Inflammatory Disorders Associated with Allergy

Overview of Immunopathogenesis and Implications for Treatment

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KEYWORDS

• Cytokine • Eosinophil • Atopic dermatitis • Chronic rhinosinusitis • Nasal polyp • Asthma • Monoclonal antibody

KEY POINTS

- Over the past 2 decades, the pathogenesis of chronic inflammatory conditions associated with allergy has been increasingly characterized.
- A large number of T-cell subsets have been identified that appear to play active roles in coordinating the pathologic responses in atopic dermatitis, chronic rhinosinusitis, and asthma.
- With the improved understanding of potential molecular targets in these diseases, it is now possible to provide specific therapies that block relevant cytokines.

INTRODUCTION

Over the past 2 decades, we have witnessed consistent increases in the prevalence of chronic inflammatory diseases that are associated with immunoglobulin (Ig)E-mediated immunologic hypersensitivity. During this same period, there have been major advances in our understanding of the natural history and pathogenesis of these diseases. Innovative use of mouse experiments has helped uncover the presence of new T-cell subtypes and cytokines and the development of relevant knockout models has been essential in characterizing the functionality of these cells and proteins. Subsequent studies in humans have sought to determine the relevance of these cells to specific forms of allergic disease. In addition to these developments, a great deal has been learned about the clinical and pathogenetic heterogeneity of atopic diseases. Large-scale epidemiologic studies have revealed that there are distinct phenotypes that are characterized by differences in both clinical (eg, age of onset, severity

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level, medication responsiveness, specific IgE, and eosinophils in body fluids) and molecular (eg, cytokines, chemokines, and protein products) profiles. In this review, the pathogenesis of atopic dermatitis, chronic rhinosinusitis with nasal polyposis, and asthma is considered, with a special emphasis on relevant inflammatory cells and molecules that might ultimately serve as therapeutic targets.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by skin dryness, pruritis, erythema, papule formation, and lichenification. It most often begins in early childhood but occasionally starts during the adult years. It is usually the first of the chronic allergy-associated inflammatory diseases to be expressed. It is associated with elevated serum IgE and often occurs with other atopic diseases, including asthma, rhinitis, and food allergy. There are a number of important factors that contribute to the symptoms of AD, including alterations of the skin barrier, abnormalities in innate immune function, alterations of microbial colonization of skin, and increases in Th2 adaptive immune responses. However, despite the tremendous progress made in the characterization of the pathology and molecular biology of AD, many aspects of its pathogenesis remain poorly understood (Fig. 1).

Skin Barrier Function

The main function of the skin is to form a physical barrier against external insults. In patients with AD, there is a significant degree of barrier dysfunction that is central to the disease. Among the causes of altered barrier function, many patients have been

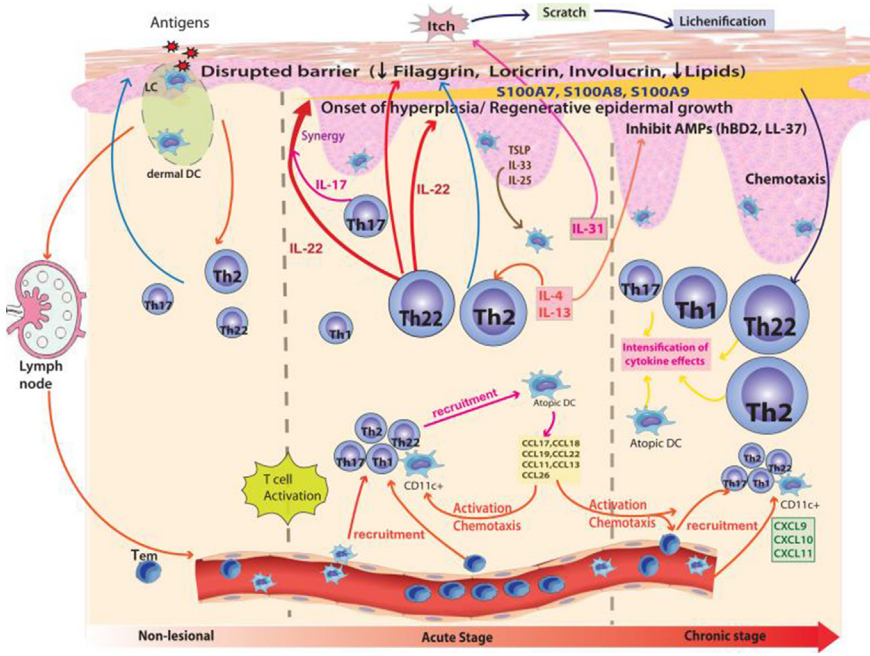

Fig. 1. Immunologic pathways involved in different phases of AD. (*From* Gittler J, Shemer A, Suárez-Farinas M, et al. Progressive activation of T(H)2/T(H) 22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012;130:1344–54; with permission.)