ATOPIC DERMATITIS: New insights and opportunities for therapeutic intervention
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Atopic dermatitis (AD) is a complex chronic inflammatory skin disorder associated with cutaneous erythema, indurated papules, severe pruritus, elevated serum IgE, and eosinophilia. It frequently predates the development of allergic rhinitis and/or asthma. Quality of life can be severely impaired due to disruption of school, family and social interactions as well as sleep deprivation from their intense pruritus which is exacerbated at night. The current lecture will examine the cellular and immunologic mechanisms that are thought to play an important role in the pathogenesis of chronic AD. Acute AD skin lesions are characterized by a mononuclear cell infiltration with a predominance of activated memory Th2 cells expressing the CLA skin homing receptor. Chronic skin lesions are characterized by increased expression of Th1 cytokines accompanied by the infiltration of macrophages and eosinophils. Recent studies have demonstrated the complex interrelationship of genetic, environmental, skin barrier, pharmacologic, allergic and immunologic factors which contribute to the development and severity of AD. The triggers that exacerbate and sustain this skin disease include foods, aeroallergens, infection and autoantigens. Careful study of how these triggers induce AD has provided significant new insights into the pathogenesis of this skin disease.

An understanding of the mechanisms underlying AD has important implications in our approach to its management. New therapies for patients with this common illness will involve optimizing current therapeutic approaches, e.g. combination topical antibiotic/corticosteroid preparations, or the development of new biologicals or drugs which reduce the inflammatory processes in the skin. This will include reduction of IgE-mediated and Th2-mediated immune responses.

One particularly exciting new class of non-steroid, anti-inflammatory drugs are macrolide immunosuppressives. It has been known for many years that systemic cyclosporin is highly effective at reducing skin severity of AD. However, systemic toxicity has limited its use. Recently, a new class of macrolide immunosuppressants has been developed for topical use, i.e. tacrolimus (FK506). Tacrolimus, a macrolide lactone isolated from Streptomyces tsukbaenesis, is a potent immunosuppressive agent with a spectrum of activity similar to cyclosporin. Its smaller molecular size and 100-1000 fold greater potency compared to cyclosporin suggested it could be effective as a topical agent. Multiple multi-center, controlled studies have demonstrated that FK506 in ointment form (tacrolimus) can effectively reduce the clinical symptoms of AD with markedly diminished pruritus within five days of initiating therapy with no evidence for systemic side effects nor any risk for skin atrophy. Since the T cell activation in AD is biphasic with activation of the Th2-like cytokines during the acute phase and increased expression of the Th1-cytokines in chronic lesions, the capacity of tacrolimus to inhibit the activation of multiple cell types and different cytokines may account for their ability to effectively reduce skin inflammation in AD. Since it’s action is independent of the glucocorticoid receptor, tacrolimus is also ideal for treatment of corticosteroid resistant patients and works very effectively in face and neck dermatitis.