Montagna Symposium on the Biology of Skin

Montagna Symposium 2016—The Skin: Our Sensory Organ for Itch, Pain, Touch, and Pleasure

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The 65th annual Montagna Symposium on the Biology of the Skin, "The Skin: Our Sensory Organ for Itch, Pain, Touch and Pleasure," was held October 20–24, 2016, in Gleneden Beach, Oregon, USA. Gil Yosipovitch (University of Miami, Florida) served as Program Chair, with Ethan Lerner (Harvard Medical School/Massachusetts General Hospital, Boston), Diana Bautista (University of California, Berkeley, California), Ellen A. Lumpkin (Columbia University, New York, New York), and Francis McGlone (Liverpool John Moores University, UK) serving as Session Chairs.

Although knowledge gained from research on each class of skin sensory nerve fiber—in health and disease—has been substantial in recent years, these classes have largely been studied separately, and crucial questions remain unanswered regarding the overlap and integration of these parallel cutaneous somatosensory pathways. For example, both itch and pain interact in an antagonistic manner: scratch-induced pain can relieve itch, frequently producing pleasure; opioids can induce itch, and their receptor antagonists have been shown to be effective in its treatment. There are broad overlaps, with evidence of a common mechanism in peripheral sensitization and in central sensitization to itch and pain, implicating Aβ- and C-fiber nociceptors. Presenting up-to-the-minute research on the multifaceted properties of skin sensory receptors, nerves, and central projections highlighted the often unrecognized strong interactions between them and provided exceptional opportunities for the fertile discussions that followed each talk, touching on the potential to translate across experimental and clinical contexts.

The symposium began with a keynote lecture from Francis McGlone on the role of C fibers in humans. Although C fibers have a classic role as polymodal nociceptors, pruriceptors, and autonomic efferents, Dr. McGlone emphasized that in humans, and in all mammalian skin, a subset of C fibers called C-tactile afferents (CT) responds to low-force touch. Their discovery in human hairy skin has led to a view of the skin as a "social organ" as well as a "protective organ." Dr. McGlone introduced the concept of a "hedonic homunculus" to emphasize that these fibers have a distinct central projection to a para-limbic brain area, the insular cortex, that processes information concerned more with "feeling" than "sensing."

The presentations in the "Itch" session were primarily neurocentric and incorporated crosstalk with the immune system and the cutaneous environment. The use of state-of-the-art techniques was a feature of this session, including the power of genetics to investigate neurocircuits, optogenetics, ex vivo preparations consisting of skin attached to the spinal cord, and imaging. These approaches allowed for detailed information to be communicated with respect to current knowledge regarding mediators, modulators, neurocircuitry, and therapeutic targets.

Session Chair Ethan Lerner set the tone with provocative questions: "Why do we itch (To remove pathogens? To keep the immune system active?)" and "What is the sequence of events? (Is it the itch that "rashes" or the rash that itches?)" Dr. Lerner then shared work from his laboratory, first focusing on the role of sensory neurons in the development of skin inflammation and itch using in vivo imaging in a mouse ear skin allergic hypersensitivity model and then showing that substance P-evoked scratching, which was originally thought to be mediated by the neurokinin-1 receptor (i.e., NK1R), is mediated by Mrgpr receptors.

Earl Carstens (University of California, Davis) presented behavioral and expression data suggesting that neurokinin-1 receptor is a key component of itch-specific spinothalamic projection neurons. He also highlighted recently developed genetic and induced models of chronic itch (including mouse models of psoriasis and a model with dietary deprivation of polyunsaturated fatty acids that results in skin rash), as well as methods for studying enigmatic neuropathic itch, or alloknesis.

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Abbreviations: CT, C-tactile afferent; LTMR, low-threshold mechanosensory neurons

Sonja Ständer (University of Münster, Germany) presented findings from clinical studies using quantitative sensory testing on patients in conjunction with experimental therapies to treat neuropathic and recalcitrant itch. Of the topical treatments, they have tested an 8% capsaicin patch and found significant relief of chronic itch for months after just a single 1-hour application.

Diana Bautista followed up with her laboratory's recent work on mouse models of acute and chronic itch. She provided behavioral data showing that certain immune cells, previously implicated in pain hypersensitivity, play a role in both acute and chronic itch. Her group has found that a chemokine associated with human atopic dermatitis is sufficient to evoke itch behaviors and is correlated with itch in a mouse model of atopic dermatitis, extending her previous study, which exploited natural variation in itch behaviors among genetically distinct mouse strains to identify itch-associated candidate genes in sensory neurons and spinal cord.

Mark Hoon (National Institute of Dental and Craniofacial Research, Bethesda, Maryland) related his laboratory's recent work on the role of somatostatin-expressing sensory neurons in itch. His group has found that natriuretic peptide precursor B-expressing somatosensory neurons, thought to specifically transmit itch signals, co-express the neurotransmitter somatostatin. Dr. Hoon detailed a variety of optogenetic and genetic tools being used (i) to test the hypothesis that somatostatin is an important itch-specific neurotransmitter required for spinal processing of itch via inhibition of inhibitory interneurons and (ii) to understand how the release of somatostatin from primary afferents modulates spinal cord processing of itch and response to counter stimuli.

Sarah Ross (University of Pittsburgh, Pennsylvania) focused on the role of counter stimuli in itch inhibition via a specialized class of spinal cord neurons that her group discovered, the Bhlhb5-expressing inhibitory neuron (B5-I), and their importance in integrating itch and pain signals. Her group used a system for ex vivo stimulation of the periphery or dorsal root ganglion while simultaneously recording from the Bhlhb5-expressing inhibitory neuron population in the dorsal horn of the spinal cord. They have shown an electrophysiological basis for the inhibition of itch via soothing menthol or painful capsaicin via activation of the Bhlhb5-expressing inhibitory neuron population, which expresses neuronal nitric oxide synthase and galanin, and have also shown a role for dynorphin tone in the spinal cord as a means by which Bhlhb5-expressing inhibitory neuron activity is modulated and itch is actively suppressed.

The "Itch" session closed with a talk from Nicole Ward (Case Western Reserve University, Cleveland, Ohio), who related her laboratory's work on the interplay of neurons and immune cells in genetic and induced mouse models of psoriasis. Dr. Ward described the dermatome-specific manifestation of psoriasis in humans and the role of skin innervation in the pathogenesis of the *KcTie2* and the imiquimod psoriasis mouse models, showing that denervation leads to skin thinning and attenuation of disease phenotype.

Discussion of the relationship and the molecular level between itch and pain, for example, through release of factors in itch that block pain, provided an intriguing segue to the next session.

The "Pain" session, chaired by Diana Bautista, focused on the molecular and cellular mechanisms underlying acute and chronic pain in the periphery and spinal cord. Presentations and productive discussion introduced cutting-edge techniques and novel therapies and centered on three issues: (i) the use of novel molecular genetic tools to define and manipulate the molecules, cells, and circuits of pain; (ii) the pros and cons of distinct animal models of pain; and (iii) the identification of novel therapeutic targets and approaches and how to move them from the bench to the clinic.

The use of sophisticated tools to define and manipulate the molecules, cells, and circuits that drive pain was a major theme of this session. Cheryl Stucky (Medical College of Wisconsin, Milwaukee) shared work on the use of optogenetics to examine the role of calcitonin gene-related peptide-positive dorsal root ganglion neurons in neuropathic, incision, and inflammatory pain. Rebecca Seal (University of Pittsburgh, Pennsylvania) discussed her study of transgenic mice that express designer receptors exclusively activated by designer drugs, or DREADDs, in the vesicular glutamate transporter type 3-positive dorsal horn neurons in neuropathic and inflammatory pain models. She described the identification of novel neuronal populations that are unique to distinct pain models. For example, the spared nerve injury model of neuropathic pain and the Complete Freund's Adjuvant model of inflammatory pain engage very different cells and circuits. Finally, Qiufu Ma (Harvard Medical School, Boston, Massachusetts) presented his studies of cre-recombinase lines that mark distinct populations of spinal neurons, showing that there are many subpopulations that each contribute differentially to itch and/or pain. Although these studies share the common goal of defining cell types that promote acute and chronic pain, the parallel approaches yielded unique insights into the underpinnings of pain. The talks triggered a timely discussion on the pros and cons of distinct mouse models and the increasing number of studies showing that constitutive ablation and acute silencing of cells in the pain circuit are not equivalent. Overall, the discussion highlighted the importance of using different approaches and pain models to gain insights into pain circuit function.

Allan Basbaum (University of California, San Francisco) and Daniel Bruce (University of Minnesota, Minneapolis) provided information on two therapeutic strategies for combating pain. Dr. Basbaum showed that transplanting medial ganglionic eminence neurons from the cortex of embryonic mice into the dorsal horn of adult mice dramatically attenuated neuropathic pain or itch. The transplanted neurons integrated into local circuits, restored normal γ-aminobutyric acid inhibitory signaling in the dorsal horn, and did not affect other sensory modalities. Dr. Bruce showed evidence that dual treatment with the peripherally restrictive and selective opioid agonists loperamide and oxymorphindole attenuates chronic inflammatory pain.

The session ended with Martin Schmelz (University of Heidelberg, Germany) discussing the nerve growth