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RESEARCH HIGHLIGHT

# Pain-induced skin autoimmunity

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**A recent paper published in *Nature* reports sensory nerve fibers in the skin that give local immune cells important instructions for the organization of an immune response; in this particular case the cooperation between the nervous and immune systems had disastrous consequences, namely an auto-destruction of the skin.**

The relationship between the immune and nervous systems has been traditionally viewed as neutral at best: the systems "ignore" each other. This is highlighted by the anatomical structure of the blood-brain barrier, a border between the bloodstream and nervous tissue that nearly completely inhibits the entry of immune cells and soluble factors from the periphery into the central nervous system (CNS). When this border is breached, for example after trauma, stroke or (autoimmune) inflammation, the influx of immune cells can have dramatic consequences for the integrity of the CNS. However, there is also another, "social" side to the relationship between the immune and nervous systems. Immune cells in the area surrounding the CNS (the meninges and the perivascular space) effectively shield the nervous tissue from pathogenic intruders, helping the nervous system to function undisturbed. Activated T cells can even overcome the blood-brain barrier and patrol the nervous tissue for damage without causing perceptible problems. Immune cells also play an active role in neuronal function. For example, microglial cells, recognized as brain-resident immune cells, contribute to synaptic pruning and maturation by phagocytizing discarded synapses. A disturbance in the microglia function leads to severe neurological deficits [1].

Conversely, the nervous system exerts a regulatory influence on the immune system. For example, the activation of the hypothalamic-pituitary-adrenal axis induces the release of glucocorticoids, which can strongly modulate immune reactivity [2]. In addition, the CNS can directly act on the immune system through its widely distributed nerve fiber network: in the inflammatory reflex, a prototypical neural-immune reflex, vegetative nerves innervating the visceral organs upon activation secrete neurotransmitters that act directly on T cells and macrophages. A hyper-activation of these neuronal inputs, e.g. occuring after stroke, can bring drastic down-modulations in the immune function with life-threatening infectious consequences [3]. Interestingly, not only vegetative nerve fibers but also unmyelinated temperature and pain fibers participate in the cross-talk between CNS and immune system. Upon closer scrutiny, a synergy between innervatory pain fibers and immune cells is plausible: 1) These fibers are present in all types of tissue communicating with the outside; 2) Pain stimuli often occur together with tissue damage that requires an immune response; 3) Pain fibers express danger and damage receptors (e.g., TLRs and purine receptors) and thereby can directly react to immune-relevant stimuli; 4) Although pain fibers are among the slowest conducting fibers, electrical conduction is still much faster than immune cell mobilization; and 5) Pain fibers can conduct signals not only orthodromically (from periphery to CNS), but also antidromically (from CNS to periphery), inducing the release of neural mediators that can act locally on immune cells.

In their *Nature* paper, von Andrian and colleagues shed light on a specific facet of this synergy between the immune and nervous systems, namely how unmyelinated pain and temperature fibers in the skin affect the reaction of local dendritic cells and thereby contribute to a psoriasis-like autoimmune reaction [4]. Based on the clinical observation that psoriasis skin lesions are regularly accompanied by symptoms of irritation such as itchiness and pain and that the surgical or pharmacological impairment of peripheral nerve function in psoriatic lesions results in an amelioration of skin inflammation, the authors investigated how nerve fibers influence skin immune reactions in a mouse model of psoriasis induced by topical application of imiquimod (IMQ), an immune stimulating compound. This was achieved by an elegant complementary approach including pharmacologic, genetic and imaging tools. The authors showed that a specific subset of sensory fibers co-expressing the cation channel TRPV1 and the sodium channel $Na_v1.8$ and functionally responsible for the sensation of heat and pain, initiated the cutaneous immune response by inducing IL23 release by dermal dendritic cells (DDCs). IL23 then acted directly on resident γ/δ T cells, the main skin cell population expressing IL23 receptor, to induce IL17 and IL22 secretion with subsequent recruitment of immune infiltrates and thus the initiation of a pathogenic inflammatory response (Figure 1). This chain of events was thoroughly tested. The essential role of the unmyelinated sensory fibers was demonstrated by pharmacological

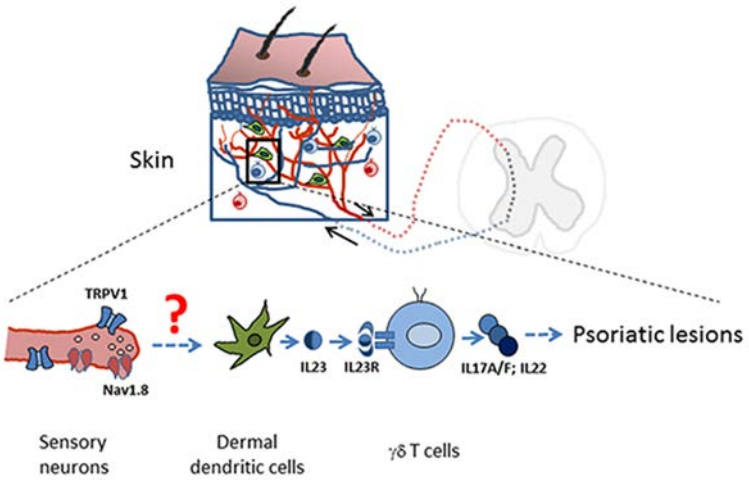


**Figure 1** Schematic drawing of intact skin. Afferent nerve (red); efferent nerve (blue). Magnification of the chain of events that drives the formation of the psoriatic lesions upon activation of the TRPV1$^+$ and Na$_v$1.8$^+$ sensory neurons.

silencing of their neuronal function by application of resiniferatoxin, a kind of ultrapotent chili pepper. This chemical completely suppressed IMQ-induced effects, which was verified by genetic ablation of the sensory nerves. In contrast, a sympathetic fiber pharmacological blockage by the catecholaminergic neurotoxin 6 hydroxy-dopamine did not change the IMQ-mediated inflammation. Of note, when IL23 was injected topically after sensory denervation, the inflammatory response was restored, pointing to a crucial effect of sensory neurons on the DDCs. The interactions between DDCs and sensory nerve fibers were corroborated by eye-catching imaging data. Intravital two-photon microscopy of intact skin in transgenic mice in which both the cutaneous nerves and the dendritic cells could be visualized elucidated the strategic location of the DDCs: around 75% of DDCs established close interactions with the sensory fibers along the entire length of the nerves.

By its very nature this impressive insight into such a complex immune-neuronal interaction raises numerous questions. For example, which signals regulate the communication between dendritic cells and nerve fibers? This also applies to the initial simulation of pain fibers, still completely unclear for human disease and also not fully understood for the IMQ model. IMQ exerts a stimulatory effect via the TLR signal cascade. Apart from DDCs, pain fibers also express TLRs. Are these fibers stimulated directly by IMQ or by factors from the DDCs or by other stromal or immune cells? Moreover, which neuronal signals stimulate the dendritic cells to release IL23? Do neuropeptides play a role that may be assumed from studies on "neurogenic inflammation" [5]? Neuropeptides like the CGRP, vasointestinal peptide or substance P have been associated with the regulation of skin Langerhans cells [6] and experimental inflammation in joints [7] and liver [8]. Although von Andrian and colleagues did not observe an effect of CGRP antagonists on skin inflammation, a role for CGRP cannot be completely ruled out, due to its complex modular structure and manifold biological effects. The observation that DDCs seem to be in direct physical contact with axons also suggests that electrical impulses or transmitter-type substances released at the contact points might influence DDC function. It is very likely that neuronal signals do not exclusively contribute to DDC activation but also control their "quiescence state". In this respect, neurotrophins such as NGF have been shown to downregulate the immune reactivity of microglia within the CNS [9]. A forced neuronal inactivity causes a reduction in neurotrophin secretion and an upregulation of MHC molecules. Interestingly, in psoriasis NGF has been assigned an active role in the induction of skin lesions via stimulation of epidermis epithelial cells, T cells and pain fibers [10]. Ultimately this interesting work by von Andrian and colleagues will surely inspire researchers to examine the stimulation mode of sensory fibers more closely, such as to name the receptors involved and to find out the extent to which electrical stimulation of sensory fibers play a role and whether the catalyst for the release of stimulatory nerve factors is an axonal reflex or local stimulus.

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