Nerve and Nerve Fiber Damage

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Abstract

Although sensory neurons play a significant role in regulating cutaneous inflammation, little was understood about how neurons contribute to host antimicrobial defence. Ray and colleagues have now shown that nociceptive fibers in the dermis, through their influence on dermal dendritic cells and production of IL-17A, play a critical role in antifungal defenses.

Keywords: Multiple sclerosis • Dermal Dendritic Cells • Neuropeptide • Chronic mucocutaneous candidiasis

Introduction

Mammalian skin is a highly innervated organ, but it has only recently been shown that there is a clear and direct connection between these sensory fibers and the cutaneous immunological network. Notably, local denervation has been seen to cause a remarkable improvement in mice models of psoriasis-like skin inflammation, suggesting that nerve fibers beneath the skin may play a crucial role in sustaining inflammation [1]. The revelation that Dermal Dendritic Cells (dDCs) trigger IL-23 production from nociceptor sensory neurons helped to partially explain the processes underlying this phenomenon. According to Moll, N. M et al (2013), these dDCs then stimulate skin-resident gd T cells to generate IL-17A, a key mediator of psoriasiform inflammation [2]. Clinical data in people showing that psoriatic plaques go better after local nerve injury further validated these findings. However, it was still unclear whether the skin sensory nerve system might be directly related to the antimicrobial capabilities of the cutaneous innate immune response.

The idea that nerves may detect germs is being supported by a growing corpus of research. For instance, it has been shown that a variety of membrane-bound receptors allow nerve fibers to directly feel bacteria [3,4].These fibers are activated before clinical inflammation appears which suggests that the sensory consequences of bacterial infections are caused by direct microbial stimulation of neurons rather than a consequence of inflammatory processes. Indeed, studies using in vitro and in vivo models have shown that bacteria and their products trigger a variety of quick sensory reactions, including the release of neuropeptides, vasodilation, and pain [5-8]. As a result, it is becoming more and more obvious that the peripheral nervous system is able to detect the microbiome and, as a result, is in a position to affect innate immunological processes existing in the skin and other organs [9,10].

In this issue of Immunity, Ray and colleagues add to this increasing body of research by establishing that cutaneous sensory neurons may identify *Candida albicans* and trigger IL-17-mediated protective immune responses [11]. The authors demonstrate that neurons cause the CD301b+ fraction of dDCs to create IL23, which in turn triggers the skin-resident gd T cells to produce IL-17A. This work lends credence to the idea that microorganisms can directly stimulate neurons.

The authors further demonstrate that enhanced neuropeptide CGRP release as a result of exposure to *Candida albicans* is both adequate and essential for inducing IL-23 expression in dDCs. The ability of the peripheral nervous system to detect the microbiome and, as a result, be in a position to influence innate immune processes present in the skin and other organs, is thus becoming more and more clearer.

The synthesis of IL-17 family cytokines and Th17 responses play a well-known part in cutaneous defence against a variety of pathogenic microorganisms, such as bacteria, fungi, and viruses. Patients with a number of diseases that affect Th17 cell formation and function exhibit greater susceptibility to infection with this bacterium, and protection from Chronic Mucocutaneous Candidiasis (CMC) appears to be mainly mediated by IL-17. Innate sources of IL-17 production in the skin have also been discovered in addition to traditional Th17 cells, most notably several classes of gd T cells, including Dendritic Epidermal T Cells (DETCs) [12-14]. IL17A produced by DETC is crucial for controlling skin defences and wound healing. According to MacLeod et al. (2013), this appears to be partially mediated by actions that stimulate the generation of Antimicrobial Peptide (AMP) by epidermal keratinocytes [15].

Although the current study by Ray and colleagues fails to clarify the mechanisms underlying IL-17A-mediated death of *Candida albicans*, it is likely that AMP generation and the attraction of phagocytic effectors to the infection site are components of the pathogen clearance processes.

Despite the fact that the precise effects of sensory neurons on cutaneous immunity are still being clarified, intriguing data has emerged demonstrating both the advantageous and disadvantageous consequences of their activation.

On the one hand, neuropeptide release appears to make the unjustified inflammation that causes the disease psoriasis worse.

The findings that sensory neuron ablation reduces psoriatic inflammation [1,2] serve as an illustration of this harmful effect of neuron activation. The data presented by Ray and colleagues illustrate the issue with immune-dampening effects of neural ablation, as it is predicted that attempts to treat disease by blocking nociceptive fibers will make the host more susceptible to infection with *C. albicans* [14]. It is interesting to note that Staphylococcus aureus activation of sensory neurons was shown to have immunosuppressive effects, as in this study neural ablation eliminated the pain response but increased cytokine production and inflammation [4]. The levels of gd T cell-derived IL-17A were not examined in this study, despite the fact that it has been demonstrated to be crucial for the innate immune response to *S. aureus* [7]. It is intriguing to think about how important the context of the interactions between immune cells, microorganisms, and brain cells will be for result prediction. It's possible that some infections have evolved to use neural activation as a virulence component or a means of establishing in comparison to other microorganisms. The pathogenesis of *S. aureus* may be facilitated by brain activity, but *C. albicans* survival appears to be adversely affected by same mechanisms. Co-infections with *S. aureus* and *Candida albicans* are very rare in patients with a healthy immune system.

It is generally known that psychological stress negatively affects cutaneous immunity as well since continuous stress delays healing and increases the likelihood of skin infections. The neuroendocrine circuits that stress signals trigger cause AMP synthesis to diminish, making the skin more susceptible to bacterial infections. Different from the nociceptive fibers revealed in the current work are neuroendocrine circuits. The immune system may respond differently to activation of various skin neural components, which could increase or decrease natural antimicrobial defences. Future research should explore the underlying molecular mechanisms that enable sensory neurons to recognize C. albicans. Through a number of processes, including formyl peptide receptors (FPRs), LPS activation of Toll-like receptor 4 (TLR4) and the cation channel TRPA1, and direct perforation of cell membranes by pore-forming toxins, bacteria are identified by and activate these nerve fibers.

TLR2 and Dectin-1 are known to be used by immune cells to detect C. albicans, although it is unknown if these receptors are expressed on sensory neurons. Finding out how *C. albicans* interacts with sensory neurons and figuring out whether or not various morphological forms or strains with various virulence exhibit altered capacity to trigger nociceptive fibers in the skin would be crucial.

For the first time, Ray and colleagues have demonstrated that a fungal pathogen activates sensory fibers to start an efficient antimicrobial response, adding significant new information to the growing body of evidence illustrating a complex neural-cutaneous immune axis [16]. These findings, together with previous evidence linking the neurological and immune systems directly, suggest that IL-17A production in the skin is rather nerve-wracking.

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