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CONTINUING MEDICAL EDUCATION

CURRENT STATUS OF LANGERHANS CELLS

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Tissues which are exposed to the external environment have been shown to have a closely-knit, organ-related immune system. The aggregate lymphoid tissue beneath the epithelium of gut and a distinct population of lymphocytes which recirculate continually between the systemic circulation and the gut lymphoid tissue, constitute a functionally independent unit i.e. gut-associated lymphoid tissue (GALT).[1] A similar unit linked to the pulmonary system has been identified as the bronchus-associated lymphoid tissue (BALT).[2] Toews et al[3] have proposed the concept of SALT (skin-associated lymphoid tissue). It has been suggested that SALT has four components[4] : (1) Peripheral lymph nodes draining the skin. (2) A clone of T-lymphocytes which have a special affinity for skin and recirculate between peripheral lymph nodes and skin. (3) Keratinocytes which not only provide micro-environment for immunological reactions but also secrete immunologically active factors, and (4) Network of antigen-presenting and processing cells, the epidermal Langerhans cells (LCs).

LCs are the only cells within the epidermis that bear Fc and C_3b receptors[5] and express Ia antigens.[6] They thus belong to the macrophage-monocyte-histiocyte series. Ontogenically unrelated to the epidermis melanocytes, these epidermal cells originate from a mobile pool of bone marrow derived precursor cells and migrate to the epidermis.[7] Electron microscopic studies have shown them to cross the basal lamina from dermis to the epidermis.[8] These cells are seen in H and E sections as high-level clear cells in the epidermis. Their dendritic character can be demonstrated by the gold chloride stain[9] or histochemical stains detecting ATPase or amino-peptidase enzymes.[10] However, these methods are not always very specific. Now a days, monoclonal antibodies directed against surface antigens are used for quantitative and immuno-pathological studies of LCs; Ia antibodies and antibodies against human thymocyte antigen (HTA) i.e. OKT6 and NAI34, are said to be quite specific for LCs.[11] Recently, Schuler et al,[12] using lectin binding patterns of lectin receptors on the surface of LCs, have pointed towards the existence of LC subsets. But the most reliable method of identifying LCs is by their ultrastructural features[13] : presence of typical racquet shaped Birbeck granules and absence of organelles which are characteristic for keratinocytes and melanocytes i.e. tonofilaments, desmosomes, pre-melanosomes and melanosomes.

LCs function as specialized macrophages in the epidermis. They have been shown to replace the Ia bearing macrophages in their ability to present the antigen to sensitized T-lymphocytes and induce antigen-specific and allogeneic T-cell activation in mixed lymphocyte reactions.[14,15] This property of LCs could be altered by UV-B irradiation.[16] These cells are also required for epidermal cell induced

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generation of cytotoxic T-lymphocyte response against alloantigens or TNP (Tri-nitro-phenyl)-modified syngeneic cells.[17] LCs have also been reported to produce a factor with Interleukin-I like activity.[18] Considering these properties of LCs, it is logical to postulate that LCs could provide the necessary stimulus to initiate the rejection of allograft, and successful elimination of all LCs from allografts of epidermis might lead to permanent graft survival.[19] Authentic studies have shown that LCs play a pivotal role in the pathogenesis of contact sensitization since they are the only antigen-processing and presenting cells in the epidermis.[20] When the agent is applied to the skin, the Ia component of LC conjugates the agent (hapten) and forms an immunogenic complex which is then transferred to T-lymphocytes[21] in the epidermis or dermis or in the regional lymph node; Silberberg et al[22] have demonstrated LCs in the dermal lymph vessels 2-3 hours after application of DNCB (dinitrochlorobenzene), and in the lymph node after four hours. It has been well documented that an optimum number of LCs is essential for induction of contact sensitization to chemical allergens. Application of DNFB (dinitrofluorobenzene) to dorsal body wall of normal mice resulted in strong contact sensitization, but when mice were exposed to DNFB through the skin deficient in LCs, either tail skin[23] or UVL-treated body wall skin,[24,25] no contact sensitization developed, rather they developed a specific unresponsive state or tolerance.[26,28] This effect of exposure to the chemical allergen in the absence of LCs is similar to the state of specific unresponsiveness or tolerance which develops after I.V. injections of haptens.[27] Ptak et al have shown that the type of response elicited is dependent upon the anatomical site where the antigen is first encountered.[27] When the antigen is given I.V., a state of specific tolerance develops due to direct activation of the splenic suppressor cells; intraperitoneal administration of cyclophosphamide shortly before contact sensitization reversed the unresponsiveness[24], suggesting that tolerance in these animals is mediated by suppressor cells. Crucial role that LCs play in the induction of positive immune response to antigens is further supported by the observations that when TNP was presented to the immune system by I. V. injection of TNP-conjugated epidermal cells, long lasting form of contact sensitization resulted.[27] This approach induced contact sensitization even when the suppressor circuit was activated by the I.V. co-administration of TNP-conjugated peritoneal exudate cells. This implies that these epidermal antigen presenting cells (LCs) are unable to interact with cells of the suppressor circuit.

Importance of LCs in infectious diseases is still not adequately explored. Nagao et al[29] have demonstrated vaccinia virus in LC at the site of inoculation. Braathen et al [30,31] have recently shown that LCs may play some role in processing the viral and fungal antigens. In-vitro studies showed that LCs were able to induce a cellular immune response to trichophytin, herpes simplex virus and PPD. Recently, using ATPase staining to identify LCs, we have observed a gradual reduction in the number of LCs towards the lepromatous pole of leprosy.[32] Ultra-structural study of LCs in patients of lepromatous leprosy (LL) has revealed dense matrix and indistinct cristae of mitochondria; decreased number of lysosomes and rough endoplasmic reticulum, and numerous vacuoles in the cytoplasm. These findings are suggestive of functionally inactive LCs in LL. We have suggested that specific unresponsiveness to lepra bacilli seen in LL cases could be because of *M. leprae* antigen directly reaching the central lymphone compartment either through the gut respiratory route or through the nerves without being processed by the epidermal LCs, whereas at the TT pole, the M. *leprae* antigen is processed and presented to the immune system by the epidermal LCs, leading to a long-lasting specific sensitization. A significantly lower number of LCs in the epidermis overlying the un-involved, sarcoidal, and Kveim-positive skin has been

reported by Fox et al.[34] Whether the reduced number is due to a local and/or a systemic effect of sarcoidosis, or it reflects the anergic state of these patients, is not clear.

A significant reduction in the number of LCs was observed in 24 patients with AIDS (acquired-immuno-deficiency syndrome).[33] Authors have suggested that functional alterations in the LCs, and perhaps also in the antigen-presenting cells in other tissues, may be involved in the pathogenesis of AIDS; either the LC abnormality superimposed on an already deficient helper T-cell function leads to an irreversible immunodeficiency or a poor antigen presentation to the helper T-cells results in defective proliferation, which could be a very important link in a chain of events resulting ultimately in extreme immuno-deficiency.

The strong clinical association between a prolonged exposure to actinic radiation and markedly increased incidence of cutaneous neoplasms has been postulated to be related to a chronic deficiency of LCs produced by repeated exposures to UVL.[4,28] LCs are thought to perform the function of immuno-surveillance by detecting the neo-antigens on the surface of epidermal cells during the early stages of neoplastic transformation; LCs process and present the neo-antigen in an immunogenic form leading ultimately to destruction of the neoplastic keratinocytes.[4] UVL-induced inability of LCs to process the neo-antigens effectively could lead to specific unresponsiveness, leading to a widespread growth of cutaneous cancer. This hypothesis of immuno-surveillance by LCs is supported by a recent observation that the number of LCs is significantly low in patient with AIDS and Kaposi's sarcoma.[33]

In mycosis fungoides, the density of LCs in the epidermis and the dermis is increased, they are always present in Pautrier microabscesses and are often seen in direct apposition to the lymphoid cells.[35,36] These observations support the view that mycosis fungoides starts as an immunologic disorder and only later develops into a lymhoma. It has been postulated that interaction of LCs with the T-lymphocytes in the epidermis initiates the development of Pautrier micro-abscesses.[37] Probably, due to some defect in the processing by LC of the hitherto unidentified antigen, this process becomes chronic and ultimately leads to malignant transformation.[38,39]

Histiocytosis X is a disease characterised by marked accumulation of histiocytes in the cutaneous and visceral lesions. These histiocytes have been noted to have marked resemblence with LCs viz, presence of typical LC granules,[40] similar shape and structure of the nucleus,[41] presence of ATPase and leuyl-beta-naphthylamidase,[41] surface receptors for C_3 and Fc[42] and capacity to phagocytose erythrocytes in culture.[42] It has thus been postulated that histiocytosis X is a proliferative disorder of LCs.[43]

The number of LCs have been demonstrated to be altered in some disorders of keratinization. They have been reported to be decreased in hyperkeratotic warts and normal in plane warts.[44] In psoriasis, the number of LCs was found to be decreased[45] but LCs could be shown to be present in the stratum corneum.[46] LCs were increased in ichthyosis.[45] They were noted in the epithelium of trachea and urinary bladder after squamous metaplasia due to vitamin-A deficiency.[47] These observations suggest that LCs might be playing an important role in the organisation of epidermis; they may be concerned with cytolysis or separation of the corneocytes.[45,48]

Cells containing typical LC granules have been observed in the dermis in—pityriasis rosea, Ehler-Danlos syndrome, necrobiosis lipoidica, granuloma annulare and actinic reticuloid.[49,50] In vitiligo, the number of LCs in the epidermis has been reported to be increased and they have been shown to replace the basal melanocytes.[51] Significance of all these findings is still unknown.

To conclude, LCs appear to play a significant role as a peripheral out-post of skin-associated lymphoid tissue (SALT). Further understanding of the biology of this cell is sure to clarify many hitherto unexplained facts related to pathogenesis of a variety of diseases.

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