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Editorial: Accessory Cells of Sensory Systems and Their Functional Roles

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Editorial on the Research Topic

Accessory Cells of Sensory Systems and Their Functional Roles

INTRODUCTION

Humans experience the world through the five primary senses: sight, touch, hearing, smell, and taste, most of which are conserved across the animal kingdom. Acute loss of one of these senses can be disorienting and prolonged sensory impairments can greatly impact one's quality of life. Environmental stimuli are received by specialized sensory structures innervated by neurons to elicit an appropriate behavioral response (Roper and Chaudhari, 2017; Seabrook et al., 2017; Driver and Kelley, 2020; Ray and Singhvi, 2021), for example, the retraction of a hand from a hot or freezing surface. Sensory neurons are accompanied by a diverse group of non-neuronal cells including glia. Accessory cells/glia are essential regulators of neuronal health through direct metabolic coupling and through careful maintenance of ionic balance at peripheral and central synapses (Ray and Singhvi, 2021). An increasing body of evidence has revealed that glia are not only "support" cells, but directly influence circuit architecture and signaling (Lago-Baldaia et al., 2020; Perez-Catalan et al., 2021; Ray and Singhvi, 2021). In this issue, "*Accessory Cells of Sensory Systems*," new studies highlight the importance of non-neuronal cells to *Sight*, *Touch*, *Hearing*, and *Smell*, from phagocytic function following injury, to tuning of neuronal activity.

SIGHT

Müller cells are a major type of glial cell in the retina, and they are responsible for homeostatic and metabolic support of retinal cells (Reichenbach and Bringmann, 2013). In particular, Müller cells mediate transcellular ion, water and bicarbonate transport, glutamate uptake, and they provide trophic and anti-oxidative support to the cells of the retina. In addition, Müller cells guide light through the inner retinal tissue, thus enhancing the signal/noise ratio (Franze et al., 2007). In disease conditions, a subset of Müller cells may differentiate into neuronal progenitor cells, thereby giving rise to new photoreceptors and neurons (Das et al., 2006; Bernardos et al., 2007; Roesch et al., 2008). Müller cells also have phagocytotic functions (Long et al., 1986).

In this issue, Lew et al. investigated the molecular underpinnings of Müller cell-mediated phagocytosis, a process still largely uncharacterized, and its consequences on photoreceptor degeneration. Using in culture phagocytosis assays, two distinct *in vivo* models, western blots, and

immunocytochemistry, the authors demonstrate that phagocytosis of photoreceptor outer segment fragments (POS) by human and murine Müller cells is mediated by the TAM engulfment receptor tyrosine kinase MERTK, which has been implicated also in Retinal Pigmented Epithelium (RPE)-mediated phagocytosis (Gal et al., 2000; Parinot and Nandrot, 2016). The authors also show that MERTK utilizes both galactin-3 and protein S as its ligands. These two ligands most likely share the same binding site because their effect on phagocytosis is not additive. Knockout of *mertk* or of the gene encoding galactin-3, *lgals3*, lead to degeneration of photoreceptors by postnatal day 35 and activation of the Müller cells as measured by Glial fibrillary acidic protein (GFAP) expression. Interestingly, $mertk^{-/-}$ and $lgals3^{-/-}$ double knockout mice show significantly enhanced Müller cell activation and photoreceptor degeneration as compared to the single knockouts. The authors exclude the involvement of microglia in this effect and thus conclude that it must be mediated by the Müller cells themselves. To conclude, this study identifies galactin-3 acting on Müller glial cells, as a protective factor in photoreceptor degeneration. Notably, previous studies showed that microglia activation is reduced in galactin-3-defective models, highlighting that galactin-3 may have opposite effects on microglia vs. Müller cells. This urges the consideration of cell-specific approaches for the studies of these mechanisms and for the identification of future therapeutical approaches.

TOUCH

Four of the five types of touch receptors embedded in the human skin are composed of nerve endings and accessory cells. These include the Pacinian, Meissner, and Ruffini corpuscles, and the Merkel disks. In addition, the Krause bulbs, which detect vibrations in addition to cold temperature, are also composed of nerve endings and accessory cells. On the other hand, the free nerve endings that detect temperature, painful stimuli, and light touch, are unencapsulated dendrites of sensory neurons voided of any type of accessory cells. In a review published in this issue, Suazo et al. update us on what is known about the anatomy, development, as well as function of Meissner and Pacinian corpuscles that detect light touch and vibration, respectively, primarily focusing on their accessory cells. Indeed, in both the Meissner and Pacinian corpuscles, flattened Schwann cells form lamellae organized in parallel (Meissner) and concentric (Pacinian) structures around the nerve terminal. Both corpuscles also have outer capsules composed of perineurial fibroblast-like cells and contain a complex extracellular matrix. While initially the lamellae of the Meissner and Pacinian corpuscles were thought to primarily provide structural integrity to the corpuscles, their cellular and functional features suggest that they have major roles in the transduction of touch. Indeed, recent work on the Meissner and Pacinian corpuscles from the duck bill (called Grandry's and Herbtst corpuscles, respectively, in the duck) by the lab of Bagriantsev has shown that these cells are endowed with mechanically gated ion channels. The lamellae of the Meissner corpuscles also express R-type voltage gated calcium channels and can fire action potentials when stimulated by current injection or by mechanical forces (Nikolaev et al., 2020; Ziolkowski et al., 2022). These exciting new data not only support that these cells are intrinsically mechanosensitive, but also that they can propagate this information potentially to other cells. Intriguingly, electron micrographs of the lamellar cells from the cat show that they have clear core vesicles and electron dense regions near the plasma membrane reminiscent of synapses (Pawson et al., 2009). Furthermore, lamellar cells from the Pacinian corpuscles of the cat express synaptic proteins synaptobrevin VAMP2 and SNAP-23 (Pawson et al., 2009). Pawson and colleagues using electrophysiological techniques on the Pacinian corpuscles of the cat, demonstrated that GABA released by the lamellae inhibits action potentials in the nerve ending during the static portion of the indentation (Pawson et al., 2009). They also showed that glutamate released by the nerve ending is responsible for action potentials during the static portion of the indentation and that most likely induces GABA release from the lamellar cells (Pawson et al., 2007, 2009). These older data combined with new results obtained from Meissner and Pacinian corpuscles of the duck paint a picture of a complex cross talk between accessory cells and nerve endings in these corpuscles that might be crucial for touch sensation. Intriguingly, a similar mechanism of cross talk and analogous mechanosensitivity of accessory cells have been described for the nose touch receptors of the nematode *C. elegans*, suggesting conservation of function across species (Fernandez-Abascal et al., 2022). Future studies leveraging the power of genetics in the duck and in invertebrate models should help dissect this mechanism of cross talk even further and should identify the mechanosensitive channels expressed in the lamellar cells.

HEARING

Hearing is an essential sense that not only allows us to enjoy the world around us, but also to navigate our environment with high precision. The sensory organ required for proper hearing is called the organ of Corti, housed in the cochlea (inner ear). In the cochlea, sound vibrations activate mechanosensory cells called hair cells, which decode vibrational information (sound) to precisely stimulate the auditory nerve and in turn, auditory cortex. Proper signaling within auditory circuits requires a variety of both peripheral and central glia, including Support Cells within the organ of Corti, Schwann cells, Satellite Glia, Oligodendrocytes, and Astrocytes (Kohrman et al., 2021). Another prominent, non-neuronal cell population within the cochlea are tissue-resident macrophages, which are thought to carry out homeostatic roles in healthy tissues (Hough et al., 2022).

Chronic exposure to loud noises can lead to long-term hearing loss due to loss or dysfunction of hair cells and associated glia (astrocytes and microglia). In addition, deleterious sound is followed by a robust increase in macrophage populations within the cochlea (Hirose et al., 2005). Shortly following noise exposure, immune cell engulfment of damaged hair cells is important for cochlear health; however, long-term inflammation can ultimately lead to hearing loss (He et al., 2020). In this issue, Shin et al.

characterize the source and trajectory of cochlear immune cells in a mouse model of acoustic overstimulation. Using RNAseq, they find that the pro-inflammatory cytokine *Ccl2* is upregulated in the cochlea a mere 3 h following noise exposure. Within 1–2 days post noise, peripherally-derived monocytes infiltrate the cochlea, where they subsequently transform into macrophages. Importantly, depletion of monocytes (and thus macrophages) following overstimulation does not prevent hearing loss, consistent with the early requirement of macrophages in debris clearance (Bae et al., 2021). Together, these findings suggest that anti-inflammatory therapies to prevent noise induced hearing loss must be temporally restricted.

SMELL

Olfaction, the perception of volatile chemosensory cues, is one of the most ancient sensory modalities. Olfactory sensory neurons sense odor molecules at either the olfactory epithelium in vertebrates, or in specialized sensory units in invertebrates, called sensilla (Vosshall, 2000; Buck, 2004). These anatomical structures house both neurons and glia. The underlying sensory neuron transduction machinery that transmits odor information has been exquisitely dissected (Shirsat and Siddiqi, 1993; Wilson, 2013), and glia have been shown to secrete odor binding proteins and clearance enzymes (Sun et al., 2018). However, how sense-organ glia impact olfactory perception is only recently being explored (Bianchi, 2020; Duan et al., 2020).

Drosophila sense odorants at structures on their antenna called sensilla, that house 2–4 sensory neurons and three support cell sub-types called trichogen, thecogen, and tormogen (Sen et al., 2005). Using genetically encoded sensors for K^+ and Ca^{2+} expressed in different support cells, Prelic et al. uncovered active cellular responses in glia. First, they observed that thecogen and tormogen glia exhibit distinct patterns of ion fluxes upon presentation of the odor proxy VUAA1, concomitant with neuron activation. Next, by genetically ablating thecogen glia in adults, they found that individual sensory units exhibit altered mechanical sensitivity without alteration of resting neuron activity. This suggests the intriguing notion that these glia may contribute to odor processing by aiding detection of spatiotemporal odorant pulses as would be experienced during the air turbulence experienced during the animal flight. These findings parallel recent work in *C. elegans* showing glial responses to odorants (Duan et al., 2020).

CONCLUSION

Emerging studies, including those described above, reveal more active participation by glia and other accessory cells in sensory perception than previously appreciated. Mechanistically, these cells do so by phagocytosis of sensory endings and cells (Raiders et al., 2021; Lew et al.), modulation of ionic milieu (Ray and Singhvi, 2021), and release of neuromodulators (Pawson et al., 2007, 2009; Duan et al., 2020; Fernandez-Abascal et al., 2022). This is of note since at least in *C. elegans*, glia can respond to diverse external stimuli independent of neurons (Procko et al., 2011; Duan et al., 2020; Fernandez-Abascal et al., 2022). How different glia across sensory systems regulate these functions in response to sensory cues remains largely a mystery to date, presenting a rich avenue for future inquiry. We propose that an understanding of how sensory percepts are processed in the periphery in health or sensory disorders requires not only a dissection of how a sensory cell or neuron functions, but rather a composite study of how sense-organ glia-neuron units coordinately respond to environmental cues.

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SDA wrote the Hearing and Introduction sections. AS wrote the Smell and Conclusion sections. LB wrote the Sight and Touch sections, and curated literature citations and final edits. All authors contributed to the article and approved the submitted version.

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