Immunopathology of atopic dermatitis

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that frequently occurs in patients with a personal and/or family history of atopy [19, 31]. Its onset usually occurs during infancy or early childhood. Recent studies suggest that approximately 10% of children are affected by AD. During infancy, AD is typically characterized by an erythematous papulovesicular rash, i.e., acute eczematoid lesions, on the face and the extensor surfaces of the extremities. In more severe cases, generalized skin involvement with weeping lesions and impetiginization is often seen. Childhood AD is characterized by an erythematous papular rash involving the flexural surfaces as well as the face and neck. In adults, AD also involves the flexural regions but is characterized by dry, scaly, papular and lichenified lesions, i.e., chronic lesions. In practice, however, patients with chronic AD usually do not clearly segregate into distinct eczematoid reaction patterns. Indeed, adult patients with severe chronic AD are more likely to have a persistent infantile pattern to their skin disease. At all phases of illness, these patients suffer from marked pruritus that is exacerbated by multiple triggers including allergens, infection, reduced humidity, excessive sweating and irritants such as wools, acrylics, soaps or detergents.

During the past 10 years, there has been considerable progress in our understanding of the immunologic basis of allergic diseases. The functional distinction between T helper cells on the basis of the cytokines they produce, in particular, the compartmentalization of IL-4 and IL-5 to T helper type 2 (Th2) cells has provided an important immunologic framework to study allergic diseases [42]. This review will describe the immunoregulatory features of AD and the insights they provide into the pathogenesis of this fascinating disease.

Pathologic features of AD

The alterations observed by routine histology of AD skin lesions are not specific and can frequently be found in a variety of inflammatory skin disorders, including
contact dermatitis, acute photoallergic dermatitis and inflammatory pityriasis rosea. The histopathology of AD generally depends on the stage of the dermatitis [29, 40]: acute eczematoid lesions are characterized by intraepidermal vesicles, intercellular edema (spongiosis) of the epidermis, and a dermal perivenular inflammatory cell infiltrate consisting predominantly of lymphocytes, and occasional monocyte-macrophages. Only rare eosinophils, basophils, and neutrophils are present. Mast cells are frequently hypogranulated and present in normal numbers when compared with clinically uninvolved skin or skin from normal control subjects. The endothelial cells of the superficial venular plexus, a site where inflammatory cells egress, are frequently enlarged and contain large nuclei with prominent nucleoli.

In chronic lichenified lesions, the epidermis is hyperplastic with elongation of the rete ridges, prominent hyperkeratosis and minimal amounts of spongiosis. There is an increase of Langerhans cells in the epidermis, and macrophages dominate the dermal infiltrate. The number of mast cells are increased in number and are generally fully granulated. Alterations of the superficial venular plexus and deep venules include endothelial cell hypertrophy with enlarged nuclei and prominent nucleoli, and basement membrane thickening. Demyelination and fibrosis of the cutaneous nerves can be seen at all levels of the dermis in the chronic lesion.

Using monoclonal antibodies on frozen skin sections, immunohistochemical staining of acute and chronic skin lesions in AD reveal that the lymphocyte infiltrate consists predominantly of T cells bearing the CD3, CD4 and HLA-DR surface antigens with only occasional CD8+ T lymphocytes [30]. There are no natural killer cells or B cells. Increased numbers of Langerhans cells expressing the CD1 surface antigen and HLA-DR surface antigen are present in the dermis and epidermis of chronic lesions to a greater degree than in acute lesions. Langerhans cells as well as macrophages infiltrating into the AD skin lesion have been found to have surface-bound IgE molecules [32].

Intact eosinophils are infrequently observed in the lesional skin of AD. However, Leiferman and co-workers [27] have reported that extracellular major basic protein (MBP) derived from the eosinophil granule can be detected by immunofluorescence in a fibrillar pattern resembling the distribution of elastic fibers throughout the upper dermis. In more than half of AD specimens examined they also found MBP deposition in a granular pattern deeper in the dermis. When involved and uninvolved areas of skin were compared, extracellular MBP deposition was much more extensive in the involved areas. Although the role of MBP in the pathogenesis of AD is unknown, it has been postulated that it may contribute to tissue injury in AD through its cytotoxic properties and its capacity to induce basophil and mast cell degranulation [17].

**Role of IgE and allergens in AD**

Several observations suggest that IgE and allergens contribute to the pathogenesis of this skin disease. Of AD patients 80%-90% have a family history of atopy.