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Researchers Discover Key Gene for Making Motor Neurons

Simple, everyday movements require the coordination of dozens of muscles, guided by the activity of hundreds of motor neurons. Now, researchers have revealed an important step in the process that guides the early development of neurons themselves, as they establish the precise connections between the spinal cord and muscles. This knowledge will help scientists search for drugs to treat diseases that destroy motor neurons, such as amyotrophic lateral sclerosis, or Lou Gehrig's disease.

As a vertebrate organism develops, the long, outstretched processes of motor neurons wend their way from the spinal column to wire up every muscle in the body. In mammals, many hundreds of different types of motor neurons are needed to control the variety of muscle types used to coordinate movement. The highly specialized motor neurons that innervate muscles in the arms, legs, hands, and feet are the most recent of these to evolve. As an animal develops, these neurons become increasingly specialized - first establishing themselves as motor neurons, then taking on the characteristics needed to control a limb, then preparing to target a specific muscle. Proper function depends on each of these neurons finding its way from the spinal cord to the group of muscle cells that it is equipped to control.

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— Thomas M. Jessell

Now, Howard Hughes Medical Institute investigator Thomas M. Jessell, working together with Jeremy Dasen of New York University and Philip Tucker of The University of Texas at Austin, has discovered the genetic recipe for making these specialized motor neurons. The key ingredient is a gene called *Foxp1*, which regulates the activity of a series of crucial patterning genes of the Hox family, and thereby coordinates the identity and connectivity of motor neurons. Without FoxP1, the axons of motor neurons that extend into an animal's limb wander aimlessly and connect to muscles at

random, Jessell and Dasen have found. The paper describing these findings is published in the July 25, 2008, issue of the journal *Cell*.

The *Hox* genes are among the most highly conserved of the developmental genes and are best known for their role in controlling the overall pattern of body development. Like many developmental regulators, the proteins produced by *Hox* genes control the activity of a diverse assortment of target genes. In previous work, Jessell, who is at Columbia University Medical Center, and Dasen discovered that 21 of the 39 mammalian *Hox* genes orchestrate the program of motor neuron development and connectivity. Their new work shows that FoxP1 is an essential co-factor for the entire set of *Hox* proteins that generate the motor neurons that control limb movement. Intriguingly, the level of FoxP1 expressed by developing motor neurons determines the precise subtype that they will form.

This paper makes the surprising discovery that one accessory co-factor, FoxP1, is needed for the output of each of the 21 *Hox* proteins that make motor neurons different, says Jessell. Depending on which *Hox* gene is turned on, FoxP1 is induced to different levels. And this difference in level programs which motor neuron subtype is generated. It is a complicated but satisfying genetic logic, one that appears to have evolved to ensure the generation of the diverse array of motor neuron subtypes needed for fine motor control of the limbs.

To emphasize the importance of this highly-evolved class of motor neurons, Jessell points to a relatively primitive vertebrate, the eel-like jawless fish known as a lamprey. Lampreys don't play the violin and they don't run - their motor programs are designed for simple swimming behaviors, Jessell says. The lamprey represents the most extreme example of vertebrate organisms whose lifestyle permits them to survive with a highly reduced array of motor neuron subtypes.

At some point in evolution, vertebrates acquired the ability to generate hundreds of motor neuron subtypes, presumably to accommodate the appearance of limbs new muscle classes, says Jessell. He and his colleagues suspect this diversity may have arisen when *FoxP1* began to be expressed in the spinal cord. But exactly when *FoxP1* expression first appeared in the spinal cord and how its expression is linked to *Hox* activities remain unsolved puzzles that Jessell and Dasen are now pursuing. Together with Sten Grillner of the Karolinska Institute and Manuel Pombal of the University of Vigo in Spain, they are beginning these studies by analyzing the expression and function of the *FoxP1* gene in lampreys.

Jessell, Dasen, and Tucker demonstrated the significance of FoxP1 in mice by inactivating the gene and showing that the spinal cord lacked the full repertoire of motor neurons without it. This mutation, in effect, reverts the spinal cord to a primitive ancestral state, generating a lamprey-like spinal cord encased in a mammalian body, Jessell says. Mice without FoxP1 die before birth because the gene is also critical for heart development, so the scientists are now analyzing genetically-modified mice in which FoxP1 is

deleted selectively from motor neurons. We anticipate that these animals will have a severe impairment in motor behavior, and studying later phases of FoxP1 function should reveal insights into the assembly of motor circuits in the spinal cord as well as the periphery he says.

Jessell's Columbia colleagues Hynek Wichterle and Mirza Peljto, in work supported by ProjectALS, are already using the Fox-Hox recipe in their attempts to create better ways of screening for drugs to treat Lou Gehrig's disease and other types of motor neuron degeneration. Fine-tuning the expression of these proteins has recently permitted Wichterle and Peljto to convert embryonic stem cells into the highly-specialized motor neurons that innervate limb muscles.

This is a promising screening strategy for identifying drugs that prevent or slow the degeneration of motor neurons, says Jessell. Hopefully, many researchers will build upon these advances in basic motor neuron biology to design better and more predictive therapeutic screens.