Developmental control of amygdalar fear circuit formation and its relationship to Autism Spectrum Disorders

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Autism Spectrum Disorders (ASDs) are some of the most heritable neural development disorders, and while approximately 1 in 110 children in the United States currently live with an ASD, the early pathogenesis remains unknown. Autistic patients show impairments in emotional reactivity, fear response, and in recognizing emotional facial expressions. The amygdala in the ventrolateral region of the cerebrum has been implicated in the normal control these affected behaviors. The SEMA5A gene encodes a secreted ligand that plays roles in neuronal migration and axonal connectivity, and has recently been suggested to be an autism susceptibility gene. In fact, the normal expression of SEMA5A in the cerebral cortex is reduced in autistic patients. Unfortunately, no analysis of SEMA5A expression in the amygdala was reported. We have taken a mouse genetics approach to identify genes crucial for in amygdalar circuit assembly. We have analyzed Sema5A/B double KO mice and observed intercalated (ITC) cells, which are normally found in the paracapsular regions, abnormally located in the in the lateral amygdala and basolateral amygdala, two major nuclei in the fear circuit. ITC cells, which can be characterized by their expression of the transcription factors FoxP2 and Tshz1, play a fundamental role in modulating the fear response. We have also analyzed Tshz1 mutant embryos and found large clusters of Tshz1 mutant cells that express FoxP2 in the medial paracapsular region, implicating Tshz1 in normal migratory behaviors of ITC neurons. Moreover, we have analyzed FoxP2 mutant adult brains and found a large decrease in the generation of ITC neurons in the paracapsular region. Our data suggest that both Tshz1 and Sema5A/B are required for the normal migration or placement of ITC neurons, where as FoxP2 is crucial for the generation of ITC neurons. We will continue to study the requirements of FoxP2, Sema5A/B, and Tshz1 in the normal assembly of the amygdalar fear circuit and it potential relevance to ASDs.

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