Published in final edited form as:

Pain. 2019 May ; 160(5): 987–988. doi:10.1097/j.pain.0000000000001537.

Untangling a canopy of spinal itch circuits

Jose G. Grajales-Reyes^{1,2,3}, Vijay K Samineni^{1,3}

¹Department of Anesthesiology, Division of Basic Research, Washington University in St. Louis, 660 S. Euclid Ave, Box 8054, 63110 St. Louis, MO, USA

²Medical Scientist Training Program, Washington University in St. Louis, 660 S. Euclid Ave, Box 8054, 63110 St. Louis, MO, USA

³Washington University Pain Center, Washington University in St. Louis, 660 S. Euclid Ave, Box 8054, 63110 St. Louis, MO, USA

Chronic pruritus or itch represents a significant toll on society, both clinically and economically[3]. It has been proposed that itch can be as debilitating as pain, when taking in consideration the quality of life of patients suffering from such diagnosis[10]. Most common treatment options to treat chronic pruritus are antihistamines, which are often ineffective[1; 4; 15]. Though itch signals, like pain, processed in the periphery but they are relayed to the spinal cord via itch-specific labelled lines[2; 6; 11]. This discovery of unique cells and neural circuits that encode specifically for itch offers an exciting opportunity to develop non-histaminergic therapeutic interventions to treat such a debilitating disorder.

In an effort to untangle spinal itch circuitry, here, Fatima and colleagues use intersectional genetics, to selectively ablate spinal cord (SC) neurons that co-expressed somatostatin (SOM) and the transcription factor Lbx1[5]. Deleting selectively SOM^{Lbx1} neurons in adulthood, using a diphtheria toxin dependent approach, translated into a reduction in the chemical-evoked scratching to pruritogens such as compound 48/80, chloroquine, SLIGRL, 5-HT and β -alanine. Additionally, SOM⁺ neuron are composed of excitatory interneurons that co-express natriuretic peptide receptor A (Npra) and a smaller portion that also express gastrin-releasing peptide (GRP). Interestingly, SOM^{Lbx1} ablated animals exhibit a diminished response to intrathecal administration of natriuretic peptide B (Nppb), but not to administration of GRP. These results would suggest that SOM/Npra⁺ excitatory neurons are upstream of GRPR expressing excitatory interneurons that transmit itch. Next, they evaluated the consequences of ablating SOM and Npra expressing neurons on chemical itch. Loss of function of SOM and Npra significantly blunted but did not completely abolish response to chemically evoke itch. These results suggest that while SOM/Npra⁺ excitatory neurons form a parallel itch pathway in addition to the neuron that release GRP. To understand the larger circuit in which these SOM neurons might play a role in, they further characterized the function of SOM receptor (Sst2A) expressing interneurons in itch modulation. Behaviorally, blockade of Sst2A⁺ using an antagonist (CYN154806), reduces

Corresponding author: Vijay K Samineni, 660 S. Euclid Ave., Campus Box 8054, St. Louis, MO, 63110, vksamineni@wustl.edu, Phone Number: 314-362-8795.

The authors declare no competing financial interests.

evoked scratching to pruritogens such as compound 48/80 and chloroquine. Interestingly, pharmacological blockade of Sst2A⁺ has similar effects to SOM-ablation after intrathecal administration of SOM. Sst2A is known to express on Bhlhb5⁺ inhibitory interneurons[8; 9]. Additionally, spinal inhibitory neurons that transiently express *Bhlhb5* during development were shown to suppress itch[12]. So, these findings only add to complexity of growing literature on this spinal circuitry.

These findings reveal a fascinating paradoxical circuit, where SOM neurons can facilitate itch and inhibit itch, depending the context of the incoming signal. The authors propose a disinhibitory circuit in which SOM^{Lbx1} neurons mediate itch by their possible interaction with Sst2A expressing neurons. According to the data presented in this paper, these cells exist upstream of GRPR⁺ neurons. However, it is unclear how these neurons modulate competing states of facilitation and inhibition? It is also unclear whether patterned electrical activity encodes the modulatory state of these neurons. Additionally, whether SOM^{Lbx1} neurons play a role as a source of SOM for Sst2A expressing interneurons to disinhibit downstream GRPR neurons or Sst2A expressing interneurons also express SOM is not clearly shown. Thus, their finding of SOM^{Lbx1} ablation leading to a significant reduction of intrathecal SOM induced itch, and comparable to Sst2A antagonist pre-treatment, only reveals the circuit's complexity. The authors suggest that this finding recapitulates the important role of these neurons in general itch processing, but leaves the question of why does elimination of a potential source of SOM leads to a complete elimination of the effects of exogenous SOM administration? Was it due to loss of Sst2A?. Alternatively, it is possible that SOM expressing neurons also express Sst2A.

Albeit, the results presented by Fatima and colleagues not only confirm the importance of SOM in itch processing but present convincing and strong evidence for the necessity of SOM neurons in this process, expanding from what we know from SOM deletion in spinal cord neurons[8]. It has been proposed by others that SOM neurons are upstream of dynorphin (Dyn) expressing inhibitory interneurons that co-express Sst2A and Bhlhb5, which are responsible for disinhibition of GRPR cells[8; 9]. These GRPR cells not only form part of this circuit but have been identified as the crucial downstream hubs for many pathways of itch sensation, thus the understanding of how information reaches those cells is of the outmost importance[13]. As other have shown, interneuron networks within the dorsal horn of the spinal cord are essential for the not only the sensation of itch but also for modulating the sensitivity of such system to a variety of stimuli[7; 14]. In brief, Fatima and colleagues further present a refined look into spinal itch circuitry and highlight the complexity of spinal itch processing.

Acknowledgments

This work was funded by NIDDK Career development award (K01 DK115634) to VKS, and NINDS NRSA F31 NS103472 (JGGR).

References:

- [1]. Akiyama T, Carstens E. Neural processing of itch. *Neuroscience* 2013;250:697–714. [PubMed: 23891755]

- [2]. Bautista DM, Wilson SR, Hoon MA. Why we scratch an itch: the molecules, cells and circuits of itch. *Nat Neurosci* 2014;17(2):175–182. [PubMed: 24473265]
- [3]. Carstens E Many parallels between itch and pain research. *Eur J Pain* 2016;20(1):5–7. [PubMed: 26415674]
- [4]. Davidson S, Giesler GJ. The multiple pathways for itch and their interactions with pain. *Trends in neurosciences* 2010;33(12):550–558. [PubMed: 21056479]
- [5]. Duan B, Cheng LZ, Bourane S, Britz O, Padilla C, Garcia-Campmany L, Krashes M, Knowlton W, Velasquez T, Ren XY, Ross SE, Lowell BB, Wang Y, Goulding M, Ma QF. Identification of Spinal Circuits Transmitting and Gating Mechanical Pain. *Cell* 2014;159(6):1417–1432. [PubMed: 25467445]
- [6]. Han L, Dong X. Itch mechanisms and circuits. *Annu Rev Biophys* 2014;43:331–355. [PubMed: 24819620]
- [7]. Han L, Ma C, Liu Q, Weng HJ, Cui YY, Tang ZX, Kim YS, Nie H, Qu LT, Patel KN, Li Z, McNeil B, He SQ, Guan Y, Xiao B, LaMotte RH, Dong XZ. A subpopulation of nociceptors specifically linked to itch. *Nature Neuroscience* 2013;16(2):174–182. [PubMed: 23263443]
- [8]. Huang J, Polgar E, Solinski HJ, Mishra SK, Tseng PY, Iwagaki N, Boyle KA, Dickie AC, Kriegbaum MC, Wildner H, Zeilhofer HU, Watanabe M, Riddell JS, Todd AJ, Hoon MA. Circuit dissection of the role of somatostatin in itch and pain. *Nat Neurosci* 2018;21(5):707–716. [PubMed: 29556030]
- [9]. Kardon AP, Polgar E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai XY, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, Koerber HR, Todd AJ, Ross SE. Dynorphin Acts as a Neuromodulator to Inhibit Itch in the Dorsal Horn of the Spinal Cord. *Neuron* 2014;82(3):573–586. [PubMed: 24726382]
- [10]. Kini SP, DeLong LK, Veledar E, McKenzie-Brown AM, Schaufele M, Chen SC. The Impact of Pruritus on Quality of Life The Skin Equivalent of Pain. *Arch Dermatol* 2011;147(10):1153–1156. [PubMed: 21680760]
- [11]. LaMotte RH, Dong X, Ringkamp M. Sensory neurons and circuits mediating itch. *Nat Rev Neurosci* 2014;15(1):19–31. [PubMed: 24356071]
- [12]. Ross SE, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu LD, Mok SI, Shah A, Savner EM, Tolias C, Corfas R, Chen SZ, Inquimbert P, Xu Y, McInnes RR, Rice FL, Corfas G, Ma QF, Woolf CJ, Greenberg ME. Loss of Inhibitory Interneurons in the Dorsal Spinal Cord and Elevated Itch in Bhlhb5 Mutant Mice. *Neuron* 2010;65(6):886–898. [PubMed: 20346763]
- [13]. Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature* 2007;448(7154):700–U710. [PubMed: 17653196]
- [14]. Wang XD, Zhang J, Eberhart D, Urban R, Meda K, Solorzano C, Yamanaka H, Rice D, Basbaum AI. Excitatory Superficial Dorsal Horn Interneurons Are Functionally Heterogeneous and Required for the Full Behavioral Expression of Pain and Itch. *Neuron* 2013;78(2):312–324. [PubMed: 23622066]
- [15]. Weissshaar E, Mattered U. Epidemiology of Itch In: Carstens E, Akiyama T, editors. *Itch: Mechanisms and Treatment*. Boca Raton (FL), 2014.