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Sensory Systems in the Peripheral and Central Nervous Systems Shape Host Response During Infections

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Abstract—The function of sensory cells has been largely investigated in the field of neuroscience for how they report the physical and chemical changes of the environment (''exteroception'') and of internal physiology (''interoception''). Investigations over the last century have largely focused on the morphological, electrical and receptor properties of sensory cells in the nervous system focusing on conscious perception of external cues or homeostatic regulation upon detection of internal cues. Research in the last decade has uncovered that sensory cells can often sense polymodal cues, such as mechanical, chemical, and/ or thermal. Furthermore, sensory cells in the peripheral as well as in the central nervous system can detect evidence associated with the invasion of pathogenic bacteria or viruses. The corresponding neuronal activation associated with the presence of pathogens can impact their classical functions within the nervous system and trigger the release of compounds modulating the response to intruders, either triggering pain to raise awareness, enhancing host defense or sometimes, aggravating the infection. This perspective brings to light the need for interdisciplinary training in immunology, microbiology and neuroscience for the next generation of investigators in this field.

Sensory cells form a widely distributed net of cells throughout the body (Kandel et al., 2000). Exteroceptive cells in the peripheral nervous system are displayed at its interface with the environment: (i) under the skin, in muscle spindles, or in Golgi tendon organs for the dorsal root ganglia (DRG) neurons (Giacobassi et al., 2020; Körner and Lampert, 2022), (ii) in the mucosa of the lungs, with solitary chemosensory cells (Shah et al., 2009), in the gut, with tuft cells, and in the gingiva with solitary chemosensory cells (Zheng et al., 2019; Xi et al., 2022). In contrast, interoceptive cells are located within the nervous system itself such as nociceptors at the interface with the cerebrospinal fluid (CSF) in the meninges or polymodal mechano- and chemo-receptors in the central canal (Pinho-Ribeiro et al., 2023; Orts-Del'Immagine and Wyart, 2017).

Sensory cells are often polymodal: DRG neurons sense temperature (García-Ávila and Islas, 2019), as well as chemical and mechanical cues (Berta et al., 2017; Lee and Chen, 2018). Other sensory neurons, referred to as cerebrospinal fluid-contacting neurons or CSF-cNs, are also chemosensory and mechanosensory cells (Böhm et al., 2016; Jalalvand et al., 2016; Orts-Del'Immagine et al., 2020; Wyart et al., 2023).

SENSORY CELLS RESPOND TO PATHOGEN INTRUSION, MODULATE PAIN AND ALTER HOST DEFENSE

In the peripheral nervous system, sensory cells can detect the intrusion of pathogens from the skin or in the different mucus such as in the nose, mouth or lungs (Lagomarsino et al., 2021). In particular, solitary chemosensory cells (SCCs) act as epithelial sentinels in the human respiratory epithelium and respond to harmful chemical and biological agents via taste receptors (Finger et al., 2003). In the upper respiratory epithelium, both bitter (T2R) as well as sweet taste receptors (T1R2/3) are present in nasal SCCs and can be activated by bacterial byproducts, bacterial cell-wall components (*i.e.*, D-amino acids) or changes sugar content in airway surface liquid, resulting in the modulation of the innate immune response by releasing antimicrobial peptides (Lee et al., 2014, 2017). Moreover, motile cilia of human airway epithelia are also sensory organelles dotted with bitter taste recep-

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tors (T2R). The activation of these receptors by bitter compounds resulted in increasing cilia beating, suggesting that these receptors can detect harmful substances and contribute to their active elimination from the lungs (Shah et al., 2009). Furthermore, some bacteria such as *Mycobacterium tuberculosis* activates airway sensory neurons via a different mechanism – the direct detection of sulfolipid-1 – which promotes the coughing reflex (Ruhl et al., 2020), suggesting there are potentially multiple mechanisms for sensory neurons to detect irritants and clear the airway.

The role of nociceptive dorsal root ganglion neurons in responding to cutaneous infections is complex and context-dependent. TRPV1-positive cells respond directly to bacterial infections (e.g. *S. aureus*) as a consequence of bacterially-secreted pore forming toxins increasing nociceptor activity (Chiu et al., 2013; Blake et al., 2018; Yang et al., 2021); they also express Toll-like receptor (TLR) 4 and 5 which respond to lipopolysaccharide and flagellin respectively (Hayashi et al., 2001; Wadachi and Hargreaves, 2006). The detection of N-formyl peptides by formyl peptide receptors (FPRs) represents a third avenue by which nociceptive neurons are activated during infection. Though the direct activation of nociceptive neurons by these bacterial components most obviously causes pain, there are additional downstream ramifications with respect to host defense. The consequence of TRPV1 + nociceptor activation is typically calcitonin gene-related peptide (CGRP) release. This in turn can suppress neutrophils and monocytes (effectively a maladaptive response) and ablating these neurons leads to greater recovery from *S. pyogenes* infection (Pinho-Ribeiro et al., 2018). However, in other contexts, CGRP release has protective effects. Ablating nociceptive neurons increases susceptibility to *C. albicans* infection, and in experiments where TRPV1 + cells are optogenetically activated, animals exhibit reduced susceptibility to *S. aureus* infection (Cohen et al., 2019). The specific spatiotemporal context of nociceptor recruitment is therefore likely to be determinative of whether that recruitment is beneficial or harmful overall.

In the gut, the gastrointestinal epithelium is similarly protected by nociceptive neurons in communication with immune cells. Enteric neurons secrete the chemoattractant colony stimulating factor 1 (CSF-1) which acts to maintain resident macrophages in the gastrointestinal niche (Muller et al., 2014). Innate lymphoid type 2 cells (ILC2s) respond to neuronally-secreted neuromedin U and, in fact, knockout mice for the cognate receptor are indeed more susceptible to parasitic *N. brasiliensis* infection (Cardoso et al., 2017; Klose et al., 2017).

The symbiosis between the gut microbiome and sensory neurons is perhaps even more profound. It is characterized by a fascinating degree of bidirectional communication. This is perhaps most apparent in the apparent synthesis of neurotransmitters by gut microbes. Specifically, *Lactobacillus* and *Bifidiobacterium* genera release GABA and in doing so reduce visceral pain (Barrett et al., 2012; Li et al., 2013) while a particular strain of *E. coli* modulates a GABAB receptor by synthesizing the analgesic lipoprotein C12AsnGABAOH (Pérez-Berezo et al., 2017). Gut symbiotic bacteria generate a number of short chain fatty acids by fermentation (SCFAs, e.g. butyrate, proprionate, and acetate) which regulate neuronal activity and act as analgesics against visceral pain (Gschossmann et al., 2001; Russo et al., 2016; Dalile et al., 2019; Van Thiel et al., 2020). Investigating the way gut microbes communicate and collaborate with sensory neurons in the enteric nervous system or visceral DRG will no doubt prove to be a fascinating course of inquiry for years to come.

The central nervous system has historically been seen as an immune privileged site and research on the innate immune response upon pathogen invasion has focused mainly on cells in the brain, including neurons, while not much is known about the role of sensory neurons (Forrester et al., 2018). However, recent studies have shown that sensory neurons in the dura and cerebrospinal fluid-contacting neurons (CSF-cNs) play a role in the pathogenesis and control of central nervous system infections (Pinho-Ribeiro et al., 2023; Prendergast et al., 2023; Wyart et al., 2023). Pinho-Ribeiro et al. showed how common causative agents of meningitis,*Streptococcus pneumoniae* and *S. agalactiae*, activate the Nav1.8 channel on dural somatosensory neurons, which release the CGRP neuropeptide (Pinho-Ribeiro et al., 2023). Ablation of Nav1.8 in DRG blocked CGRP production in response to bacteria (Pinho-Ribeiro et al., 2023). The bacterial pore-forming toxins pneumolysin and beta hemolysin, a ligand-receptor interaction shown previously by this group for staphylococcal alpha hemolysin in skin infection, were instrumental to activate the Nav1.8 channel (Pinho-Ribeiro et al., 2023). Once produced, CGRP bound its receptor RAMP1 on dural macrophages to signal suppression of chemokines and cytokines- this process leads to failure to clear bacteria and subsequent death of the mice (Pinho-Ribeiro et al., 2023). In our study, we showed that *Streptococcus pneumoniae* can activate CSF-cNs in the central canal of zebrafish larvae during central nervous system infection *in vivo* (Prendergast et al., 2023). Interestingly, bacterial and viral metabolites induce similar activation of CSF-cNs Prendergast et al., 2023. Upon activation, CSF-cN neurosecretion is important to control central nervous system infection by *Streptococcus pneumoniae* in zebrafish larvae (Prendergast et al., 2023; Wyart et al., 2023).

Signaling via sensory cells can sometimes induce pain and awareness, as well as benefit unconsciously to host defense. However, recent studies have provided evidence that sensory systems can also be hijacked to promote pathogen invasion. In addition to interactions between sensory and immune signaling, neuroimmune interactions can also occur via the autonomic nervous system (Udit et al., 2022).

Future research should focus on unraveling the detailed interaction between these sensory neurons and innate immune cells using advanced imaging and molecular techniques. We have shown that the zebrafish can be used as a powerful tool to study the role of CSF-contacting neurons during infection because of its genetic tractability and optical translucency at the

early stages of development (Lieschke and Currie, 2007; Prendergast et al., 2023; Wyart et al., 2023). This allowed us to visualize real-time *in vivo* the activity in CSF-cNs in response to pathogen invasion (Prendergast et al., 2023). The next step would be real-time *in vivo* imaging of interaction dynamics between sensory cells and components of the innate immune system based on our transcriptome analysis, and to elucidate the signaling pathways and activation in both cell types. Spatial transcriptomics, which allows the measurement of gene activity (Marx, 2021), could enable to map which transcripts are only expressed in the cells whose neuronal activity is abnormal.

A promising new model species for neurophysiological studies of the central nervous system is *Danionella*, a small teleost fish with the smallest known vertebrate brain that remains transparent until adulthood (Schulze et al., 2018). As compared to wild-type rodent and zebrafish models, the power of this model lies in the fact that the central nervous system, the behavior and brain body interactions of an adult animal can be studied across all cells of the body in real-time *in vivo* (Penalva et al., 2018; Schulze et al., 2018; Lam, 2022).

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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