

Atopic Dermatitis May Be a Genetically Determined Dysmaturation of Ectodermal Tissue, Resulting in Disturbed T-lymphocyte Maturation

A Hypothesis

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Although atopic dermatitis is a skin disorder, it includes immune deviations such as T-cell accumulation and activation in the skin, resulting in chronic, relapsing eczema. The T-lymphocyte activation in the skin is not accompanied by specific allergies in up to two thirds of the patients. It has been shown that T-cell lines and clones can be established from skin biopsies of patients with atopic dermatitis showing cytokine-dependent, but antigen-independent, continuous growth in vitro. This indicates the existence of skin-homing T-lymphocytes with growth requirements different from those of mature T-lymphocytes in the blood.

We suggest that atopic dermatitis is a genetically determined change of ectodermal tissue. The thymic epithelium is derived from the ectoderm, and because of that we hypothesize that the maturation of the T-cell immune system of persons who develop atopic dermatitis is disturbed due to a faulty selection of T-lymphocytes in the thymus. "Dys"-matured T-cells leave the thymus as a consequence of faulty selection and continue their growth in the skin. The cells are eventually eradicated by the immune surveillance conducted by the normal part of the patients' immune system and as a consequence of diminished output of faulty selected T-lymphocytes during maturation. Because of the increased proliferation capacity of the aberrant T-cells, a cytokine imbalance occurs and in some patients this leads to the development of type I allergies due to a skewing of the humoral immune system towards IgE production.

(Accepted July 29, 1996.)

Acta Derm Venereol (Stockh) 1997; 77: 20–21.

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Atopic dermatitis is a skin disorder primarily affecting young children. In some population studies it has been shown to have an incidence of up to 20% (1–10). According to Hanifin & Rajka's definition of atopic dermatitis (11) the following must be present in order to establish the diagnosis: 1) strong family association, 2) typical morphology and distribution of eczema, 3) recurrent or chronic eczema and 4) severe itching. Several other minor symptoms are often present. One of the most studied is the increased total serum IgE found in one third of the patients with atopic dermatitis only. The specificity of the IgE antibodies is often unknown. Recent studies indicate deviations in the cytokine profile of T-lymphocytes as a possible explanation of increased IgE production and some of the ensuing allergic manifestations of atopic dermatitis (12).

T-cell clones from the skin of patients with atopic dermatitis

The cellular infiltrate in atopic eczema shows an almost pure accumulation of T-lymphocytes which are mostly CD4+

T-cells expressing activation markers such as HLA-DR and CD25, the receptor for interleukin 2 (IL-2).

Antigen-specific T-cells have been cloned from the skin of patients with atopic dermatitis. Most clones were selected to be house dust mite antigen-reactive (13–15), but clones reactive to other environmental allergens such as pollen can also be established (16). The cytokine profile of allergen-specific clones is predominantly of the Th2 type.

We have recently described a different set of T-lymphocytes from the skin of patients with atopic dermatitis. These cells do not require accessory cells, antigen or mitogen stimulation, but require only IL-2 and IL-4 for in vitro growth (17, 18). During prolonged culture the cells can show growth beyond the limit for normal cell growth in vitro and may become continuous. This happens in approximately 60% of T-cell lines from atopic skin biopsies. Nine continuous cell lines have been established so far; all are clonal and have the following phenotype: CD2+, CD3+, CD4+, CD8-, CD21-, CD25+, CD29+, CD44+, CD45RO+, CD56-, HLA-DR+, and TCR-2+. They have a cytokine phenotype of Th0 cells at the transcriptional level.

Several different clones occur between different patients based on their TCR beta-chain specificity. Five different T-cell clones were established from one patient, where a total of four skin biopsies were performed. Our in vitro culture system selects the fastest growing cell after addition of high amounts of T-cell growth factors (IL-2 and IL-4) (17,18). The finding of two different continuous clones from one skin biopsy in the same patient indicates that many skin-homing T-lymphocytes have the potential for establishing a continuous, cytokine-dependent in vitro growth.

Cytolytic effector cells from blood can be established in vitro towards the patient's own aberrant T-cell clones. In preliminary experiments we have observed that the lymphokine-activated killer cells (LAK cells) and specific cytotoxic T-cells from peripheral blood could be established in vitro towards a patient's own skin-homing T-cell clones, leading to an efficient elimination of the skin-homing T-lymphocytes. Thus, the patient's own mature T-lymphocytes in blood provide immune surveillance of the aberrantly growing skin-homing T-lymphocytes.

We speculate that skin-homing T-lymphocytes could be T-cells that escape selection in the thymus. This is indicated by their capacity to show cytokine dependent and antigen-independent growth in vitro, corresponding to what occurs in the thymus during maturation of the T-cell immune system (19).

HYPOTHESIS

Atopic dermatitis is a genetically determined disease, which primarily affects the ectoderm. The thymus is an invagination

from the 2nd and 3rd pharyngeal pouches (20), and the thymic epithelium is of paramount importance for proper maturation of the T-lymphocyte system (21,22). Animal experiments have shown that up to 95–98% of bone marrow cells entering the thymus undergo apoptosis. The selection and maturation of T-cells is complex and involves many steps including contact with epithelial tissue (19–22).

If the thymic epithelium is not functioning properly, subsets of faultily selected T-lymphocytes could escape and enter into the periphery. These cells then 'home' to the skin because the ectodermal compartment resembles the epithelium in the thymus. Contact with ectodermal cells could create an environment in which skin-homing T-cells could be activated. The activated, aberrant T-lymphocytes would send signals, i.e. secretion of cytokines, to other mature T-cells, and due to the normal T-cell receptor activity of these cells, they could become sensitized to environmental allergens.

We believe the basic defect is linked to the presence of improperly controlled T-lymphocytes with cytokine-dependent growth. The ectodermal defect, which is probably linked to an abnormal lipid metabolism that is genetically determined, would account for the abnormal skin physiology with increased transepidermal water loss, xerosis of the skin and increased scaling (23,24), thus forming a setting for the accumulation of *S. aureus* on the skin (25). The bacteria or their products may further augment the immune inflammation in the dermis (26).

Inflammation in atopic dermatitis is thus a summation of several mechanisms: 1) antigen-specific reactions involving a few (less than 1%) of the activated T-lymphocytes (if these are present at all), 2) possible "mitogen-like" or superantigen stimulation from staphylococcal products, 3) antigen-independent, but cytokine-dependent proliferation of skin-homing T-lymphocytes which probably forms the major part of the activated T-cells in the tissue, and 4) cytotoxic reactivity of mature, blood-derived T-lymphocytes towards the cytokine-proliferating skin-homing T-lymphocytes.

CONCLUSION

Our hypothesis is supported by clinical, epidemiological and experimental observations. Our concept of the pathophysiology of atopic dermatitis focuses on factors other than the allergic phenomena.

ACKNOWLEDGEMENTS

This work has been supported by grants from The Danish Health Research Council, grant no. 12–1330, Nycomed-DAK, Alfred Benzon's Foundation, the Danish Asthma Allergy Foundation of Denmark and of the County of Aarhus, and Willy Heises Legat. We thank Professor Peter S. Friedmann, Liverpool, for constructive criticism during the preparation of this manuscript.

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