Immunomodulating Agents as Antipruritics

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KEYWORDS

• Itch • Pruritus • Immunomodulator • Atopic dermatitis • Urticaria • Prurigo nodularis • Chronic idiopathic pruritus

KEY POINTS

- Chronic pruritus, or itch lasting longer than 6 weeks, is an increasingly common and debilitating condition.
- Itch involves complex interactions between the skin, immune, and nervous systems.
- Recent studies have implicated type 2–associated cytokines, such as interleukin (IL)-4, IL-13, and IL-31, as critical regulators of itch.
- Blocking the neuroimmune axis has emerged as a novel immunomodulatory approach to treat chronic itch disorders.

INTRODUCTION

Pruritus or itch is defined as any sensation that elicits the desire to scratch. Although scratching may be beneficial by removing pathogens or noxious environmental stimuli from the skin, in its chronic form, itch becomes highly pathologic. Chronic itch, defined as itch lasting greater than 6 weeks, is a symptom that profoundly and negatively affects quality of life.[1–3] Furthermore, chronic itch is common, with an estimated prevalence of 15% and increases with age, affecting 12.3% of those 16 years old to 30 years old and up to 25% of those over 60 years of age.[4–6] Despite its debilitating nature and high prevalence, the biological mechanisms underlying chronic itch remain poorly understood.

It is widely appreciated that skin inflammation leads to itch. Thus, in chronic inflammatory skin disorders, such as atopic dermatitis (AD), chronic itch presents as the central symptom and problem. In both AD and other conditions, such as prurigo nodularis (PN), it has been proposed that inflammation can arise secondary to scratching, which in turn exacerbates the itch-scratch cycle. In the setting of chronic idiopathic pruritus (CIP), it remains even less clear whether immune dysregulation precedes or is secondary to the onset of itch. Regardless of the etiology of inflammatory chronic itch, most therapeutic approaches involve

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disrupting the inflammatory process to ultimately limit symptoms of itch. Notwithstanding this, the molecular and cellular mechanisms by which inflammation leads to itch remain to be clearly defined.

Recent seminal discoveries have identified itch-specific receptors, such as the gastrin-releasing peptide receptor and the Mas-related G protein–coupled receptor family, as critical mediators of chronic itch.[7,8] Along these lines, recent studies have also demonstrated that proinflammatory cytokines can function as itch-inducing factors or pruritogens to directly stimulate itch-sensory nerve fibers to evoke symptoms of itch. Collectively, these discoveries have unveiled a new paradigm in which the immune system can directly communicate with the nervous system to mediate itch. Thus, a better understanding of the molecular pathways that regulate the neuroimmunologic interface may offer new therapeutic approaches to treat chronic itch. Herein, by highlighting new studies, this article reviews how proinflammatory responses promote itch and how novel immunomodulatory approaches can be used to treat chronic itch disorders.

THE PATHOGENESIS OF SKIN INFLAMMATION

The immune system is generally divided into 2 broad categories: (1) the innate immune system, which responds directly and rapidly to nonspecific stimuli, such as pathogen-associated molecular patterns, and various inflammatory factors, such as epithelial cell–derived cytokines, and (2) the adaptive immune system, which can form memory and recognize antigens by generating highly specific receptors as on T cells. Innate and adaptive immune cells are present at the skin barrier and can be functionally divided into 3 distinct responses, known as types 1, 2, and 3 immunity (**Fig. 1**). Type 1 immunity involves responses mediated by adaptive cells, such as type 1 helper T (T_H1) cells and cytotoxic T cells, and innate immune cells, such as group 1 innate lymphoid cells (ILC1s) and natural killer (NK) cells. These cells are characterized by the production of interferon (IFN) gamma and tumor necrosis factor (TNF) alpha, which can act on other cells, such as macrophages. Generally, the type 1 immune response is used to protect against intracellular pathogens and tumor cells, but it can also promote chronic inflammatory processes as in autoimmune skin diseases and allergic contact dermatitis (ACD).[9]

Type 2 immunity is mediated by adaptive type 2 helper T (T_H2) cells as well as innate immune cells, including group 2 innate lymphoid cells (ILC2s), basophils, mast cells, and eosinophils. Collectively, these cells produce the effector type 2 cytokines interleukin (IL)-4, IL-5, and IL-13, which promote allergic inflammation and

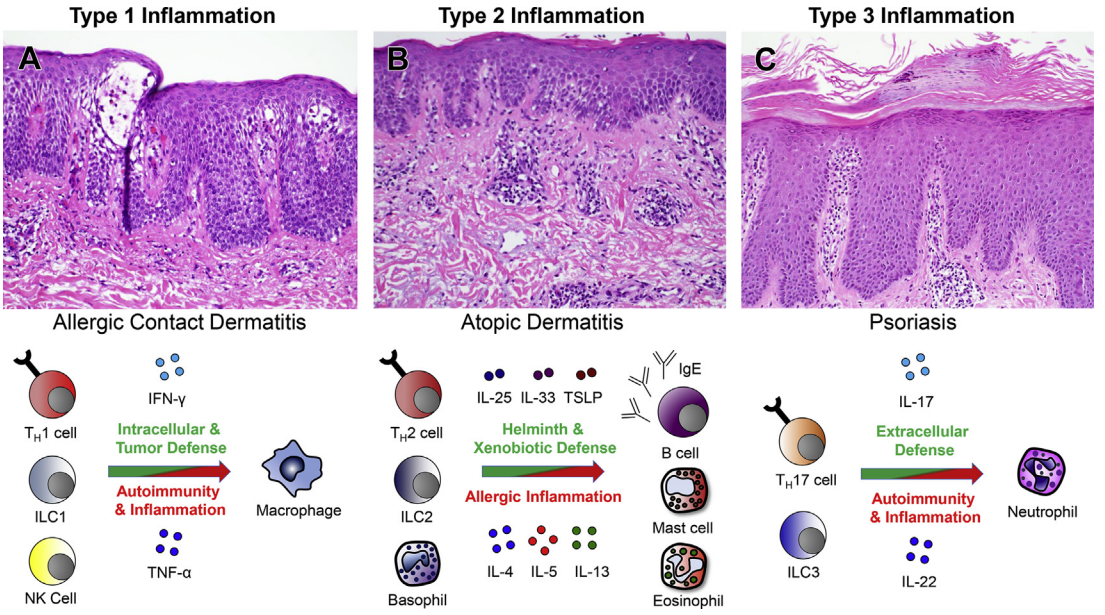

Fig. 1. Distinct immune axes underlie various pruritic inflammatory skin disorders. (*A*) Type 1 inflammation is composed of T_H1, ILC1, and NK cell responses and has been implicated in ACD. (*B*) Type 2 inflammation underlies AD and is composed of pathogenic T_H2 cells, ILC2s, and basophils. (*C*) Type 3 inflammation is associated with T_H17 and ILC3 responses in the setting of psoriasis. Hematoxylin-eosin, ×200 magnification.