REVIEW

A New Concept of Skin-associated Lymphoid Tissue (SALT): UVB Light Impaired Cutaneous Immunity Reveals a Prominent Role for Cutaneous Nerves

J. Wayne Streilein, Pascale Alard and Hironori Niizeki

The Schepens Eye Research Institute and Department of Dermatology, Harvard Medical School, Boston, MA, USA

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Abstract. More than 20 years have passed since the concept that the skin has its own associated immune system was first proposed by Streilein. This proposal was advanced in part on evidence that cutaneous contact hypersensitivity (CH) reactions are closely correlated with Langerhans cells (LC). Recent reports have demonstrated that LC have neural connectivity with cutaneous nerve termini containing calcitonin gene-related peptide (CGRP), suggesting that a link exists between innervation and immune responses in the skin. Here we discuss the neural components which have recently been found to be participants in skin-associated lymphoid tissue (SALT). In part, discovery of a functional link between the nervous system and SALT is based on studies in which cutaneous immunity was impaired by ultraviolet-B radiation (UVR). The deleterious effects of UVR on cutaneous immunity include failed CH induction and promotion of hapten-specific tolerance, effects that are mediated by tumor necrosis factor-α and interleukin-10, respectively. The source of these cytokines after UVR appears to be dermal mast cells. Evidence indicates that mast cells are triggered to release these cytokines in response to CGRP, which is released from UVR-damaged cutaneous nerve endings. Moreover, a substance P agonist was able to reverse the deleterious effects of UVR on CH induction, rendering the mice able to develop intense CH. These observations indicate that two cell types not originally included in the SALT concept are critical to the functional integrity of cutaneous immunity: mast cells and cutaneous nerves. We propose that cutaneous nerves dictate whether antigen applied to or arising within skin will lead to sensitivity or tolerance. (Keio J Med 48 (1): 22–27, March 1999)

Key words: Langerhans cells, contact hypersensitivity, neuroimmunology, calcitonin gene-related peptide (CGRP), substance P

Introduction

More than 20 years have passed since the concept that the skin has its own associated immune system was first proposed by Streilein in 1978.[1] This proposal was advanced primarily based on the then recent evidence[2] that cutaneous contact hypersensitivity (CH) reactions are closely correlated with class II Major Histcompatibility Complex-bearing epidermal cells, namely Langerhans cells (LC). When originally described by Paul Langerhans in 1868, these dendritic epidermal cells reacted with gold salts and gave the appearance of neurons.[3] Consequently, Langerhans considered them to belong to the nervous system. Since then, LC were thought to be related to melanocytes, a view that was widely held until the signal observations of Silberberg[4] and Stingl *et al.*[5] Together these laboratories unequivocally defined LC as bone marrow-derived cells, similar to macrophages, but more closely related to dendritic cells described first by Steinman and Cohn.[6] Since then a large body of evidence has accumulated to reveal the functional capacity of LC in presentation of antigens to T cells. Now, as though the path had come full circle, attention has recently been called to the neural

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Reprint requests to: Dr. J. Wayne Streilein, Schepens Eye Research Institute, 20 Staniford Street, Boston, MA 02114, USA, e-mail: waynes@vision.eri.harvard.edu