

Scientists Crack Code for Motor Neuron Wiring

Understanding how a developing chick embryo assigns different functions to nerve cells in the spinal cord may yield clinical payoffs for humans.

AS YOU TURN THE PAGES OF THIS *BULLETIN*, MOTOR NEURONS that project from your spinal cord are coordinating the precise actions of more than 50 muscles in each of your arms. Each muscle is individually controlled by its own motor neuron cluster, which has a distinct identity and pattern of connectivity. “Motor neurons represent an extreme example of neuronal diversification,” says HHMI investigator Thomas M. Jessell, whose research group at Columbia University Medical Center is seeking to understand how a developing embryo delegates specialized functions to different nerve cells.

“Its first task is to make motor neurons, as a class, different from all the other classes of neurons,” says Jessell. “And once the embryo has solved that problem it has to generate distinct columns of motor neurons in the spinal cord, with each column controlling a particular body region, such as a limb. Then, within each column, the embryo has to generate motor neuron pools, each of which activates one particular muscle.” Motor axons must then grow from the spinal cord into the limbs and elsewhere and target the right muscle.

Jessell’s team recently deciphered the code that assigns unique identities to the motor neuron pools. This code, as the researchers explained in the November 4, 2005, issue of *Cell*, is written in the language of Hox proteins—a family of transcription factors (proteins that activate specific sets of genes) found in virtually all organisms.

Scientists have long recognized that Hox proteins, by orchestrating a cascade of gene expression in the early embryo, ensure animals’ overall body plan. They place the head at the top, the feet below, and the correct arrangement of ribs in between.

Four years ago, the Columbia group discovered that Hox proteins also influence the arrangement of the motor

neuron columns within the spinal cord. That finding prompted the recent study, in which Jeremy S. Dasen, an HHMI research associate in Jessell’s lab, painted chick embryos with a palette of fluorescently tagged antibodies directed against many of the 39 Hox proteins. The experiments were painstaking and meticulous, says Jessell. Merely generating the antibodies was a 5-year effort by Bonnie C. Tice and Susan Brenner-Morton, Dasen’s labmates and coauthors of the *Cell* paper.

The hard work paid off. What has emerged from these experiments is a detailed motor neuron atlas that shows the locations of relevant Hox proteins in the chick embryo at different times during development. The appearance and disappearance of the different protein types in distinct motor neuron pools revealed the molecular logic at work to Dasen and his colleagues. “Different Hox proteins have specific tasks that progressively determine motor neuron identity,” Jessell explains.

What’s more, it became clear from the pictures that certain pairs of Hox proteins exclude each other from an individual neuron, whereas other combinations of Hox proteins can coexist. In effect, the Hox proteins wage a battle for dominance within the cells of each pool. “Hox protein A may win out in one

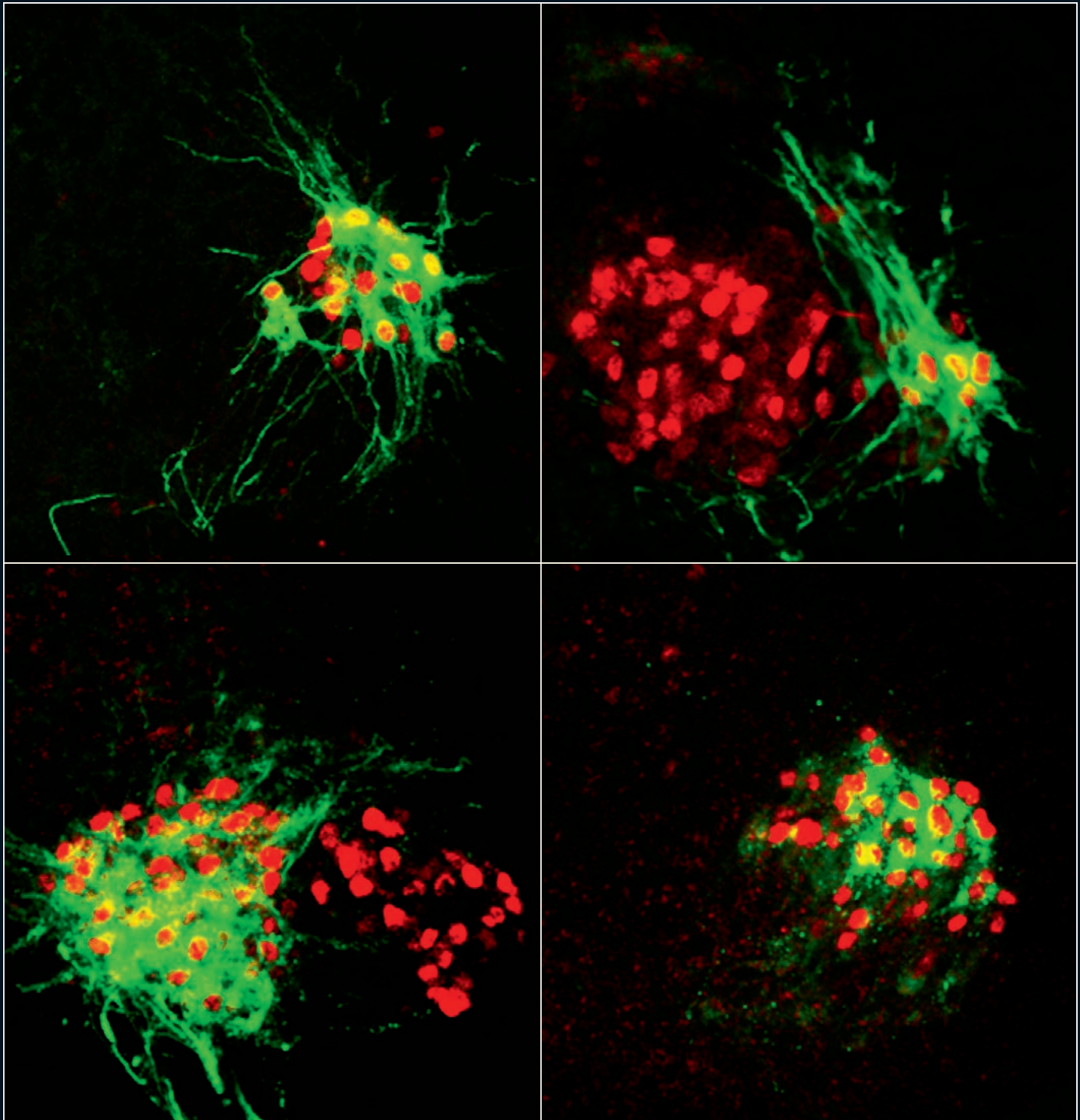
neuron, and Hox protein B may prevail in another neuron,” says Jessell. “And since the emergence of that final Hox pattern determines identity, the nature of the interactive circuit between Hox proteins is in itself driving the diversification of neurons.”

These findings may have broad implications. “We already know that the basic organization of the chick motor system is conserved within higher vertebrates, including humans,” Jessell says. “If you look at chick locomotor behavior, it’s strikingly similar to humans walking.” It’s possible, then, that understanding the Hox code may one day help guide progress in restoring motor neuron function in people whose spinal cords have been damaged by trauma or disease. —Paul Muhlrud ■



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THOMAS JESSELL



Outfitting Motor Pools

Researchers in Thomas Jessell's lab have created an atlas of images that shows the location of various Hox-related proteins in the chick embryo at different developmental times.

For this set of images, the researchers injected different muscles in the chick forelimb with a green tracer, which then spread to the corresponding motor neuron pools in the spinal cord.

Each panel shows cell nuclei stained with red-tagged antibodies that bind to different transcription factors. The transcription factors, shown clockwise from top left, are Runx1, Pea3, Scip, and Pea3.

The images demonstrate that different combinations of transcription factors are present in different motor neuron pools.