Recent Progress in Understanding the Mechanisms of Pain and Itch: the Second Special Issue

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In 2012, we published the first special issue on mechanisms of pain and itch in *Neuroscience Bulletin*, which covered the peripheral, central, and glial mechanisms of pain and itch [1–5]. In the last 5 years, the field has seen tremendous progress in the molecular and functional characterization of primary sensory neurons [6, 7], neurocircuits of pain and itch [8–10], immune and glial modulation of pain and itch [11–15], molecular mechanisms of pain [16, 17], and identification of brain signatures of pain [18]. Thus, it is timely to highlight the recent progress in a second special issue. I invited the previous authors and new authors from China, the USA, and Japan, and they have contributed 20 mini-reviews and original articles to this special issue.

Primary sensory neurons of the dorsal root ganglion (DRG) consist of pain-sensing nociceptive neurons and itch-sensing pruriceptive neurons. Significant progress has been made in the molecular and functional characterization of these sensory neurons, thanks to the development of novel techniques and approaches [6, 7]. Using a combination of functional characterization and high-coverage single-cell RNA sequencing, Zhang and colleagues identified 11 types of somatosensory neurons [19]. In addition to single-cell analysis, Dong and coworkers investigated sensory neuron activation and pain mechanisms using Ca^{2+} imaging in intact animals following various sensory

stimuli. They also discuss the advantages and potential methodological considerations of GCaMP imaging [20].

Sodium channels play a critical role in the pathogenesis of pain and itch. For example, the TTX-resistant Na^+ channel subunit Nav1.8 contributes to the development of bone cancer pain in rodents [16]. To enhance the translational potential of preclinical studies, Chang *et al.* compared the expression of TTX-sensitive and TTX-resistant Na^+ channel subtypes in mouse and human DRG neurons and demonstrated striking species differences: the human DRG has much higher expression of the Nav1.7 subtype and lower expression of Nav1.8, whereas the mouse DRG has higher expression of Nav1.8 but lower expression of Nav1.7. The authors also established a translational model in which to study “human pain in a dish”, induced by the chemotherapeutic drug paclitaxel [21]. Human genetic study revealed a critical role of Nav1.7 (*SCN9A*) in human pain perception, but specific targeting of Nav1.7 has been a challenge. Bang *et al.* tested a monoclonal antibody that targets the voltage sensor of Nav1.7 (SVmab) and showed that it selectively inhibits Nav1.7 but not other Na^+ channel subtypes in HEK293 cells. They also showed that SVmab inhibits Na^+ currents in native sensory neurons and reduces neuropathic pain in mice. Furthermore, they revealed different activities of hybridoma-derived and recombinant SVmab, which will lead to new strategies for therapeutic development [22]. Latremoliere and Costigan discuss how a combination of human and mouse genetics helps to identify new pain targets and analgesics. Using an approach of reverse translation (from human to mouse), they have identified tetrahydrobiopterin (BH4) as a novel pathway for pathological pain, as well as new compounds that can block this pathway for pain relief [23].

It is noteworthy that pain and itch often accompany infections caused by viral, bacterial, parasitic, and fungal

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pathogens. Chiu presents evidence that sensory neurons are able to sense pathogens that can trigger pain or itch responses *via* specific receptors on pruriceptive and nociceptive neurons [24]. Apart from changes in somatosensory neurons, Li and colleagues demonstrated inflammatory changes (macrophage responses, satellite glia activation, and T cell infiltration) in paravertebral sympathetic ganglia after spinal nerve injury, along with increases in sympathetic neuron excitability. These findings suggest a role of sympathetic neurons in the development of pathological pain [25].

One of the most significant advances in neuroscience in the last 5 years was the identification of specific neurocircuits for specific behaviors. Bo and Ma review current advances in spinal circuits transmitting mechanical pain and itch, with special focus on gate control theory. They also discuss how disruption of the “Gate Control” could cause pain or itch following innocuous mechanical stimuli [26]. Chen and colleagues review cellular mechanisms of itch, with special emphasis on neuronal populations that express gastrin-releasing peptide (GRP) and the GRP receptor (GRPR) [27].

Our understating of the molecular mechanisms of itch has also improved. In addition to GRP and GRPR mentioned above [27], Zhou *et al.* reveal oxidative stress as an important mechanism of acute and chronic itch *via* both central and peripheral regulation. They also demonstrate that anti-oxidants are effective in treating pruritus [28]. TNF- α is one of the best-known cytokines and drives pathological pain. Miao *et al.* demonstrate that TNF- α /TNFR1 signaling also regulates acute and chronic pruritus through spinal and peripheral mechanisms [29].

Transient receptor potential ion channels, such as TRPV1, TRPA1, TRPV4, and TRPM8 play a critical role in regulating pain in various animal models. Increased evidence suggests that these TRP channels also contribute to acute and chronic itch. Liedtke, Jordt, and their coworkers discuss the mechanisms by which the TRP channels modulate pain and itch. They also emphasize the translational potentials for treating pain and itch with TRP channel modulators [30].

Increasing evidence supports a role of chemokines in pain control [14]. Xie and co-authors report an active role of the chemokine CCL2 in promoting central sensitization, long-term potentiation, and inflammatory pain [31]. Little is known about the involvement of chemokines in pruritus. Jiang *et al.* present evidence that the chemokine CXCL10 and its CXCR3 receptor in the spinal cord contribute to chronic itch [32].

Recent advances have also revealed the important roles of glial cells such as microglia and astrocytes in the pathogenesis of chronic pain and chronic itch. Tsuda discusses how spinal glial cells regulate chronic pain and chronic itch *via* distinct signaling mechanisms [33]. In the

spinal cord, chemokines are produced by both glial cells and neurons, but the chemokine receptor CX3CR1 is specifically expressed by microglia. Wang *et al.* show an active involvement of CX3CR1 signaling in neuropathic pain induced by tetanic stimulation of the sciatic nerve, a stimulus that induces long-term potentiation in the spinal cord [34]. Increasing evidence suggests that spinal microglial signaling is sex-dependent. Chen and collaborators compare sexual dimorphism in microglial and astroglial signaling in the spinal cord. Their findings show that spinal microglia regulate inflammatory and neuropathic pain only in male mice, while spinal astrocytes regulate neuropathic pain in both sexes [35].

Pain is a subjective and complex phenomenon, and multiple component processes, including sensation, affect, and cognition, contribute to its experience and reporting. Therefore, it is essential to study and image pain in the brains of humans, non-human primates, and rodents. Recent efforts have been made to identify human pain networks and build models of network interactions that yield testable predictions about pain-related outcomes. Marianne and Wager discuss how to model pain using fMRI and reveal ‘signatures’ of pain in human brains [36]. Chen reviews evidence of the cortical representation of pain and touch in non-human primates using combined functional neuroimaging and electrophysiology. New evidence reveals that cortical circuitry engaged in nociceptive processing is much more complex than previously recognized [37]. Depression is often associated with chronic pain as a comorbidity. Guo *et al.* present data from proteomic analysis in the hippocampus of animals with trigeminal neuralgia and depression [38], revealing the molecular pathways that regulate both chronic pain and depression.

Empathy for pain is emerging as a hot research topic. Traditionally, it was believed that empathy is a unique ability of humans to feel, understand, and share the emotional states of others. However, recent studies suggest that rodents are also able to show empathy for pain. From an evolutionary perspective, Chen discusses the concept of empathy for pain and distress in both humans and rodents. The neurocircuits that regulate this higher brain function have also begun to be revealed [39].

The cover image of this special issue illustrates a Chinese traditional myth “Hou Yi Shooting the Sun”. Hou Yi was a mythological Chinese archer. According to Chinese lore, there were 10 suns over the Earth, scorching the field and turning the world into a wasteland. Houyi saved the world by shooting down 9 Suns, but leaving the last one alive. This is a perfect analogy to physiological pain and pathological pain, since pathological pain is a greatly amplified condition of physiological pain. As we need Sun, we need physiological pain for our survival. However, pathological pain or clinical pain is redundant

and detrimental, like other 9 Suns. It is my best wish that the second special issue presented here will provoke future studies to expand our knowledge of pain and itch regulation in physiological and pathological conditions. Our ultimate goal is to develop more efficacious and safe treatments for the pain and itch management, so that they can shoot town 9 Suns (pathological pain and itch), leading the last Sun (physiological pain and itch) alive.

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