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Research Update (Minireview)

Mast Cells and Microbiome in Skin Immunity

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The skin functions as a physical barrier against entry of pathogens while concomitantly supporting a myriad of commensal organisms. The characterization of these microbial communities has enhanced our knowledge of the ecology of organisms present in normal skin, and studies have begun to illuminate the intimate relationship between the host and resident microbes. The cutaneous innate and adaptive immune responses can modulate skin microbiota, while simultaneously, the microbiota educates the host immune system. A crucial element of the innate immune response is mast cells, which reside strategically in tissues that are commonly exposed to the external environment, such as the skin and mucosae. Mast cells are present on the frontline of defense against pathogens, suggesting they may play an important role in fostering the host-microbiota relationship. In this review, we highlight findings regarding the interaction between skin microbiota and mast cells and the resulting outcomes in skin homeostasis.

Key Words: Skin microbiome, Mast cell, Skin immune response, Skin homeostasis

INTRODUCTION

Compartmentalized barrier tissues such as skin contain a complex composite of microbes. Development of the immune system, particularly adaptive immunity, coincides with the acquisition of a complex microbiota. In turn, the microbiota regulates multiple aspects of the immune system. Skin commensal microbial communities not only co-exist, but also modify immunity, influencing normal skin health as well as participating in various dermatological conditions. For example, changes in the microbiome have been connected with different skin diseases, including atopic dermatitis, acne, and psoriasis (1~3).

Mast cells are tissue-resident immune cells predominantly located in organs that border the outside environment, including airways, intestine, and skin. Mast cells are major effector cells of immunoglobulin (Ig) E-mediated allergic inflammatory reactions. Mast cells also possess multifunctional properties apart from their involvement in allergies. First, they exploit mediators to crucially assist in maintaining integrity and function in all tissues. Second, mast cells regulate defense by acting as innate immune cells, interacting with the specific immune system, and inducing and regulating inflammation. Lastly, they regulate homeostasis through critical contributions to tissue remodeling, including wound healing (4).

There is emerging evidence that mast cells play an important role in microbiota-host communications, particularly regarding certain microbes and components of the micro-

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biota that influence the development and severity of allergic disease by modulating mast cell functions. Beyond allergies, mast cells translate signals between nervous, immune, and endocrine systems in order to modulate biological responses (5). The specialized localization of mast cells (e.g., skin mast cells are located predominantly in the dermis near blood vessels, lymphatic vessels, and nerve endings) support their involvement in microbiota-host interactions. Therefore, microbial modulation of mast cell function has the potential to influence a broad range of physiological parameters.

Thus far, the role of mast cells in the host-microbiome relationship has been primarily focused on the gut microbiome. Here, we review highlights of the current knowledge regarding microbiotic interactions in the skin with mast cells and the resulting outcomes.

SKIN MICROBIOME AND IMMUNE TOLERNACE

Despite constant exposure to large numbers of microorganisms, the skin is able to discriminate between harmless commensal microorganisms and harmful pathogenic organisms. The mechanism of this discrimination is not fully known, but may involve the induction of immune tolerance. Specificity may also be achieved by combined recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs). *Staphylococcus epidermidis*, a commensal bacterium, modulates the composition of the microbiome to maintain homeostasis. Phenol-soluble modulins produced by *S. epidermidis* can selectively inhibit skin pathogens, such as *Staphylococcus aureus* and Group A *Streptococcus*, and can even cooperate with host antimicrobial peptides (AMPs) to enhance killing (6, 7). In fact, *S. epidermidis* triggers keratinocyte expression of AMPs in a Toll-like receptor (TLR) 2-dependent manner (8).

SKIN MICROBIOME AND MAST CELL MATURATION

Mast cells originate from hematopoietic precursor cells in bone marrow. They are released as progenitor cells that circulate in the blood and finally mature from mast cell-committed progenitors when entering tissue. The maturation and differentiation are determined by growth factors and cytokines present in the tissue microenvironment. Among all mast cell maturation factors, the most essential protein is stem cell factor (SCF), which binds to the reciprocal receptor, KIT, a transmembrane tyrosine kinase. KIT is expressed 10-fold higher in mast cells relative to other human cells, and is the dominant regulator of mast cells. SCF binding to KIT promotes mast cell survival, differentiation, migration, mediator production, and release (9). In the skin, SCF is produced by various skin cells, including keratinocytes. In a recent study, Wang *et al*. reported that the skin microbiome acts as a stimulus to produce SCF in keratinocytes (10). This keratinocyte-derived SCF induced by the skin microbiome ultimately leads to mast cell maturation.

In the skin, gram-positive bacteria predominate, with *S. epidermidis* being a commonly isolated bacterial species (11). Lipoteichoic acid (LTA) is a prominent component of the bacterial cell wall, and elicits cellular responses by binding to TLR2. LTA is one of the most abundant molecules on the surface of the skin and could be acting as a stimulus on keratinocytes. Wang *et al*. also found that LTA dose influences mast cells, not through direct interaction, but through triggering the production of SCF in neighboring keratinocytes (10). In their study, germ-free mice express abnormally low levels of SCF and contain mast cells that are largely undifferentiated. Reconstitution of the microbiota or injection of LTA rescued the mast cell phenotype to normal. Further, transgenic mice lacking SCF in keratinocytes show no evidence of mast cells in the skin, but the cells were present in other tissues such as the small intestine and bone marrow. Remarkably, intradermal injection of LTA did not induce mast cell recruitment to the SCF-depleted skin. Instead, direct injection of SCF into the dermis led to mast cell recruitment. Taken together, these data suggest that LTA signals to mast cells by inducing expression of SCF in keratinocytes, indicating that communication between the microbiome and host cells is indispensable for maintaining normal skin mast cell physiology.

SKIN MICROBIOME AND MAST CELL ANTIVIRAL ACTIVITY

The microbiota can also directly activate mast cells. Nakatsuji *et al*. found that the skin microbiota can extend into the dermis, thereby establishing physical contact between bacteria and various cells below the basement membrane (12). The study does not distinguish between viable and dead cells, so does not indicate whether or not live bacteria colonize or inhabit the dermis. However, it is not necessary for microorganisms to be viable in order to exert influence on the host immune system. Bacterial components or products, including LTA, commensal microbial DNA, adenosine triphosphate (ATP), and polysaccharide A, can all exert effects on host cells (13~16). For example, LTA from *S. epidermidis* is abundant in normal human skin epidermis and follicles and is in close contact with mast cells. Based on a study demonstrating that LTA induces higher expression of cathelicidins, a class of antimicrobial peptides, in mast cells compared to lipopolysaccharide (LPS) (17), Wang *et al*. challenged mouse mast cells with LTA and subsequently inoculated with vaccinia virus (VV), and found that LTA stimulates mast cells to suppress viral growth by inducing cathelicidin production (18). This antiviral activity is mediated in a TLR2-dependent manner, as LTA-preconditioned wild-type mast cells demonstrate a greater antiviral response compared to pretreated *Tlr2*$^{-/-}$ mast cells. Further, LTA-induced antiviral activity is primarily due to the induction of cathelicidin because cathelicidin-deficient mast cells do not improve their VV killing activity capacity after stimulation with LTA. Thus, the presence of bacterial byproducts at the skin surface participate in the regulation of mast cell antiviral activity through TLR activation.

SKIN INFLAMMATORY DISEASE

Atopic dermatitis

Studies of the skin and allergic dermatitis indicate a causal relationship between specific microbiota changes. The skin of atopic dermatitis (AD) patients has greatly reduced microbial diversity relative to the same skin area of healthy controls. *S. aureus*, rarely present on healthy skin, is present on the skin of more than 90% of atopic dermatitis patients (19). AD lesions are characterized by relatively low levels of AMP compared with normal skin (20). This phenomenon may be linked to disturbance of the homeostatic composition of *S. epidermidis*, a natural inducer of AMP expression in the skin. A byproduct of colonized *S. aureus* in AD affects skin inflammation; peptidoglycans from *S. aureus* stimulate epidermal keratinocytes to produce transforming growth factor (TGF)-β, which subsequently promotes mast cell recruitment to the dermis (21). Furthermore, *S. aureus*-derived δ-toxin, a potent mast cell degranulating factor, is produced in large amounts by *S. aureus* isolates recovered from patients with atopic dermatitis (22). Skin colonization with wild-type *S. aureus*, but not a mutant deficient in δ-toxin, promotes IgE and interleukin (IL)-4 production, as well as inflammatory skin disease. Enhancement of IgE production and dermatitis by δ-toxin is abrogated in *Kit*$^{W\text{-}sh/W\text{-}sh}$ mast cell-deficient mice and restored by mast cell reconstitution. Thus, δ-toxin is a potent inducer of mast cell degranulation and a mechanistic linker between *S. aureus* colonization and allergic skin disease.

The lipophilic yeast, *Malassezia*, is part of the normal cutaneous flora but can elicit IgE and T cell responses in patients with atopic eczema (AE). In particular, *Malassezia sympodialis* is among the species most frequently isolated from both AE patients and healthy individuals. Several IgE-binding components have been identified and approximately 10 allergens have been cloned and sequenced from *M. sympodialis* extracts. Interestingly, the relatively high pH level in the skin of AE patients compared to healthy skin stimulates the release of *M. sympodialis* allergens (23).

Due to the ruptured skin barrier present in AE, it is likely that *M. sympodialis* comes into contact with mast cells in the skin. Selander *et al*. demonstrates that extracts from *M. sympodialis* activate nonsensitized, IgE-sensitized, and IgE receptor cross-linked mast cells, but do not induce degranulation of nonsensitized mast cells, instead stimulating release of cysteinyl leukotrienes. However, upon addition of *M. sympodialis* extracts, IgE-sensitized and IgE receptor

cross-linked mast cells degranulate, release cysteinyl leukotrienes, and produce monocyte chemotactic protein (MCP)-1 and IL-6 (24). These data indicate that *M. sympodialis* can activate mast cells and thus exacerbate the inflammatory response present in AE.

Psoriasis

Psoriasis is a chronic, relapsing inflammatory skin disease characterized by abnormal keratinocyte differentiation and proliferation. In addition to genetic predisposition, many endogenous and exogenous provoking factors play an important role in the development of psoriasis. Infections have been recognized as a trigger for the onset or exacerbation of psoriasis (25). Several studies suggest that various microorganisms such as β-hemolytic *Streptococcus*, *S. aureus*, and *Candida albicans* may release factors that act as superantigens and thus stimulate the pathogenic process of psoriasis (2). In particular, the significantly higher prevalence of *C. albicans* in patients with psoriasis compared to healthy controls correlates with disease severity (26). *C. albicans* is an opportunistic dimorphic fungus that causes mucocutaneous and systemic candidiasis, usually colonizing humans since birth and persisting throughout life as a commensal in the skin and the oral, gastrointestinal, and vaginal mucosae. The mouth is a suitable place for colonized *Candida*, and oral candidiasis is frequently present in the mouths of patients with psoriasis (26). Indeed, treatment with a systemic antifungal is very effective in some psoriatic patients, particularly those with mouth lesions (27).

Considering the dual roles of *C. albicans* as a commensal

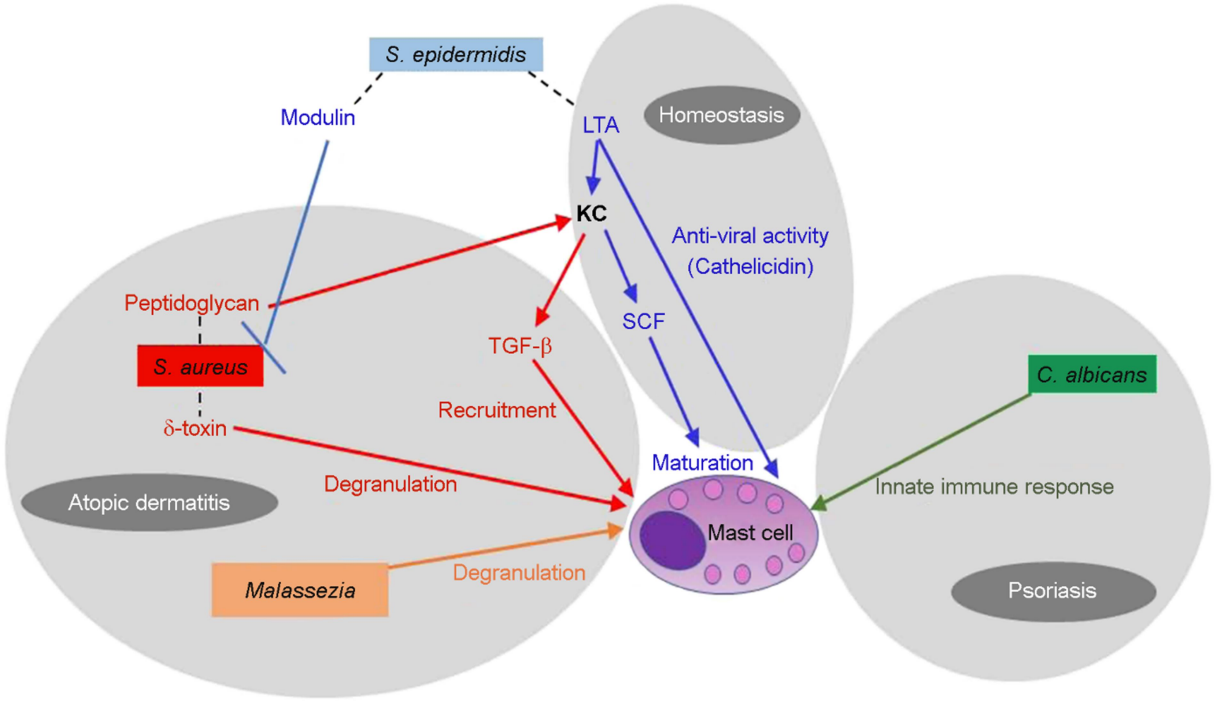

Figure 1. The network in skin microbiome and mast cells. *S. epidermidis*-derived LTA reinforces the clearance of virus (e.g., vaccinia virus) by increasing antimicrobial peptide, cathelicidin, in mast cells. LTA also promote mast cell maturation by triggering SCF in KC. *S. aureus* derived peptidoglycan can stimulate KC to produce TGF-β which lead to mast cells recruitment to the dermis in atopic dermatitis. The other byproduct of *S. aureus*, δ-toxin directly induce mast cells degranulation in the pathogenesis of atopic dermatitis. Phenol-soluble modulins produced by *S. epidermidis* can selectively inhibit *S. aureus*. The lipophilic yeast, *Malassezia sympodialis* can activate mast cells and exacerbate the inflammatory response in atopic dermatitis. *C. albicans* is frequently presented in psoriasis patients and correlate with disease severity. Mast cells produce cytokines, chemokine, and ROS in response to *C. albicans*. LTA, lipoteichoic acid; KC, keratinocytes; SCF, stem cell factor; TGF-β, transforming growth factor beta

and as a frequent human pathogen, *C. albicans* may elicit both an innate immune response and immune tolerance. As tissue sentinels, mast cells have a versatile and timed response upon encountering a fungus. Initially, human mast cells reduce fungal viability and occasionally internalize yeast cells, and secreted factors such as IL-8 in the supernatants of infected cells recruit neutrophils, critical phagocytes, to limit the infection. Late stages were marked by release of anti-inflammatory cytokines, including IL-1 receptor antagonist, suggesting a modulation of initial responses (28). In another study, *C. albicans* induces cytokine, chemokine, and reactive oxygen species (ROS) production in mast cells via Dectin-1 receptor signaling (29).

Collectively, the contribution of mast cells to the immune response to fungal infection could modulate the extension of skin inflammatory pathogenesis such as psoriasis.

CLOSING REMARKS

As an immune sentinel in the skin, mast cells are involved in both defense against pathogens and in maintaining the beneficial relationship between the host and their microbiomes (Fig. 1). The relationships between the two are wide-ranging, not only in sustaining normal skin physiology, but also in modifying inflammation and associated disease pathogenesis. Thus, enhanced understanding of the mutualistic relationship between the skin microbiome and host immune cells, such as mast cells, is necessary to gain insight into microbial involvement in human skin disorders and to enable novel therapeutic approaches for their treatment.

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