Does Stress Make My Rash Worse?

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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
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 sympathethico-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 may worsen numerous skin conditions, including hives, psoriasis, acne, and rosacea, and it is one of the most common causes of eczema. Unexplained itching may also be caused by stress.”

Source: http://umm.edu/health/medical/reports/articles/stress#ixzz39LPAaPeN

University of Maryland Medical Center Website
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In this model, mice develop dermatitis in conventional housing but not in a specific pathogen free environment. Water avoidance stress leads to dermatitis even in the SPF environment.

Reportedly, psoriasis, atopic dermatitis (AD), acne and rosacea are exacerbated by stress


Alleviation of stress reportedly improves atopic dermatitis and psoriasis


The Role of Cutaneous Sensory Nerves in the Maintenance of Psoriasis

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From the Psoriasis Research Institute, Palo Alto, California, and Deventer Hospital, Deventer, The Netherlands

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.

Fig. 1. Clearance of psoriasis at site of nerve injury on right knee.

Fig. 2. Clearance of psoriasis on right palm and elbow after nerve injury.

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

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, Ph.D

Letters to the Editor
Arch Dermatol 105: 128-129, 1972
Cutaneous Denervation of Psoriasiform Mouse Skin Improves Acanthosis and Inflammation in a Sensory Neuropeptide-Dependent Manner

Stephen M. Ostrowski1,2,4, Abdelmadjid Belkadi1,4, Candace M. Loyd2,4, Doina Diaconu2 and Nicole L. Ward1,2,3


Well Cornell Medicine

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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 (LCs), 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 LCs in skin immunity, we generated BAC transgenic mice in which the regulatory elements from human Langenmeyer were used to drive expression of diphteria toxin. The resulting mice have a nonspecific and durable absence of epidermal LCs but are otherwise intact. Unexpectedly, we found that contact hypersensitivity (CHS) was amplified rather than abrogated in the absence of LCs. Moreover, we showed that LCs were not required to play a role in the priming and/or 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 in vitro and in vivo. Blanchard et al., 2006. They can acquire antigen via multiple routes including endocytosis, phagocytosis, and direct infection by pathogens. Blanchard et al., 2006. DCs also have an array of receptors for pattern-associated molecular patterns that stimulate DC activation and maturation (Kawai et al., 2006). Though DCs as a class share those properties, they are nevertheless functionally and phenotypically diverse. They have been categorized based on the expression of numerous markers including CD8, CD4, CD11b, CD11c, and C-type lectin receptors such as DEC205 (Hert et al., 2001; Scultsman and Liu, 2005). 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 (Bowen, 2000; Steimann et al., 2003; Steiman and Norsewitz, 2005). DCs can also be categorized by whether they are resident in secondary lymphoid tissue or in nonlymphoid tissue. 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 (Steimann et al., 2003). Once activated, they migrate to T cell zones of regional lymph nodes (LN), 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 (Steimann et al., 2001; Kripke et al., 1999). Thus, they are presumed to play a key role in priming immune responses.

LC function has been examined in a number of different settings. Contact hypersensitivity (CHS) is cutaneously applied hapten, a model for contact dermatitis, is a classical skin response in which LCs are thought to play a role (Billebauer et al., 1995). Treatment with ultraviolet light prior to priming with hapten eliminates LCs from the skin and inhibits the development of CHS, thereby suggesting that LCs are required for the development of a CHS response (Betheau, 1999; Tiesse et al., 1998). Supporting this notion, more recent data have demonstrated that LCs that have emigrated to the draining LN can directly present antigen secreted from keratinocytes (Maynorovs et al., 2004). Moreover, LCs are sufficient for the development of cutaneous GRO (Mennicke 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 antigens to T cells in draining LNs did not appear to include LCs (Ahn 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 LCs and have a transient depletion of LCs after injection of DT (Bessin et al., 2005; Kierszenberg et al., 2005). Interestingly, their group observed that CHS was abolished, whereas the other group found that it was unchanged in transiently LC-depleted mice.

From these studies above, it is clear that in spite of the likely importance of LCs in skin immune responses, their role requires 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 (LcCs), 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 LcCs in skin immunity, we generated BAC transgenic mice in which the regulatory elements from human Langerin were used to drive expression of dipeptidyl peptidase IV. Their resulting mice have a constitutive and dمعرفیق‌کننده خود، واکنشهای آنتی‌ژنی در پوست جراحی و اثرات آنها بر روی واکنش‌ها از طریق یافت کننده‌ها و تولید واکنش‌های واکنشی مورد بررسی قرار گرفته. در این مطالعه، از طریق ایجاد میمون‌های بی‌لکس پوستی (LcCs) که این گروه استندارد است، واکنش‌های واکنشی واکنشی مورد بررسی قرار گرفته. در این مطالعه، از طریق ایجاد میمون‌های بی‌لکس پوستی (LcCs) که این گروه استندارد است، واکنش‌های واکنشی واکنشی مورد بررسی قرار گرفته. در این مطالعه، از طریق ایجاد میمون‌های بی‌لکس پوستی (LcCs) که این گروه استندارد است، واکنش‌های واکنشی واکنشی مورد بررسی قرار گرفته. در این مطالعه، از طریق ایجاد میمون‌های بی‌لکس پوستی (LcCs) که این گروه استندارد است، واکنش‌های واکنشی واکنشی مورد بررسی قرار گرفته. در این مطالعه، از طریق ایجاد میمون‌های بی‌لکخ 2

Introduction

Dendritic cells (DcCs) are very efficient at activating naïve T cells in vitro and in vivo (Stanley et al., 2002). They can acquire antigens via multiple routes including endocytosis, phagocytosis, and direct infection by pathogens (Stanley et al., 2002). DcCs also have an array of receptors for pathogen-associated molecular patterns that allow for phagocytosis and antigen presentation (Stanley et al., 2002). Though DcCs 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 CD80, CD83, CD103, CCR7, and C-type lectin receptors such as DC-SIGN (Parr et al., 2002; Strohman and Liu, 2003). Notably, though DcCs were initially identified because of their stimulatory capacity, a growing body of data has demonstrated that DcCs are capable of promoting tolerance rather than immune responses (Stanley and Paller, 2002; Strohman and Nussenzweig, 2003).

DcCs can also be separated by whether they are resident in secondary lymphoid tissues or in parenchymal tissues. Unlike DcCs in secondary lymphoid tissue, tissue-resident DcCs do not typically have direct access to naïve T cells. Rather, it is thought that these cells function as sentries that acquire Ag in the periphery and become activated locally (Bkraine et al., 2002). These cells are thought to have a primary role in the development of tolerance in lymph nodes (LN), where they are thought to either prevent immune maturation or transfer Ag to resident secondary lymphoid tissue DcCs for presentation, thereby determining a primary response (Duranceau et al., 2004; Romani et al., 2005). In addition, there is some evidence for priming of some immune responses both directly by secondary lymphoid tissue-resident DcCs and in other cases by tissue-resident DcCs after migration. Their relative roles remain unclear.

Langerhans cells (LcCs) are a subset of tissue DcCs that are particularly unique and are likely the first APCs to contact pathogens at the skin surface (Romani et al., 2003). Intrinsically, LcCs residing in skin contact antigens and upon various stimuli, they migrate and co-determine immune responses leading to their critical role in promoting immune responses.

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As this manuscript was being prepared, two groups reported that they had developed mice that express a dominant-negative allele in an embryonic stem cell line and generated a mouse lacking LcCs (Kaplan et al., 2003; Zou et al., 2003). Thus, it appears that further caution should be exercised in the interpretation of the results in this study.

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CD4+ T cell

Th1

Th2

Th17

Treg

IFN-γ

IL-4

IL-17

IL-22

DC

TGFβ

IL-6

TNFα

Foxp3

AHR

RORγt

GATA-3

STAT6

STAT3

STAT4

RORγt

STAT3

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LC Expression of Neuropeptide Receptors

[Image of a gel electrophoresis showing bands for PAC1, VPAC1, VPAC2, and GRP]
Antigen Presentation Assay

BALB/c LC

2 h

Wash 4X

Coculture LCs and DO11.10 T cells +/- OVA_{323-335}

48 h

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

3h

48 h

Measure cytokine production
(ELISA)
The Effect of CGRP on Biasing LC Ag Presentation Towards an IL-17A Response Does Not Depend Upon Cell-Cell Contact
Nociceptive sensory neurons drive interleukin-23-mediated psoriasisform skin inflammation

Lorena Miel-Bianco, Jose Ordovas-Montanes, Mario Peiro, Elena Navar, Aude Thrist, David Alvarez, Siba Paus, John N. Wood & Ulrich H. von Andrian

Nature 510, 157-161 (25 June 2014) - doi:10.1038/nature13199

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.
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  Pranayama
Biofeedback  Visualization
Deep breathing  Yoga Nidra
Meditation  Self-hypnosis
Mind-body relaxation  Qigong
Zen Yoga  Zhineng Qigong
Progressive Muscle Relaxation  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.