Immunity, Stress, and Nail Psoriasis

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DISCLOSURES

Galderma: Advisory Board - Honoraria
Castle Biosciences: Advisory Board - Honoraria
Vellius: Advisory Board - Stock Options
Elysium Health: Scientific Advisory Board - Stock Options
National Rosacea Society: Grant Support
NIH: Grant Support
Dinner
Stress is a medical term for a wide range of strong external stimuli, both physiological and psychological, which can cause a physiological response called the general adaptation syndrome, first described in 1936 by Hans Selye in the journal Nature.
Processive stressors are elements in the environment perceived as potential dangers. These do not cause damage directly, but are processed in the cerebral cortex. The processed information is then sent via the limbic system in the hypothalamus, where they activate the autonomic nervous system, resulting in a fight-or-flight (or sympathetico-adrenal) response.
Systemic stressors cause a disturbance in the organism's homeostasis, such as through physical perturbations (injury, illness, etc.). Often both types of stressors occur simultaneously. They are usually accompanied by pain and/or intensive emotions.
“Stress can cause psoriasis to appear suddenly (flare) or can make symptoms worse.”

Source: http://www.wakehealth.edu/Health-Encyclopedia/Health-Topics/Psoriasis.htm

Wake Forest Baptist Medical Center Website
Reportedly, Psoriasis, Atopic Dermatitis, Acne and Rosacea are Exacerbated by Stress


Alleviation of Stress Reportedly Improves Atopic Dermatitis and Psoriasis


Psoriatic Arthritis Has Also Been Reported to Worsen With Stress


Psychological Distress Impairs Clearance of Psoriasis in Patients Treated With Photochemotherapy

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**Objectives:** To assess whether psychological distress affects treatment outcome in psoriasis.

**Design:** Cohort study of patients with psoriasis receiving psoralen–UV-A (PUVA) photochemotherapy.

**Settings:** Two university hospital dermatology departments.

**Patients:** One hundred twelve patients with chronic plaque psoriasis.

**Main Outcome Measures:** We assessed clinical severity of psoriasis, psychological distress, and other potential confounders of treatment outcome such as skin phenotype, family history of psoriasis, and alcohol intake before starting PUVA therapy. Clinical severity of disease and response to therapy were assessed at every fourth appointment.

**Results:** Pathological or high-level worry was the only significant \( P < .01 \) predictor of time taken for PUVA to clear psoriasis. Event curves of time to clearance significantly differed between high- and low-level worry groups (log rank test, 6.64; \( df = 1; P = .01 \)). Patients in the high-level worry group cleared with PUVA treatment at a rate 1.8 times slower than that of the low-level worry group (ExpB = 1.81; 95% confidence interval, 1.13–2.90). Fiftieth percentile time to clearance of psoriasis in the high- and low-level worry groups showed a median difference of 19 days.

**Conclusions:** Psychological distress, in the form of excessive worrying, has a significant and detrimental affect on treatment outcome in patients with psoriasis. Patients with psoriasis who are classified as high-level worriers may benefit from adjunctive psychological intervention before and during treatment. These findings provide further evidence of the existence of a brain-skin axis.

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The Role of Cutaneous Sensory Nerves in the Maintenance of Psoriasis

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ABSTRACT: This is a case report of two patients with chronic plaque psoriasis in whom cutaneous nerve damage resulted in clearance of the disease at that site. In both patients reappearance of the psoriasis occurred with recovery of cutaneous sensation. The role of cutaneous sensation in the maintenance of skin disorders and, in particular, the role of neuropeptides in the pathogenesis of psoriasis are discussed.

induce a local remission of the disease. We report on two patients in whom established psoriatic plaques resolved following surgical trauma to cutaneous nerves.

Case Reports

Case 1

The patient, a 48-year-old physician, has been previously reported by Dewing. For 10 years he had suffered from widespread, chronic plaque psoriasis, which included documented, persistent plaques occurring symmetrically over both knees. The patient had surgery to the right knee to

Remission of Psoriasis Vulgaris From the Use of Nerve-Blocking Agents

Since that first patient treated by lidocaine, I have treated a considerable number of other patients, the subjects of long-standing psoriasis, either with lidocaine or procaine hydrochloride. Many of these patients have had striking remissions in their disease.

Henry Harris Perlman, MD, Phar D

Letters to the Editor
Arch Dermatol 105: 128-129, 1972
Reproduced from Protective [Effect of Sensory Denervation in Inflammatory Arthritis (Evidence of Regulatory Neuroimmune Pathways in the Arthritic Joint). D Kane, J C Lockhart, P V Balint, C Mann, W R Ferrell, I B McInnes, 64, 325-327, copyright notice 2005 with permission from BMJ Publishing Group Ltd.]
Cutaneous Denervation of Psoriasiform Mouse Skin Improves Acanthosis and Inflammation in a Sensory Neuropeptide-Dependent Manner

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Classically, Langerhans cells were considered to be the principal antigen presenting cells of the epidermis. When activated or matured, they have been shown to be capable of presenting haptens, alloantigens, immunogenic proteins and tumor antigens for induction or elicitation of immune responses.
Epidermal Langerhans Cell-Deficient Mice Develop Enhanced Contact Hypersensitivity

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Summary

Epidermal Langerhans cells (LcCs), a distinct skin-resident dendritic cell population, acquire antigen in the skin and migrate to draining lymph nodes where they are thought to initiate adaptive immune responses. To examine the functional requirement of LcCs in skin immunity, we generated B10 congenic mice in which the regulatory elements from human Langerhans were used to drive expression of human CD1d. The resulting mice have a consensual and durable absence of epidermal LcCs but are otherwise intact. Unexpectedly, we found that contact hypersensitivity (CHS) was amplified rather than abrogated in the absence of LcCs. Moreover, we showed that CD1d-expressing the priming and not the effecter phase. Thus, LcCs not only were dispensable for CHS, but they served to regulate the response, a previously unappreciated function.

Introduction

Dendritic cells (DCs) are very efficient at activating naïve T cells in vitro and in vivo (Blanchard et al., 2000). They can acquire antigen via multiple routes including endocytosis, pinocytosis, and direct infection by pathogens. (Blanchard et al., 2000). DCs also have an array of receptors for pathogen-associated molecular patterns that stimulate DC activation and maturation (Nakai et al., 2004). Though DCs do not appear to have these properties, they are nevertheless functionally and phenotypically diverse. They have been categorized based on the expression of numerous markers including CD40, CD80, CD86, and C-type lectin receptors such as DEC205 (Herm et al., 2001; Shottman and Liu, 2002). Although DCs were initially identified because of their stimulatory capacity, a growing body of data has demonstrated that immature DCs as well as certain subsets of mature DCs promote tolerance rather than immunity (Ryan, 2003; Steinman et al., 2003; Steinman and Nussenzweig, 2005). DCs can also be categorized by whether they are resident in secondary lymphoid tissue or in parenchymal tissues. Unlike DCs in secondary lymphoid tissue, tissue-resident DCs do not typically have direct access to naïve T cells. Rather, it is thought that these cells function as sentinels that acquire Ag in the periphery and become activated locally (Steinman et al., 2001). Once activated, they migrate to T cell zones of regional lymph nodes (RLN), where they are thought to either present tissue-acquired Ag or transfer Ag to resident secondary lymphoid tissue DCs for presentation, thereby stimulating a primary response (Carboni et al., 2004; Romani et al., 2003). Despite evidence for priming of some immune responses both directly by secondary lymphoid tissue-resident DCs and in other cases by tissue-resident DCs after migration, their relative role remains unclear.

Langerhans cells (LCs) are a subset of tissue DCs located in the epidermis and are thus the first APCs to contact pathogens at the skin surface (Romani et al., 2003). Immature LCs residing in skin collect antigen, and upon various stimuli, they mature and migrate to draining LNs (Steinman et al., 2001; Kajiya et al., 1999). Thus, they are presumed to play a key role in promoting immune responses. LC function has been examined in a number of different systems. Contact hypersensitivity (CHS) is extraordinarily applied haptens, a model for contact dermatitis, is a classical skin response in which LCs are thought to play a role (Lilleberg, 1981). Treatment with ultraviolet light prior to priming with hapten eliminates LCs from the skin and initiates the development of CHS, thereby suggesting that LCs are required for the development of a CHS response (Schwartz, 1995; Tewes et al., 1986). Supporting this notion, more recent data have demonstrated that LCs that have emigrated to the draining LN can directly present antigen secreted from keratinocytes (Mayerova et al., 2004). Moreover, LCs are sufficient for the development of cutaneous GVHD (Mentzel et al., 2004). Although these studies indicate that LCs can promote and are possibly necessary for T cell priming, opposite conclusions have been reached in other settings. After HSV infection of either vaginal epithelium or abraded flank skin, the DCs presenting HSV antigen to T cells in draining LNs did not appear to include LCs (Nakanishi et al., 2003; Zhao et al., 2003). Thus, it appears that under certain circumstances, LCs may be dispensable for stimulation. As this manuscript was being prepared, two groups reported that they had developed mice that express the diphtheria toxin (DT) receptor on LcCs and have a transient depletion of LcCs after injection of DT (Bienz et al., 2005; Klesse et al., 2005). Interestingly, our group observed that CHS was diminished, while the other group found it was unchanged in transiently LcC-depleted mice.

From these studies above, it is clear that in spite of the likely importance of LCs in skin immune responses, their roles require more precise definition. We have addressed this by generating transgenic mice that contain an attenuated form of diphtheria toxin under control of genetic elements that restrict expression to LCs. These...
**CALCITONIN GENE-RELATED PEPTIDE (CGRP)**

CGRP IS A NEUROPEPTIDE AND POTENT VASODILATOR PRESENT IN CENTRAL AND PERIPHERAL NERVES.

A NUMBER OF EFFECTS OF CGRP ON IMMUNE FUNCTIONS HAVE BEEN REPORTED:

- Association with LC in esophageal mucosa
- Inhibits T cell proliferation and IL-2 production
- Presence of specific receptors on macrophages
- Inhibits several macrophage functions including antigen presentation
DC Lymph Node T Cells

Immunization Elicitation
Dose-dependent inhibition of DTH by CGRP

Footpad Swelling (0.01mm)

CM  0  10pM 100pM 1nM 10nM

24h  38h

+ TAA
Many epidermal LC are closely-associated anatomically with nerves that contain CGRP, a peptide that appears to regulate LC function.

A small proportion of LC in normal skin appear to have immunoreactive CGRP at their surfaces.

These results illustrate a possible locus of interaction between the nervous system and cutaneous immune function.
Epidermal Langerhans Cell-Deficient Mice Develop Enhanced Contact Hypersensitivity

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Summary

Epidermal Langerhans cells (Lcs), a distinct skin-resident dendritic cell population, acquire antigens in the skin and migrate to draining lymph nodes where they are thought to initiate adaptive immune responses. To examine the functional requirement of Lcs in skin immunity, we generated BAC transgenic mice in which the regulatory elements from human Langerin were used to drive expression of diphtheria toxin. The resulting mice have a constitutional and dually penetrant skin disease resembling dermatitis (Kaplan et al., 2005). Unexpectedly, we found that contact hypersensitivity (CHS) was augmented rather than abrogated in the absence of Lcs. Moreover, we showed that Lcs act during the priming and not the effector phase. Thus, Lcs not only were dispensable for CHS, but they served to regulate the response, a previously unappreciated function.

Introduction

Dendritic cells (DCs) are very efficient at activating naive T cells and in vivo in vivo (Banchereau et al., 1991). They can acquire antigen via multiple routes including endocytosis, phagocytosis, and direct infection by pathogens (Banchereau et al., 1991). DCs also have an array of receptors for pathogen-associated molecular patterns (Dendritic Cell-Activating Lipopolysaccharide and Medullin, 2004). Though DCs as a class share these properties, they are nonetheless functionally and phenotypically diverse. They have been categorized based on the expression of numerous markers including CD86, CD80, CD1b, B220, and C-type lectin receptors such as DEC205 (Pant et al., 2001; Stromman and Lio, 2002). Although DCs were initially identified because of their stimulatory capacity, a growing body of data has demonstrated that DCs can induce both tolerance to self and tolerance to self-reactive T cells in vivo via the secretion of IL-10 (Shlomchik et al., 2003). Stromman and Lio, 2002). DCs can also be related by whether they are resident in secondary lymphoid tissue or in parenchymal tissues. Unlike DCs in secondary lymphoid tissue, tissue-resident DCs do not typically have direct access to naive T cells. Rather, it is thought that these cells function as sentinels that acquire Ag in the periphery and become activated locally (Shlomchik et al., 2001). This study was performed to determine whether Langerhans cells (Lcs) function as a competence is also thought to play a role in the development of CHS (Schwarz, 1989; Tawes et al., 1985). Supporting this notion, mice with defective Lcs is a crucial skin response in which Lcs are thought to play a role in the development of CHS (Schwarz, 1989; Tawes et al., 1985). Supporting this notion, mice with defective Lcs

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CD4+ T cell

DC

IL-12
IFN-γ

TGFβ

IFN-γ

Th1

GATA-3
STAT6

IL-4

Th2

IL-17
IL-22

RORγ
STAT3

Th17

IL-17

RORγ
STAT3

IL-22

AHR

Th22

TGFβ

TNFα

FoxP3

Treg
LC Expression of Neuropeptide Receptors

PAC1  VPAC1  VPAC2  GRP
Antigen Presentation Assay

1. BALB/c
2. LC
3. +/- PACAP or VIP
4. 2 h
5. Wash 4X
6. Coculture LCs and DO11.10 T cells +/- OVA\textsubscript{323-335}
7. 48 h
8. Measure cytokine production (ELISA)
PACAP and VIP Enhance Presentation for an IL-17 Response
VIP and CGRP concentrations are elevated in the plasma of patients with psoriasis


CGRP is present on the surface of endothelial cells in lesions of psoriasis

Systemic administration of CGRP or substance P significantly inhibits loss of the phenotype with denervation.
Co-culture of Endothelial Cells in Antigen Presentation Assay

- Endothelial cells
- +/- CGRP or +/- NE
- Wash 4x
- Co-culture endothelial cells, LCs and DO11.10 Tg CD4+ T cells +/- OVA\textsubscript{323-339}
- Measure cytokine production (ELISA)
- 48 h
Exposure of bEnd.3 cells to CGRP or NE biases LC Ag presentation towards an IL-17A response while decreasing IL-4 and IFNγ responses
The Effect of CGRP on Biasing LC Ag Presentation Towards an IL-17A Response Does Not Depend Upon Cell-Cell Contact
Reprinted from Immunity, Kashem SW, Riedl MS, Yao C, Honda CN, Vulchanova L, Kaplan DH, Nociceptive Sensory Fibers Drive Interleukin-23 Production from CD301b+ Dermal Dendritic Cells and Drive Protective Cutaneous Immunity, 515-26, copyright 2015, with permission from Elsevier.
PACAP, VIP, CGRP, (NE) and skin nociceptors have activities that may promote IL-17/Th17 activity. If stress induces release of these factors and/or the activity of skin nociceptors, such mechanism(s), may account for stress induced exacerbation of psoriasis, including nail psoriasis.
Has the time come for stress management techniques to be part of the armamentarium for treating skin disorders? If so, which one(s)?

Autogenic training
Biofeedback
Deep breathing
Meditation
Mind-body relaxation
Zen Yoga
Progressive Muscle Relaxation

Pranayama
Visualization
Yoga Nidra
Self-hypnosis
Qigong
Zhineng Qigong
Et cetera…….
• Inflammatory skin disorders almost certainly are influenced by stress and neurologic status.
• Inflammatory skin disorders induce stress and affect quality of life.
• Pathways by which the nervous system can influence cutaneous immunity and inflammation have been uncovered.
• In selected patients, it is reasonable to consider stress-alleviation strategies including counseling, support groups and psychotherapy.