For the majority of my career, I have been interested in dermatology and somatosensation. After university, I worked for Dr. Diana Bautista at U.C. Berkeley for 2 years studying the molecular mechanisms underlying the sensation of itch. Specifically, I studied how Thymic Stromal Lymphopoietin (TSLP), a cytokine involved in atopic dermatitis, is released by keratinocytes and activates primary afferent neurons to trigger robust itch behaviors (*1*). Last January I began to rotate in Dr. Wenqin Luo's lab, and my interest in itch associated with dermatological diseases was reignited. My current project focuses on how the nervous system, the immune system, and the skin interact to cause the sensation of itch in allergic contact dermatitis (ACD).

Itch is an irritating sensation that triggers the desire to scratch and is a major symptom of many local and systemic diseases, particularly dermatological diseases. According to a European study, the prevalence of itch among dermatological patients is 54.4% (*2*). Itch-inducing chemicals are first detected by primary sensory neurons, whose cell bodies are located in the dorsal root ganglion (DRG) or trigeminal ganglion (TG) and form free nerve terminals in the skin. DRG and TG neurons then relay the signal to the brain. In addition to the nervous system, the immune system and integumentary systems both play a critical role in triggering pathological itch sensation, especially in allergenic itch. One common allergenic dermatological illness characterized by itch is ACD, in which activation of memory T cells, by re-exposure to allergens, causes an inflammatory cascade that results in skin injury and enhanced itch (*3-5*). At present, many molecular players in ACD, which could be potential targets for treatment, are still unknown.

Transient receptor potential (TRP) channels form nonselective cation channels and function in a variety of sensory pathways (*6, 7*). TRPC3 is a cation channel that can function as a receptor by itself or downstream of a G-protein coupled receptor (*7*). Previous studies from the Luo lab showed that TRPC3 is expressed in potential itch-sensing neurons, but *TrpC3* knockout (KO) mice exhibited no phenotypic differences in a variety of behavioral tests for acute pain and itch sensation (*8*). **Interestingly, we recently discovered that *TrpC3* KO mice show a significant increase in scratching behavior compared to wild type (WT) mice in a model of ACD, contact hypersensitivity (CHS)**. These results suggest TRPC3 plays an important role in dampening itch triggered by ACD, but the mechanism through which TRPC3 acts is currently unclear. Our preliminary results through Qin Liu's lab at Washington University in St. Louis found that **reciprocal bone marrow transplants between TRPC3 KO and WT mice did not result in a difference in CHS-induced scratching behavior**, indicating that TRPC3 is not required in the immune system for this increased itch phenotype.

I hypothesize that TRPC3 modulates itch through its function in either the nervous system or the integumentary system. Ross et. al showed *Bhlhb5* mutant mice resulted in which lack inhibitory interneurons in the dorsal spinal cord, show elevated itch (*9*). Since TRPC3 is a cationic channel, its absence in inhibitory interneurons (INs) could result in an increase in itch transmission (releasing inhibition on nociceptors). Alternatively, loss of TRPC3 may lead to increased release of pruritogens from keratinocytes and cells that infiltrate the skin during inflammation such as lymphocytes, mast cells, and eosinophils. These pruritogens activate primary afferent neurons and result in the sensation of itch (*10*). I will address this question by utilizing a combination of conditional *TrpC3* knock out mouse models (TRPC3 is ablated from the pan nervous or integumentary system or specific cell types of each system), behavior, histology, and molecular and cellular biology. Through consulting with Dr. Thomas Leung and Dr. Alan Rook, and using the dermatology histology core, I hope to utilize the expertise of the dermatology department to propel my research forward.

Numerous studies of chronic itch models have focused on the communication between skin and immune cells that promote inflammation and itch (*11*). This research aims to use ACD as a model for itch in order to learn in which cell type(s) TRPC3 functions and how it functions in those cells as to modulate the sensation of itch. Results from my project will improve our understanding of the pathophysiology of itch in ACD. In addition, given the protective role of TRPC3 in this process, it could be an important molecular target for more effective treatments for ACD-induced itch.

Citations


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