

The Fezf2-Ctip2 genetic pathway regulates the fate choice of subcortical projection neurons in the developing cerebral cortex.

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Public Summary:

A common pool of neural stem cells, or progenitor cells, give rise to different types of the neurons in the brain. We are trying to understand what genes, when expressed in a particular cell, tell the cell to become a certain types of neurons. Previously we have found that a gene called Fezf2 is essential for the generation of the type of neurons in the cerebral cortex that send their axons to the spinal cord: In the mice carrying mutations in the Fezf2 gene, the neurons in the cerebral cortex that send direct connections to the spinal cord, also called the corticospinal motor neurons, fail to be generated. In the current publication, we sought to understand what happen to the mutant neurons. We found that when Fezf2 was mutated in the mice, the neurons that was supposed to become corticospinal motor neurons switched their identity to become a different type of neurons: Instead of sending their axons to the spinal cord, the mutant neurons sent their axons to the other side of the brain, and they expressed different genes and behaved differently when stimulated electronically. We found that Fezf2 regulates the development of corticospinal motor neurons by regulating the expression of another gene called Ctip2. Putting Ctip2 back into the Fezf2 mutant neurons allowed these neurons to project their axons to the spinal cord. We also found that not only the Fezf2 and Ctip2 genes are necessary for the generation of the corticospinal motor neurons, expressing either one of them in a different cortical neuron type can change the axonal projection of these neurons. Our results shed new light on how the neural stem cells generate different neuronal types in the brain. This knowledge may help designing novel strategy for potential cell replacement therapy to replace damaged or diseased cortical neurons.

Scientific Abstract:

Pyramidal neurons in the deep layers of the cerebral cortex can be classified into two major classes: callosal projection neurons and long-range subcortical neurons. We and others have shown that a gene expressed specifically by subcortical projection neurons, Fezf2, is required for the formation of axonal projections to the spinal cord, tectum, and pons. Here, we report that Fezf2 regulates a decision between subcortical vs. callosal projection neuron fates. Fezf2(-/-) neurons adopt the fate of callosal projection neurons as assessed by their axonal projections, electrophysiological properties, and acquisition of Satb2 expression. Ctip2 is a major downstream effector of Fezf2 in regulating the extension of axons toward subcortical targets and can rescue the axonal phenotype of Fezf2 mutants. When ectopically expressed, either Fezf2 or Ctip2 can alter the axonal targeting of corticocortical projection neurons and cause them to project to subcortical targets, although Fezf2 can promote a subcortical projection neuron fate in the absence of Ctip2 expression.

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