Establishing Tolerance to Commensal Skin Bacteria

Timing Is Everything

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KEYWORDS

• Skin • Microbiome • Tregs • Tolerance • Neonatal • Commensals

KEY POINTS

- Our skin is home to many commensal bacteria that normally do not cause disease.
- Regulating our immune response, that is, establishing tolerance, to these commensals is essential to prevent chronic inflammation in skin.
- Tolerance to commensal skin bacteria is preferentially established early in life when a unique population of skin regulatory T cells encounters and responds to antigens produced by these bacteria.
- Improved understanding of how our skin establishes and maintains tolerance to commensal bacteria may lead to therapeutic approaches to prevent and treat inflammatory skin disease.

INTRODUCTION

Commensal Bacteria in Inflammatory Skin Disease

As dermatologists, we routinely diagnose and treat overt cutaneous infections, such as folliculitis or cellulitis, where a discrete pathogen is causative and antibiotics are curative. We are also familiar with autoimmune skin conditions, such as pemphigus or pemphigoid, where an immune response to a self-antigen results in destructive skin inflammation, and treatments aim to limit this via immunosuppression. However, we also care for many patients with inflammatory skin disorders that are neither infectious nor autoimmune by classical definitions. A few examples of these include atopic dermatitis, acne vulgaris, and hidradenitis suppurativa. Although the pathogenesis of these diseases is clearly multifactorial, it is likely that immune responses directed at the cutaneous microbiota help to drive inflammation (**Fig. 1**).[1]

In atopic dermatitis, hereditary defects in skin barrier integrity or host immunity can confer disease susceptibility, perhaps by driving altered responses to skin bacteria.[2] Flares are accompanied by an increase in the cutaneous burden of *Staphylococcus aureus* and *Staphylococcus epidermidis*.[3] In acne vulgaris, age of onset coincides with a shift in composition of the skin microbiome.[4] As sebaceous activity increases, the proportion of *Propionibacterium acnes* on healthy skin increases. The presence of *P acnes* alone is not sufficient to cause disease, but sequencing of *P acnes* isolates from acne lesions versus healthy skin has revealed a distinct subset of disease-associated strains.[5] In hidradenitis suppurativa, patients suffer from skin lesions that share many clinical features with infectious furuncles or abscesses. However, microbiological studies of hidradenitis lesions consistently demonstrate altered bacterial communities in which commensal strains from skin or other mucosal body sites predominate over skin pathogens.[6] Thus, in these conditions the presence of a single bacterial strain is not sufficient to initiate disease. Rather, shifts in skin flora composition, accompanied by an altered immune response to these bacteria in susceptible hosts likely trigger pathogenic inflammation.[7]

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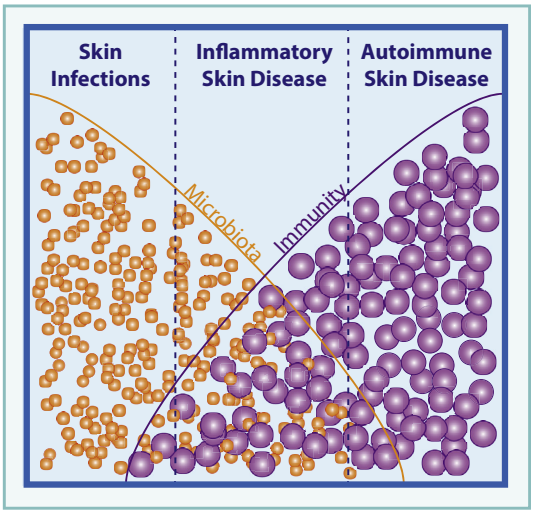

Fig. 1. Microbiota and immunity in skin disease. Our skin's microbiota and immune system contribute to the pathogenesis of many diseases. Frank skin infections by pathogens lie at 1 end of the spectrum; whereas, autoimmune noninfectious conditions resulting from aberrant immune responses to self-antigens lie at the other. The pathogenesis of many inflammatory skin diseases fall between these extremes, with important roles for both microbiota and the resulting immune response.

Present treatment for these inflammatory skin diseases include antibiotics; that is, a sledgehammer to reduce the burden of skin flora and topical or systemic immunosuppressive agents to blunt the resulting immune response. Understanding how our cutaneous immune system regulates inflammation directed against skin microbes will provide additional insight into the pathogenesis of these conditions and may open new opportunities to optimize host–microbe interactions for therapeutic benefit.

CONTENT

Skin Commensal Bacteria: How Do We Keep the Peace?

Billions of bacteria, viruses, and fungi reside on our skin's surface and in adenexal structures.[8] Langerhans cells can protrude through tight junctions to capture bacterial antigens on the skin's surface, and bacterial components have even been identified deep in the dermis.[9] This close proximity enables a constant dialogue between these commensals and our immune system. The presence of bacteria augments the skin's production of antimicrobial peptides and alters the number and function of skin-resident lymphocytes.[10,11] Indeed, individual strains of commensal bacteria, such as *S epidermidis* and *P acnes*, elicit distinct profiles of cytokine production by skin lymphocytes, demonstrating that the composition of our skin flora can influence the tissue's immunologic "tone."[12]

A primary function of our immune system is to protect us from infections by recognizing and responding to microbial antigens. The observation that our immune system is clearly responding to our skin commensal bacteria on an ongoing basis leaves us with a fundamental question that has important implications for normal skin biology and the pathogenesis of inflammatory skin disease. Why do our commensal bacteria not elicit chronic inflammation in healthy skin?

Regulatory T Cells: Our Immunologic Peacekeepers

Our immune system is constantly making decisions about whether and how to respond to antigens it encounters. Most of these antigens are our own "self" antigens. Although many self-reactive T cells are deleted during development in the thymus, others escape and their response must be regulated locally in the tissues where these antigens reside. Regulatory T cells (Tregs), a $CD4^+$ T-cell subset, play a central role in this process of immune regulation or tolerance.[13] As evidence of this, deficiency in the number or function of Tregs leads to autoimmune disease and inflammation in skin and other tissues.[14,15]

Our commensal microbes are in many ways an extension of our human "self"—not only do we rely on them for critical metabolic functions but, as noted, commensal antigens are pervasive at our body surfaces. Commensal bacteria in our gut have been shown to augment the number and function of Tregs in the intestinal lamina propria,[16,17] and gut inflammation seen in the absence of Tregs is directed in part toward luminal microbiota.[18] The skin, like the gut, has a significant population of tissue-resident Tregs.[19] However, the role of these Tregs in immune tolerance to skin bacteria was unexplored until recently.

A Good (Immunologic) Relationship Gets off on the Right Foot

The beginning of life represents a critical window of immune maturation in which our immune system is trained to recognize self and non-self. Neonates, especially in prematurity, are more susceptible to certain infections. Previously this was thought to be because of the "immaturity" of their immune systems. Instead, recent evidence suggests that the immune response in this early stage of life is not underdeveloped but rather carefully designed to promote tolerogenic responses.[20,21] In particular, Tregs generated early in life have a unique