Project Title

Understanding the role of USP15 in neuronal subtype development

Investigators

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Statement of Purpose

The project will aim to address how neurons develop into specific subtypes in the mammalian brain and leverage this knowledge to understand the biological basis of a rare neurodevelopmental disorder.

Project Summary

The higher-order brain function in mammals relies on the presence of functional diversity in projection neurons. Perturbing the correct identity of neuronal subtypes can cause structural and functional defects, as seen in many neurodevelopmental disorders such as autism spectrum disorder. However, our understanding of how neurons obtain their unique identity and develop into proper subtypes and how these processes are altered in disease is still limited.

This project will address these fundamental questions, building on the recent insights we gain from patients with a rare, previously uncharacterized neurodevelopmental disorder. These individuals show severe neurological phenotypes and malformations such as optic nerve hypoplasia, absent olfactory bulbs, abnormal brain stem and cerebral atrophy. Such functional and structural changes can result from abnormal early brain development when neurons are produced and mature. Genetic analysis reveals that these patients all carry single missense mutations in the USP15 gene that encodes a little-studied deubiquitinating enzyme. USP15 is evolutionarily conserved in mice and humans, providing an opportunity to study its role in mammalian neurodevelopment and gain insights into disease mechanisms.

Our initial studies in the mouse model and human cells show that: 1) USP15 is highly expressed in a group of projection neurons that resides in the layer V of the mouse cerebral cortex; 2) USP15 proteins are preferentially located in different subcellular compartments of these neurons. While USP15 is found predominantly in the cytoplasm of neurons with simple dendrites, neurons with complex structures have USP15 in both the nucleus and cytoplasm; and 3) mutant USP15 that harbors different patient variants show altered subcellular distribution in transfected human cell lines. While wild-type USP15 displays a dominant nuclear localization, all patient variants show aberrant accumulation in the cytoplasm to varying degrees. Based on these initial findings, we hypothesize that USP15 regulates neuronal subtype development through a nucleocytoplasmic mechanism and that patient variants may perturb USP15 localization to alter subtype development, leading to abnormal brain formation and function. Here, we will test this hypothesis and dissect the disease mechanisms.

Aim 1: To determine the role of USP15 in the development of cortical neuronal subtypes. We have generated a conditional knockout mouse line where USP15 can be selectively deleted in cortical neurons. Using histological approaches and confocal microscopy, we will analyze cortical sections to determine how the loss of USP15 affects the development of layer V cortical neurons, focusing on changes in molecular identity, morphology, and projection.

Aim 2: To delineate the nucleocytoplasmic mechanism that mediates the effect of USP15 on neuronal development. We have developed a knock-in mouse line where USP15 carries a patient-derived mutation and thereby accumulates in the cytoplasm. We will determine how patient mutation affects the development of layer V cortical neurons and will further identify USP15 targets.

This study will uncover fundamental mechanisms that instruct the development of neuronal subtypes in the mammalian brain and provide novel insights into a rare neurodevelopmental disorder.