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Langerhans Cells and Atopic Dermatitis

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The epidermal Langerhans cells are situated mostly suprabasally with long dendrites between the keratinocytes. They comprise about 2–3% of the cells in normal epidermis and can be visualized by means of antibodies directed against CD 1 or HLA-DR in immunological staining techniques.

Research in recent years has demonstrated that epidermal Langerhans cells play a major role in the immune reactions in the skin. Their main functions are uptake, processing and presentation of various types of antigens to T lymphocytes (1), and production of the immunoregulatory substance Interleukin 1 functionally similar if not identical to epidermal cell derived thymocyte activating factor, ETAF, which was first shown to be produced by keratinocytes (2).

Using a suction blister technique to obtain epidermal cells we are able to produce epidermal cell suspensions with a viability of usually more than 90%. Using these cell suspensions in functional studies, i.e. coculturing them with allogeneic T lymphocytes or autologous T lymphocytes plus antigen, we have demonstrated that epidermal cells are capable of alloactivation and that they are able to present bacterial antigens like purified protein derivative of tuberculin, live herpes simplex virus and virus antigen, candida antigen, trichophytin and the contact allergen nickel sulphate to T lymphocytes, and thereby induce an antigen specific T-cell response to these antigens in previously sensitized individuals (3–6). Preincubation of the epidermal cell suspensions with a rabbit anti-DR antiserum plus complement abrogated the responses. In the studies with nickel sulphate even preincubation with only the rabbit anti-DR antiserum alone without complement was sufficent to abrogate the responses (6), indicating that the epidermal Langerhans cells were mainly responsible for the induction of the T-cell responses.

The results of these experiments may be regarded as the in vitro equivalent of the afferent phase of the T-cell dependent delayed type hypersensitivity reaction to these antigens in the skin. Furthermore, the induction of the T-cell responses is dependent on the HLA class II DR antigens on the Langerhans cell-surface, blocking of the HLA-DR antigens abrogated the T-cell response. We have also shown that the DR antigens function as restriction elements, that is the Langerhans cells and the T-cells have to share the same DR determinants to be able to cooperate (7). By means of radioimmunoassay technique we have demonstrated that Langerhans cells express more HLA-DR than peripheral blood macrophages and the antigen presenting dendritic cells (8). A per cell comparison between Langerhans cells and peripheral blood macrophages demonstrate that Langerhans cells are much more efficient in inducing a T-cell response to nickelsulphate, indicating that they are highly specialized in antigen presentation (9).

ATOPIC DERMATITIS

Atopic dermatitis is an inflammatory skin disease with pruritus and lichenification of the skin. The patients usually have a personal or family history of allergic disease and demonstrate abnormalities in various immune functions. They have increased susceptibility to cutaneous dissemination of certain viral infections such as herpes simplex and vaccinia (10), and decreased delayed type hypersensitivity responses to common microbial antigens (11). Furthermore they have increased IgE production (12), low incidence of sensitization to contact allergens (13), decreased lymphocyte responses to mitogens and antigens (11) and defective granulocyte and monocyte chemotaxis (14).

The histopathological findings in atopic dermatitis are nonspecific. There is infiltration of mononuclear cells in the epidermis and superficial dermis together with epidermal edema in early lesions and acanthosis in chronic lesions. Increased mast cell numbers and changes in dermal nerves and vessels have also been reported (15).

These histopathological features in the clinically affected skin of patients with atopic dermatitis show similarity to those found in contact dermatitis, and eczematous changes can be induced by specific allergens such as dust mite antigen patch tests (16). The

infiltrating cells in the skin of atopic dermatitis are mainly T lymphocytes (17), with a large majority of helper T-cells and few suppressor T-cells (18). HLA-DR have been demonstrated on most of the infiltrating cells (19), and double labelling experiments demonstrated Interleukin 2 receptor positive T-helper cells indicating functional activation (20). Using the L-dopa histofluorescence technique chronic lesions demonstrate significantly increased number of Langerhans cells throughout acanthotic epidermis, with occasionally focal accumulation (21), while acute erythematous lesions do not demonstrate any change in the number of Langerhans cells in the epidermal lesions (21). Similar observations have been published by others using monoclonal antibodies directed against the T-6 antigen (19).

OKT-6 positive dendritic cells are scattered through the mid and upper dermal infiltrate, with frequent focal clumping and close proximity to T-helper cells and they number approximately 10% of the total infiltrate (22). The overwhelming majority of these dermal OKT 6 positive cells also express HLA-DR as evidenced by double staining experiments (18), and are therefore highly likely Langerhans cells. In contrast to other chronic skin conditions including contact dermatitis, which show HLA-DR positive keratinocytes, the keratinocytes in atopic dermatitis are almost completely HLA-DR negative (19).

Recently the presence of IgE molecules on epidermal Langerhans cells was demonstrated in patients with atopic dermatitis using the indirect immunoperoxidase technique (23). The phenomenon seemed to be specific for atopic dermatitis since skin sections from non-atopic controls and patients with allergic asthma and contact dermatitis did not show epidermal anti-IgE staining. The same authors also found positive dermal anti-IgE staining. Others have demonstrated coating with IgE on T lymphocytes in dermis, sometimes in conjunction with Langerhans cells possibly demonstrating the cytophilic quality of IgE (19). Using a double labelling immunofluorescence technique we have demonstrated a heterogeneous epidermal Langerhans cell population in the skin of patients with atopic dermatitis, about two thirds of the epidermal Langerhans cells carry surface IgE (24). An attempt to demonstrate birch allergen on the surface of the IgE-positive Langerhans cells failed, also after preincubation of the Langerhans cells with a high concentration of birch antigen. Furthermore, the number of IgE-positive Langerhans cells did not increase after 90 min incubation with a serum pool containing a high IgE concentration.

CONCLUSION

In the skin of patients with atopic dermatitis a mixture of type I and type IV reactions is seen, and the same antigen can induce both type I and type IV hypersensitivity reactions. The skin infiltrate consists mainly of activated T-helper cells together with a substantial number of Langerhans cells, as seen in cell mediated immune reactions. Taken together these findings may indicate an antigen-presenting function of Langerhans cells in a T-cell mediated immune mechanism, be it with inhalant, food or other antigens, as part of the pathogenesis of atopic dermatitis.

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