Mixing and matching genes to keep nerve cells straight

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With fewer than 30,000 human genes with which to work, Nature has to mix and match to generate the myriad types of neurons or nerve cells needed to assemble the brain and nervous system. Keeping this involved process on the straight and narrow requires a clever balance of promotion and inhibition, said researchers from Baylor College of Medicine in Houston in a report that appears in the current edition of the journal *Developmental Cell*.

"Our finding should have implications for the entire stem cell field," said Dr. Soo-Kyung Lee, assistant professor of molecular and cellular biology at BCM. "Scientists are seeking to make particular cell types using combinations of embryonic genes. They need to keeping mind that you do not just push them forward down one pathway. You must also suppress related pathways."

"During embryonic development, one needs to generate a lot of different types of neurons," said Lee, also a faculty member in the BCM Graduate School of Biomedical Sciences. "How are they being generated at the right time and place? To assemble the brain, you need all these different types of neurons. With a limited number of genes, how do you generate such a complex system?"

"We want to understand the molecular mechanisms that allow one gene to influence the formation of many neurons," she said.

They found that both promotion of one pathway and inhibition of

another are required to keep the cells on the right road to cell fate determination.

"One factor does not determine cell fate," she said. It's a combination of factors or genes that together affect neuron formation.

She and her colleagues concentrated their work on the development of motor neurons in mice. Two types of nerve cells – spinal motor neurons and V2-interneurons – are required for motor coordination. As they become those cells, they share important regulatory factors, said Lee.

"They share a cell lineage pathway," she said. "We asked how do we generate two different lineages from one pathway?"

A cocktail of the transcription factors Isl1 and Lhx3 can cause embryonic cells to become motor neurons, she said.

"If we put only Lhx3 into the embryonic neural stem cells, they become V2-interneurons," she said. However, deleting the genes can cause the pathways to converge, resulting in hybrid cells that result in the death of the embryos.

This does not happen in Nature, she said, and they found that a gene called Hb9, expressed only in motor neurons, blocks the ability of Lhx3 to cause embryonic neural stem cells to become the V2-interneurons.

"Once you turn on the complex of Isl1 and Lhx3, then you also turn on a repressor that blocks the cells from going down the alternative pathway to becoming V2-interneurons," she said. The motor neuron fate of those cells is sealed. They found a similar repressor function in the V2-interneuron pathway.

"We think this is a delicately developed system," said Lee. "We don't

think this mechanism is restricted to motor neurons."

Source: Baylor College of Medicine