenesis of psoriasis, we initiated studies at the Psoriasis Research Institute with Anita Naukkarinen,[11] a Finnish neuroanatomist. Dr. Naukkarinen demonstrated an increased number of SP-positive sensory nerve fibers in psoriatic lesions as compared with control skin. This encouraged many investigators to pursue extensive studies of the neuroimmunology of the skin. Subsequently, many studies have confirmed that, compared with the controls, there is a marked elevation of several neuropeptides, such as SP, vasoactive intestinal peptide (VIP), and calcitonin gene-related peptide (CGRP).[12-15] Immunohistochemical studies have revealed an abundance of cutaneous nerves (Figure 1)

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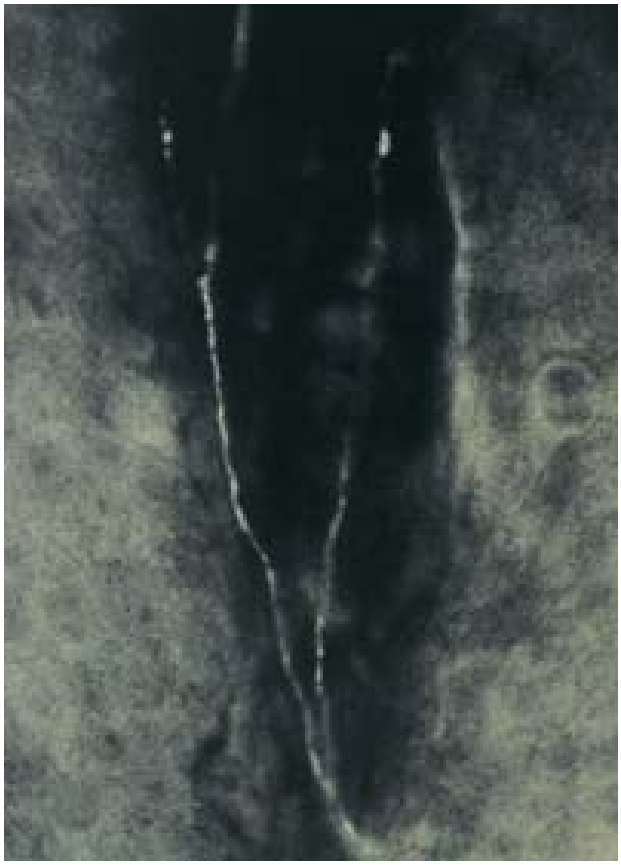

FIGURE 2. Psoriasis biopsy stained with CGRP antibody shows CGRP-positive fibers extending from the dermis to the epidermis (magnification, ×200).

with increases in SP, VIP, and CGRP (Figure 2). Neuropeptides can play a significant role in the inflammatory and proliferative processes of psoriasis. SP is chemotactic to neutrophils,[16] activates T cells,[17] and releases interleukin-1 from keratinocytes.[18] VIP is mitogenic to keratinocytes;[19] CGRP acts synergistically with SP to stimulate keratinocyte proliferation;[20] and both VIP and CGRP are potent mitogenics for endothelial cells.[21]

There is good clinical evidence that the absence of sensory nerve innervation corresponds with the absence of psoriasis.[22] A 68-year-old Caucasian male had chronic plaque psoriasis involving the elbows, forearms, knees, and legs. He underwent reconstructive surgery on the left knee for osteoarthritis. In 6 to 8 weeks following surgery, a large plaque on the lateral surface of the left leg resolved. On examination, the skin at the resolved site was found to be anesthetic due to nerve damage following surgery. A comparable plaque on the contralateral leg remained active. In another patient, it was observed that psoriasis resolved at the anesthetic area over the knee, and, with the return of sensation, psoriasis reappeared at the same site.

Is Psoriasis a Neuroimmunologic Disease?

Some investigators consider psoriasis to be an autoimmune disease induced by an unidentified antigen.[23,24] Until now, the alleged role of an antigen in psoriasis has been hypothetical—no antigen has yet been discovered for psoriasis. An antigen-induced T-cell activation

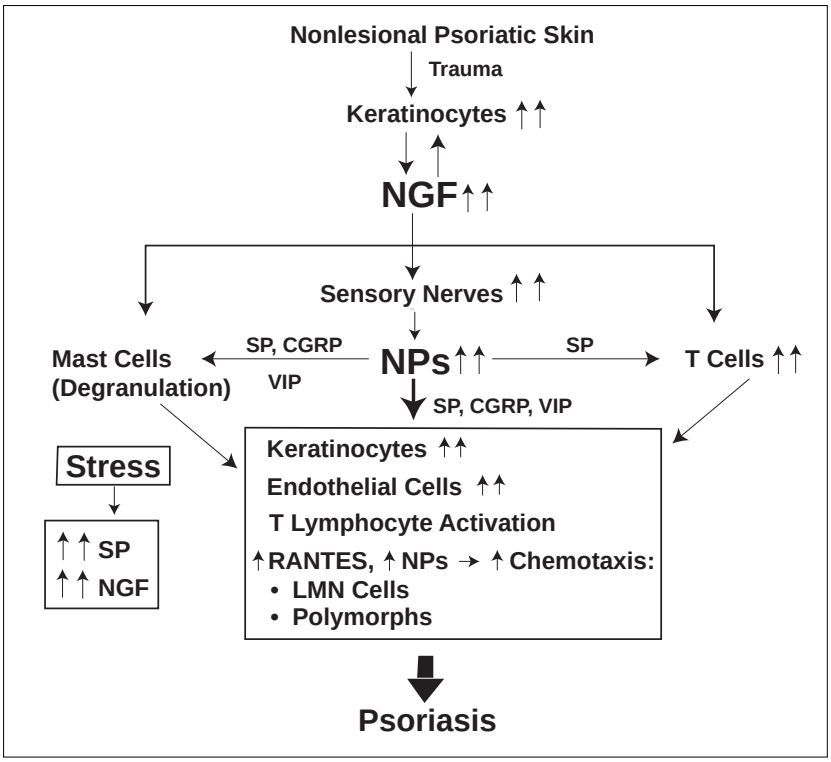

FIGURE 3. Role of neurogenic inflammation in the pathogenesis of psoriasis. ↑ indicates increase in amount;↑↑, increase in number; LMN, lymphonuclear cells; NPs, neuropeptides.

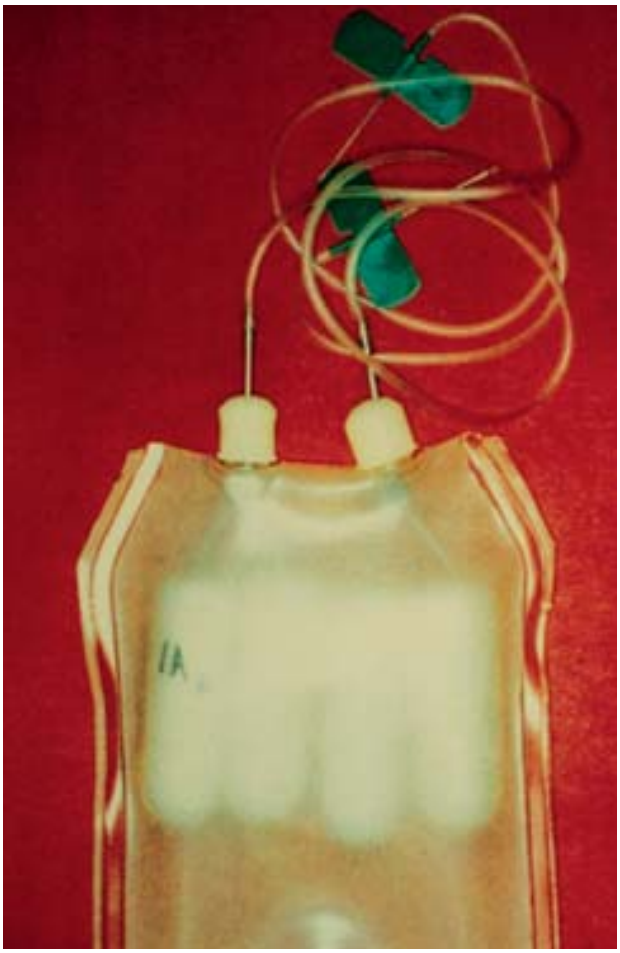

FIGURE 4. Alzet® mini-osmotic pumps.

process alone fails to clarify various salient features of psoriasis; it does not explain the Köbner phenomenon, the symmetrical distribution of psoriasis lesions, the proliferation of cutaneous nerves, and the up-regulation of neuropeptides in psoriatic tissue.[10-15] The antigen-induced T-cell activation process also does not explain the striking clinical observation that psoriasis resolves at sites of anesthesia.[22]

Therefore, a search was prompted for the underlying cause of neural influence in the inflammatory processes of psoriasis. Because nerve growth factor (NGF) plays a role in regulating innervation[25] and up-regulating neuropeptides,[26,27] we decided to investigate the expression of NGF in the lesional and nonlesional psoriatic skin, normal skin, and skin with other inflammatory diseases.

In an immunohistochemical study, we found that keratinocytes in lesional and nonlesional psoriatic tissue express high levels of NGF compared with the controls (Table I).[28] In a separate publication, we reported a marked up-regulation of nerve growth factor–receptor (NGF-R) in psoriatic lesions.[29] Similarly, Fantini et al[30] observed that levels of NGF are higher in psoriatic lesions.

Several functions of NGF are relevant to the inflammatory and proliferative processes of psoriasis. NGF promotes keratinocyte proliferation and protects keratinocytes from apoptosis.[31,32] NGF also degranulates mast cells and induces migration of these cells, both of which are early events in a developing lesion of psoriasis.[33,34] In addition, NGF activates T lymphocytes and recruits inflammatory cellular infiltrates.[35-37] We have observed that NGF induces expression of the potent cytokine RANTES in the keratinocytes. RANTES is chemotactic for resting CD4+ memory T cells and activated naïve and memory T cells.[38] It is possible that in a developing psoriatic lesion, up-regulation of NGF induces the influx of mast cells and lymphocytes, which in turn initiates an inflammatory reaction that contributes to the pathogenesis of psoriasis.

There is also a marked up-regulation of NGF in the nonlesional psoriatic skin (Table I). In another study in which we investigated NGF-R expression, we found similar results (Table I). We studied the expression of NGF and NGF-R in lichen

TABLE I.

Expression of NGF in the Keratinocytes and NGF-R Within Papillary Dermal Nerves in Lesional and Nonlesional Psoriatic Skin, Inflammatory Dermatoses Including Lichen Planus and Normal Skin

Type of Skin	NGF^+ (KC/mm^2)	$NGF\text{-}R^+$ /3mm
Lesional Psoriasis	84.68 ± 46.35 (n=8)	34.0 ± 23.0 (n=26)
Nonlesional Psoriasis	44.80 ± 29.96 (n=8)	28.1 ± 4.5 (n=8)
Normal Skin	18.88 ± 11.76 (n=5)	18.88 ± 11.76 (n=8)
Lichen Planus	7.54 ± 16.86 (n=5)	
Inflammatory Dermatoses		12.75 ± 22.0 (n=12)

All values displayed as mean number of positively stained keratinocytes/mm^2 (KC/mm^2) in epidermis and papillary dermal nerves / 3mm biopsy ± standard deviation.

NGF indicates nerve growth factor; NGF-R, nerve growth factor–receptor.

planus, which is also an inflammatory skin disease. There was no up-regulation of NGF in the keratinocytes and no increased expression of NGF-R in the cutaneous nerves of lichen planus lesions.[28,29]

Increased expression of NGF in nonlesional skin may play a key role in the development of a Köbner reaction. Up-regulation of NGF in injured skin has been confirmed.[39] Proliferation of keratinocytes induced by a wound will result in significantly higher levels of NGF in lesion-free skin compared with control skin. Elevated levels of NGF would induce an inflammatory response proliferation of nerves and up-regulation of neuropeptides such as SP and CGRP.[25-27,33-37] Neuropeptides and NGF, in addition to their pro-inflammatory effects, promote keratinocyte proliferation.[19,20,31,32] Mitogenesis of keratinocytes will result in increased levels of NGF. A vicious cycle of a proliferative and inflammatory process will be established in a person who is genetically psoriatic (Figure 3). Thus, a wound in patients with psoriasis frequently results in papulosquamous lesions (Köbner phenomenon), whereas in subjects without psoriasis, the expression of NGF is 3 to 4 times less per square millimeter of epidermis compared to nonlesional psoriatic skin (Table I). The healing events, therefore, do not generate the critical levels of NGF and neuropeptides to initiate or maintain cascades essential for a chronic inflammatory reaction.

Studies have reported that psychosocial stressful events result in increased levels of NGF in blood, as well as the NGF messenger RNA synthesis in the hypothalamus.[40-42] Thus, it is likely that a similar cascade of events as mentioned in the preceding paragraph occurs in distressed psoriatic patients. Stressful events can alter SP levels in the central nervous system and in the periphery. In an animal model, it has been reported that stress can increase levels of SP in the adrenal glands by activating the descending autonomic fibers.[43] Some of the descending autonomic fibers innervate opoid interneurons in the dorsal horn, and because interneurons exist in the spinal cord for the SP-containing nerves, it is possible that descending autonomic paths can cause release of cutaneous neuropeptides.[44] Therefore, neurogenic inflammation could play a crucial role in the development of psoriatic lesions and also be responsible for exacerbation of psoriasis during stressful life events.

Activated T cells are present in psoriatic lesions and play a key role in the pathogenesis of psoriasis. However, the key regulatory factors responsible for activation of the T cells are not known. There are studies in immunodeficient mice that suggest psoriasis can be induced by injecting activated autologous T cells in transplanted nonlesional skin.[45,46] Particularly, Wrone-Smith and Nickoloff[46] have reported that in severe combined immunodeficient mice, transplanted nonlesional psoriatic skin changes to a psoriatic plaque after intradermal delivery of autologous activated T cells. In this model, T cells were activated with an antigen cocktail.[46] Because such an artificial antigen cocktail does not exist in a lesional or nonlesional psoriatic skin, it is possible that local epidermal and dermal factors like NGF and SP may be responsible for lesional T lymphocyte activation. Recently, we have identified increased levels of RANTES, a psoriatic keratinocyte and β-chemokine.[47] Increased levels of RANTES induced by NGF may also be a contributing factor for the activation of the lesional T cells, since RANTES is a known activator of T cells.[38]

The Application of Psychoneuroimmunology to the Treatment of Psoriasis

A direct pharmacologic approach is to develop drugs that can deplete or block the release of neuropeptides or block the receptor sites of neuropeptides. So far, only a few neuropeptide-modulating agents have been evaluated. Capsaicin (*trans*-8-Methyl-*N*-vanillyl-6-nonenamide), the extract of the hot pepper, depletes neuropeptides from the sensory C nerve fibers.[48] Topical use of capsaicin has been reported to be effective in psoriasis,[49] but it is unsuitable because it causes significant burning of the skin. Somatostatin is another well-known SP inhibitor.[50] Sandostatin, a somatostatin analog, has also been reported to be efficacious in psoriasis;[51] however, a high frequency of gallstones was noted in the patients who used it.

At the Psoriasis Research Institute, we are evaluating antagonists and agonists to selected neuropeptides, with the expectancy of identifying pharmacologic agents to counter neurogenic inflammation. For evaluating the efficacy of new drugs, we have adopted a novel drug delivery system. We use 2 to 4 Alzet® 2 mL osmotic pumps placed in a pouch (Figure 4). One or 2 pumps deliver the placebo and 1 or 2 pumps deliver the active ingredient to 2 discrete lesions.[52] This method offers several advantages over systemic or conventional topical routes of administration. The problem of transfer across the stratum corneum is avoided. In addition, the direct intralesional injection of a compound into an individual psoriatic plaque permits continuous administration of microliter amounts of drug into a discrete area for several weeks.

Peptide T, a synthetic octapeptide, competes with VIP at the receptor site.[53] The first report of the efficacy of peptide T for psoriasis was in an AIDS patient, in whom psoriasis improved following intravenous infusions of peptide T.[54] We evaluated the efficacy of peptide T by direct administration into psoriatic lesions

with a mini-osmotic pump.[52] In this double-blind placebo-controlled study, there was clinical and histopathologic improvement in the treated lesions.

The discovery of the compound CP-96,345, a nonpeptide SP receptor antagonist, has created opportunities to evaluate the effects of a natural killer cell–1 (NK-1) receptor antagonist.[55] Currently, several NK-1 receptor antagonists are being evaluated for various inflammatory diseases like psoriasis, rheumatoid arthritis, and ulcerative colitis.

There is unequivocal evidence that stress is a triggering factor for the appearance or exacerbation of psoriasis.[5-7] Figure 4 provies plausible explanations as to how emotional stress can influence the inflammatory and proliferative processes of psoriasis. It is possible that relaxation measures would counter the psychoneurologic mechanisms contributing to the pathogenesis of psoriasis. Stress relaxation therapies have been reported to be beneficial for psoriasis.[56,57] Since pharmacologic antagonists to specific neuropeptides are not yet available, we are currently emphasizing a total care program for psoriasis[58] that not only includes exemplary medication but also addresses the contributing role of mind-body synchrony on human physiology. In a total care program, special attention is given to the following: (1) complete physical and psychologic evaluation to elucidate the underlying physical and mental stressful factors; (2) assessment of patient's lifestyle practices; (3) patient education (self-help/mutual aid group); and (4) stress relaxation training.

It is essential to elucidate the exogenous and endogenous factors responsible for the increased morbidity of psoriasis. Any treatment that does not address the contributing role of these factors will be only partially effective.

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