Project Title

Immune-mediated sensory impairments drive social and communication disorders in Christianson Syndrome

Investigators

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Statement of Purpose

We hypothesize that maturation defects in pain and touch pathways lead to touch aversion in infants, causing them to avoid maternal contact and impairing the development of social skills.

Project Summary

A significant challenge in our understanding of autism spectrum disorders (ASDs) is to correlate the impact of mutations in multiples genes to the resulting complex pathological symptoms. However, some disorders are monogenic, allowing a better understanding of how loss-of-function mutations lead to autistic behaviors. Christianson syndrome (CS) is a monogenic condition involving X-linked intellectual disability, autistic features and includes sensory abnormalities such as elevated tolerance to pain and aversion to touch. CS arises from mutations in the SLC9A6 gene, encoding the endosomal pH regulator (Na+, K+)/H+ exchanger isoform 6 (NHE6). This exchanger is expressed in pain-sensing neurons (nociceptors) where it controls protein turnover and trafficking, but the mechanisms through which SLC9A6 mutations cause ASD remains unknown.

To gain insights into CS disease mechanisms, we used a Slc9a6 knockout mouse. These exhibit high pain tolerance and touch aversion like that observed in CS children and suggest the following hypothesis: during the postnatal maturation of the spinal somatosensory circuits, light touch and nociceptive sensory afferents form transient contacts with nociceptive spinal neurons. The maintenance of contacts with nociceptive afferents and the detachment of touch afferents depends on electrical activity in nociceptors. Thus, when nociceptors are hypoactive, as in CS mice, their transient connections to spinal nociceptive neurons are not maintained, while the connections of light touch fibers are. This leads to a condition in which painful stimuli are not efficiently detected, and light touch stimuli evoke the sensation of pain. We posit that the touch aversion observed in developing CS infants will later impair the proper maturation of cortical circuits involved in social and communication function.

Our preliminary data indicate an increased role for immune components in the spinal cord of CS mice, which could impact the maturation of the circuits responsible for the sensations of touch and pain. In this project, we will (1) characterize how these immune cells sculpt touch and pain spinal circuits and (2) examine their link to the social defects

observed these mice. These aims will be completed using multi-disciplinary approaches and expertise available in the Sharif and Kania laboratories, which protein and mRNA detection, spinal cord slice electrophysiology, circuit tracing using viral vectors, developmental neurobiology, and behavioral studies. We have also developed a “rescuable” CS mouse model in which mice are born as knockouts for the CS gene but where the Slc9a6 gene can be re-expressed. This approach will allow us to (3) determine whether CS-associated pathologies are reversible and to identify the relevant temporal window.

The significance of the findings from this project is that they propose a critical role for neuroimmune interactions at the level of the spinal cord in social and communication deficits observed in neurodevelopment disorders. It also proposes a less conventional view of neurodevelopment disorders in that the behavioral deficits are secondary to defects in sensory pathways. The consequence will be that we may be able to rescue the social and communication deficits if we can rescue the sensory phenotype.