expression or altering the protein of a *LOG* gene prevented prickle formation.

Flowering plants have approximately a dozen *LOG* genes in their genomes, with the number varying depending on lineage-specific gene duplications and polyploidy (*6*). These duplications provide extra copies on which evolution can select for a new function. Control of prickle formation by *LOG* genes has been demonstrated in species as different as rice and barley (Poaceae) (*7*, *8*) and jujube (Rhamnaceae) (*2*), which suggests that evolution has selected repeatedly for involvement of the cytokinin pathway to drive the development of these sharp defensive structures. In most cases, the *LOG* gene copy deployed for prickle formation is from the same subclade of the gene family as *PL* and its orthologs (the *LOG1* clade), although in a few cases, such as in grasses, it is in a different subclade. The lack of strict orthology is evidence that the origins of prickles are indeed independent, as suggested by previous phylogenetic analyses (*5*).

LOG genes encode an activator of cytokinin that functions in the last step of the biosynthetic pathway (*9*). Free cytokinin is released from its precursor in a single reaction by *LOG*, a phosphoribohydrolase. In this respect, *LOG* enzymes are molecular switches, whereby the presence of a functional enzyme in a tissue drives local release of cytokinin, and the absence or loss of function of the enzyme prevents it. Correlation between prickles and the presence of a functional *PL* is observed in *Solanum*. In many cases, *PL* is a simple and direct controller of prickle formation, although other genes may be involved in a few cases (e.g., the Gboma eggplant).

PL was co-opted in *Solanum* from a conserved genetic background. *LOG* gene coexpression patterns are generally conserved among eudicots (flowering plants bearing two embryonic seed leaves), as seen in comparisons among cress (*Arabidopsis thaliana*), tomato (*S. lycopersicum*), and forest nightshade (*S. prinophyllum*). The set of *LOG* genes coexpressed with PL and its homolog in *A. thaliana* (*AthaLOG1*) is similar. Likewise, the genomic region around *PL* appears conserved at least since the common ancestor of the spiny *Solanums* and tomato (which is ancestrally prickleless). In forest nightshade, however, expression of *PL* diverges from that of its tomato ortholog, with higher expression in the floral meristem and prickles. An attractive hypothesis is that changes in the regulation of *PL* expression led to increased expression in floral tissues and ectopic expression in the epidermis of other parts of the plant, although the identity of such regulatory changes remains to be discovered.

Cytokinins are diverse compounds with multifarious roles in plant growth and development (*10*). As such, they do not seem like obvious candidates for lineage-specific and cell type–specific functions, such as promoting outgrowths from the fruit and stem epidermis. One would expect that mutations might be highly pleiotropic. However, Satterlee *et al.* disrupted *PL* in multiple species and saw no morphological or developmental changes other than loss of prickles. The specificity of *LOG* control of prickle formation and the lack of undesirable side effects help explain the repeated gain and loss of the gene and the structures that it controls over evolutionary time.

Identification of *PL*, development of extensive genomic tools, and the potential for editing of *PL* and other *LOG* genes all pave the way for experiments in both agricultural and natural ecosystems. Gene editing in a prickle-bearing species can, with one step, produce a plant with no prickles but leave all other aspects of growth and development intact. This has obvious implications for domestication and crop improvement. Gene-edited plants could also be useful for testing the ecological role of prickles. Mechanical defense can be costly for the plant (*11*), so disarmament should be favored when the price of defense is higher than the price of being attacked. A plant with a wild-type *PL* gene and its *PL*-edited progeny will otherwise be genetically identical, permitting direct assessment of the role of mechanical defenses themselves without the need to control for variance in genetic background. This approach would allow experiments that vary herbivore types and numbers to demonstrate which most affect plant fitness and thus selection on prickles. Combining such assessments with tests for selection on protein sequences and regulatory genetic elements could open new avenues for exploring natural and agronomic selection. ■

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NEUROIMMUNOLOGY

Mapping gut feelings and immune control

A chemogenetic screen reveals links between nociceptors and gut immune function

By **Nathalie Vergnolle**

The immune and neuronal systems have crucial roles in controlling tissue homeostasis. The gut, often referred to as the second brain owing to its dense innervation, also possesses a robust mucosal immune system. The gut immune system must protect against invasion by pathogens while tolerating commensal or beneficial microbes and food antigens. Although individual examples of regulatory interactions between specific neuronal subtypes and immune cells have been described (*1*, *2*), the full complexity of gut neuroimmune interactions remains poorly understood. On page 516 of this issue, Zhu *et al.* (*3*) report that dorsal root ganglion (DRG) sensory neurons are important regulators of regulatory T lymphocytes, a finding obtained by using comprehensive functional mapping to uncover discrete effects on gut immune cells by specific neurons in mice. Connecting pain and immune signals as pivotal regulators of mucosal homeostasis opens new therapeutic avenues to explore in the treatment of chronic gastrointestinal diseases.

The mammalian gut is densely innervated by a diverse range of autonomic and sensory neurons that are distributed intrinsically in gut tissues or project extrinsically from the DRG or nodose ganglia. Zhu *et al.* used a chemogenetic approach, based on the specific expression of DREADDs (designer receptors exclusively activated by designer drugs) in major classes of gut neurons, to comprehensively map how gut neuron activation affects immune cells. This allowed them to describe relationships between specific neurons and immune cells, such as nitrergic neurons regulating T helper 17–like cells or cholinergic neurons suppressing neutrophils.

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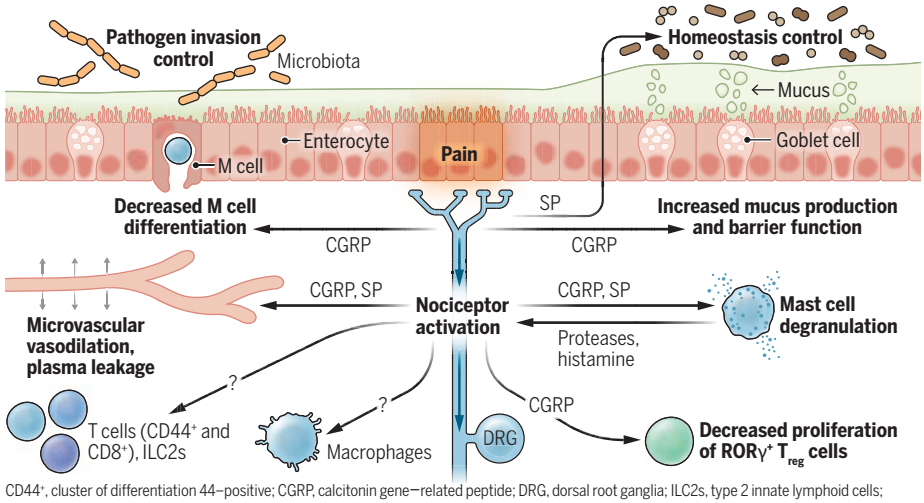
Zhu *et al.* also found that some neuronal subtypes govern multiple immune cells. For example, nociceptive neurons (cells that convey pain messages, also called nociceptors) regulate type 2 innate lymphoid cells (ILC2s), macrophages, retinoic acid–related orphan receptor-γ–positive (RORγ$^+$) regulatory T (T_{reg}) cells, and, to a lesser extent, the cluster of differentiation 44–positive (CD44$^+$) fraction of CD8$^+$ T cells. Notably, some immune cells, such as B lymphocytes, γδ T cells, and natural killer cells, remain unaffected by any neuronal subtypes. Additionally, the activation of some neurons (such as Piezo2- or vasoactive intestinal peptide–positive neurons) did not affect gut immunocytes. Although Zhu *et al.* focused on identifying the links by which cross-talk between nociceptive neurons and T_{reg} cells occurs, their findings lay the groundwork for unraveling the molecular mechanisms that underlie neuron-immunocyte interactions.

Under which physiological or pathophysiological circumstances neuronal activation affects immunocytes is unclear. Zhu *et al.* explored a semichronic (2 week) neuronal activation scenario, reminiscent of chronic inflammatory disorders. A DREADD in which a muscarinic guanine nucleotide–binding protein (G protein) q polypeptide (G_q) receptor was engineered to respond to clozapine *N*-oxide was administered to mice for 2 weeks to induce chronic activation of specific neurons. In this setting, nociceptive neurons (expressing the transient receptor potential vanilloid receptor-1) exhibited substantial immune regulation in the colon, characterized by a decreased presence of RORγ$^+$ T_{reg} cells and resulting in the exacerbation of colitis. This suggests that chronic inflammatory pain associated with prolonged nociceptor activation is not merely a consequence of immunocyte activity but also influences immunocytes in a reciprocal manner. It is worth noting that acute nociceptor activation over a few hours, as seen during infections, may also have varying effects on immunocyte function and could offer protective benefits, though this requires further validation.

Nociceptor activation (chronic or acute) can now be recognized as a key regulator of gut mucosal defense. The capacity of sensory neurons to trigger neurogenic inflammation by releasing neuropeptides, such as substance P (SP) and calcitonin gene–related peptide (CGRP), which induce microvascular vasodilation and plasma extravasation, has been extensively studied (*4*). Through SP release, nociceptors govern microbiota composition, influencing microbiota homeostasis (*5*). Sensory neurons also play a crucial role in host defense against infections by releasing CGRP, which diminishes microfold cell differentiation, restricting pathogen entry (*6*).

Pain and inflammation cross-talk

Nociceptor activation in the gut can exacerbate inflammation through the release of neuropeptides (CGRP,SP), dilation of blood vessels and plasma leakage, degranulation of mast cells, and decreased proliferation of T_{reg} cells. Nociceptor activation can also be protective, exerting homeostatic control on microbiota, increasing mucus release from goblet cells, and inhibiting microfold (M) cell differentiation, thereby limiting pathogen entry.



CD44$^+$, cluster of differentiation 44–positive; CGRP, calcitonin gene–related peptide; DRG, dorsal root ganglia; ILC2s, type 2 innate lymphoid cells; RORγ$^+$, retinoic acid–related orphan receptor-γ–positive; SP, substance P; T_{reg} cells, regulatory T cells

Although enteric neurons have been investigated as regulators of intestinal barrier function (*7*), recent studies have shown that sensory neurons also exert control over barrier integrity. Nociceptor activation stimulates mucus production by goblet cells in a CGRP-dependent manner, reinforcing the mucosal barrier and shielding mice from colitis (*8*). Furthermore, interactions between nociceptors and tissue-resident immune cells have been extensively documented. For example, in irritable bowel syndrome (IBS) patients, activated mast cells in proximity to colonic nerves have been associated with abdominal pain (*9*). Mast cells are triggered to release their granule content in response to exposure to SP and CGRP. Conversely, proteases and histamine, the major components of mast cell granules, serve as potent stimulators of nociceptive neurons, transmitting pain signals through the activation of protease-activated receptors (*10*) and histamine-1 receptors (*11*), respectively. Dysregulated communication between mast cells and sensory neurons can create a feedback loop that amplifies mucosal inflammation and pain.

The study by Zhu *et al.* highlights how gut nociceptors influence ILC2s, macrophages, CD44$^+$ CD8$^+$ T cells, and RORγ$^+$ T_{reg} cell populations in the colon. Although the mechanisms at play still need clarification, Zhu *et al.* show that sensory neurons modify T_{reg} cell proliferation through a CGRP-Ramp1–dependent pathway, resulting in heightened susceptibility to pathogen infection and colitis. Overall, nociceptors have multifaceted roles in the gut mucosa, which can either be protective, promoting tissue homeostasis, or harmful and proinflammatory, depending on their target cells and activation timelines (see the figure). The coordination between pain signals transmitted by nociceptors and immune cells could therefore be crucial for effectively managing tissue damage, with persistent pain potentially serving as an indicator of immune dysfunction.

Chronic pain is a common symptom in patients with IBS and is prevalent in a substantial portion of inflammatory bowel disease patients, even during periods of remission. Zhu *et al.* suggest that chronic pain might indicate the specific regulation of mucosal immunity through sustained nociceptor activation. In the realm of IBS, this implies that the immune aspect may have been underestimated, especially concerning T_{reg} cells, macrophages, or ILC2s. That managing pain could potentially yield beneficial effects on mucosal immunity opens new therapeutic avenues for treating gut inflammatory disorders that deserve further investigation. ■

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