connectivity of LC to c-type nerve fiber termini containing calcitonin gene-related peptide (CGRP). These termini have been found to be present on the surfaces of LC in normal skin,[7] and on dermal mast cells. Here we discuss the neural components which have recently been found to be participants in skin-associated lymphoid tissue (SALT). In part, the discovery of the link between the nervous system and SALT was based on studies in which cutaneous immunity is impaired after ultraviolet-B radiation (UVR).

Original Concept of SALT

The skin has an unusual set of immunologic requirements. It is confronted by a specialized set of pathogenic organisms armed with strategies designed to thwart the physicochemical barriers of the stratum corneum. The skin surface is also threatened by environmental chemicals with irritant properties and with the capacity to induce T cell-mediated immunity of the CH type. Moreover, the skin is bombarded with ultraviolet radiation which, in addition to its mutagenic properties, robs the skin of the immune mechanisms designed to meet the microbial and chemical challenges it faces. The notion that skin is provided evolutionarily with a specialized set of recirculating and migratory lymphoreticular cells, organized, draining lymphoid organs, and a responsive dermal microvasculature is embodied in the concept of SALT (Fig. 1). Evidence in favor of the existence of SALT includes (1) the inherent capacity of cutaneous cells to capture, process, and present nominal antigen in a manner that can be recognized by naive T lymphocytes; (2) the ability of strategically located peripheral lymph nodes to accept immunogenic signals derived from skin; (3) the resultant emergence of subsets of antigen-specific T lymphocytes that display differential affinity for skin and its associated lymph nodes, an affinity determined at least in part by differentiation signals received *in situ* from resident cutaneous cells. The cells responsible for the establishment, integration and maintenance of SALT include keratinocytes, LC, immunocompetent lymphocytes, dermal endothelial cells.[1]

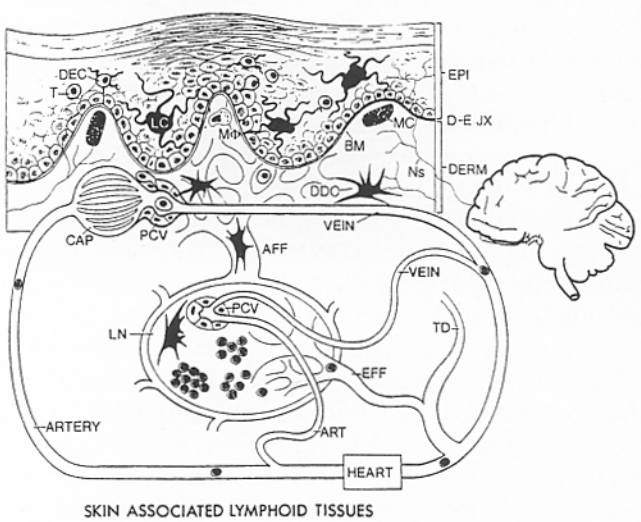

Fig. 1 Diagram of participants in Skin Associated Lymphoid Tissues, reflecting microanatomic relationships among the various cellular elements. **EPI:** epidermis, **D-E JX:** dermal-epidermal junction, **DERM:** dermis, **MC:** mast cell, **BM:** basement membrane, **Ns:** nerves, **DDC:** dermal dendritic cells, **MΦ:** macrophage, **LC:** Langerhans cells, **DEC:** dendritic epidermal T cells, **T:** T lymphocyte, **AFF:** afferent lymphatic, **EFF:** efferent lymphatic, **TD:** thoracic duct, **LN:** lymph node, **PCV:** post-capillary venule, **ART:** artery, **CAP:** capillary.

UVR of Skin and Induction of Cutaneous Immunity in Mice

Antigens that arise within the skin, or are applied epicutaneously to the cutaneous surface, are not recognized within skin by the T cells of immunologically naive animals. Instead, considerable experimental evidence supports the view that cutaneous antigens are endocytosed and/or phagocytosed by indigenous mobile antigen-presenting cells (APC), such as LC, dermal dendritic cells and macrophages.[8] Once antigen has been captured, cutaneous APC then migrate through lymph to the draining lymph node where they encounter T (and B) lymphocytes, which are constantly delivered to the site *via* high-endothelial venules. In the process of migrating from skin to lymph node, cutaneous APC acquire novel and potent co-stimulatory properties which are as essential to activation of naive T cells as is presentation of the antigen itself. This process is disrupted when the skin is exposed to UV radiation.

Actually, exposure of murine skin to UVR causes profound changes not only in local (cutaneous) immunity, but in systemic immunity.[9,10] This is somewhat surprising since UVR penetrates only into the epidermis and upper reaches of the dermis.[11] Thus, in order to account for the systemic immune deficits that arise after UVR, the most likely cellular components of SALT to carry the immune inhibitory message of UVR to the systemic immune apparatus are cutaneous APCs, rather than lymphocytes.

As an experimental tool to study the cellular mechanisms responsible for cutaneous immunity in mice, our laboratory has used an acute, low-dose UVR protocol directed at shaved body wall skin of mice.[2] When a sensitizing dose of hapten, such as dinitrofluorobenzene (DNFB), is painted on the irradiated surface immediately after the last of four consecutive daily UVR exposures, CH fails to develop in certain genetically defined strains of mice, termed UVB-susceptible (UVB-S).