

The Sensation of Itch: From Biological Discovery to Medical Treatment

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Itch is an evolutionarily conserved sensation in vertebrates, and in its acute form, elicits a scratching reflex to expel environmental irritants such as insects, parasites, and toxins. However, in its chronic form, itch becomes highly debilitating and pathologic. Although originally considered a mild form of pain, the discovery of itch-specific molecular and cellular pathways in the last 15 years have greatly emboldened itch biology as a distinct field of inquiry (Wang and Kim, 2020). Furthermore, the unprecedented success of numerous therapeutics in this nascent field has drawn tremendous interest in solving the central symptom of itch across a number of medical disorders.

As part of a collection of reviews on itch published in the *Journal's* January 2022 issue, Mu and Sun (2022) highlight how the original discovery of GRPR as an itch-specific molecule (Sun and Chen, 2007) has unveiled complex circuitry within the spinal cord whereby different neurons promote or modulate itch signals from the periphery. They then describe how prior studies have identified a number of different itch processing centers within the brain, such as foci within the cortex and thalamus, and how recent advances point to a role for the parabrachial nuclei as well (Carstens and Akiyama, 2016; Mochizuki and Kakigi, 2015; Mu et al., 2017). Within the brain, the interconnectivity

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of these areas to other regions such as the amygdala and ventral tegmental area are starting to reveal how itch is associated with different emotions (e.g., anxiety) and reward behavior, respectively (Yuan et al., 2018). However, how perception of itch is triggered in a specific manner via these circuits remains an open question. Furthermore, how these areas within the brain promote a heightened perception of itch, referred to as central sensitization, is another active area of inquiry.

Extending into the periphery, Guo et al. (2022) highlight newly identified itch-associated pathways, including the Mas-related G protein-coupled receptors and brain natriuretic peptide in sensory dorsal root ganglia neurons (Liu et al., 2009; Mishra and Hoon, 2013). By reviewing how sensory neurons have been shown to react to a variety of exogenous signals such as pathogen-associated molecular patterns and proteases and endogenous cytokines, they

put these functional studies into the context of new single-cell RNA sequencing studies that have informed and, in part, validated the itch-specific identity of pruriceptors (Usoskin et al., 2015). The effect of itch-associated molecules on neurons and their homologs on epithelial cells and mast cells, respectively, and their contribution to itch are also described.

Building on the advances in the peripheral neurocircuitry of itch, Tseng and Hoon (2022) take a single cell systems-based approach to advance the concept that there may be modules of pruritogenic pathways that are activated and aligned across immune cells, neurons, and a variety of stromal cells beyond keratinocytes, such as endothelial cells. They propose that understanding the networks of interactions across the neuro-immune-stromal triad is critical to fully informing how itch-associated tissue programs translate to behavior. Shibuya et al. (2022) then highlight how a number of these stromal cell–(IL-33 and TSLP) and immune effector cell–derived (e.g., IL-4, IL-13, and IL-31) cytokines act on sensory neuronal pathways (e.g., Jak) to promote itch. They then explain how these neuro-immune-stromal networks are disrupted in the context of emerging targeted therapies with profound effects on itch outcomes in diseases such as atopic dermatitis (AD), prurigo nodularis, and beyond (Trier and Kim, 2018; Yang and Kim, 2019).

Herein, the very pioneers of itch biology highlight a new and dynamic paradigm at the intersection of immunology, neuroscience, and stromal biology. Furthermore, they display an interdisciplinary scientific paradigm that in turn translates into multiple specialties of medicine, including allergy and immunology, dermatology, neurology, and beyond. As the mysteries of what causes itch are rapidly unraveled in the coming years, there are a number of future questions that remain. How specific are these pathways for itch at every level from the tissue to the spinal cord and brain? Can itch as a symptom be selectively targeted independently of its association with a defined disease (e.g., AD)? Finally, does the diversity of itch pathways being unveiled explain the

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heterogeneity of chronic pruritic disorders while also providing targets for new therapeutics? Ultimately, these articles by Mu and Sun (2022), Guo et al. (2022), Tseng and Hoon (2022), and Shibuya et al. (2022) spotlight how seminal new advances in itch biology are rapidly informing and translating to new therapies for this historically overlooked sensation.

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CONFLICT OF INTEREST

BSK is a Consultant for AbbVie, Cara Therapeutics, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Trevi Therapeutics. TM states no conflict of interest.

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