Advance helps explain stem cell behavior

November 21 2006

Biochemists at Oregon State University have developed a new method to identify the "DNA-binding transcription factors" that help steer stem cells into forming the wide variety of cells that ultimately make up all the organs and parts of a living vertebrate animal.

The findings were made using mouse embryonic spinal cord as a model, and will be announced this week in *Proceedings of the National Academy of Sciences*, a professional journal.

The research is an important step towards understanding stem cell behavior, how cellular development is controlled, and how a single cell – which has the genetic code within it to become any cell in the body – is told what to become, where to go, and what metabolic function to perform.

Fundamental discoveries such as this, experts say, could ultimately lead to the ability to simulate and possibly control the early developmental process, manipulating stem cells in a way that would help address disease problems, injuries, failing organs or other medical issues.

"If you have an electrical problem in a car, you can repair it a lot easier if you have a wiring diagram," said Michael Gross, an assistant professor of biochemistry and biophysics at OSU. "In a way that's what we're trying to do here, except we're trying to repair or create a certain kind of cell. To do that you need a blueprint of how these processes work, and this will help us create that blueprint."

Even though the processes of cellular development are understood in a broad sense, the detailed biochemistry that underlies and controls these processes is still poorly defined. The overall process appears to be incredibly complex with many pieces and "combinatorial interactions."

Still unknown is exactly what causes certain genes to be expressed. In other words, out of the thousands of genes that could direct the formation of a cell in many different directions, only a subset actually get turned on and become operative in each type of cell. And beyond that, the newly-formed cells then need to arrange themselves in distinct patterns to perform life functions.

"It's clear that there is an extended sequence of steps which turn some genes on and others off, allowing a cell to become a liver cell, for instance, rather than a brain cell," said Chrissa Kioussi, an OSU assistant professor of pharmacology and co-author on the study. "We were able to use a system of microarray comparisons that monitored the expression of genes and more quickly gives us an idea of how this process is working, and how patterns of development occur."

The studies were done in embryonic spinal cord in mice, although the same process ultimately takes place during development of any organ or bodily system, the researchers said. The research identified the subset of genes involved in producing the various types of spinal cord cells – there may be 10s to 100s of cell types just in the spinal cord. The cell types are created very quickly in early embryonic development by a pattern formation mechanism, and then mature more slowly as the central nervous system creates the functional neural circuits.

Understanding this pattern formation mechanism will be essential to the ultimate use of stem cells in medical research and disease treatment, the scientists said. Ideally, researchers would like to create a "transcriptional network model" that simulates all of the complex and interactive steps in this patterning process, Gross said.

Much of this process happens during a surprisingly short time and at very early stages of embryonic development. In mice, for instance, virtually all of the types of cells are formed in 12 days, during what would correspond to a fraction of the "first trimester" of the human gestational period, as genetic mechanisms guide the "readout" of DNA and control the formation of different types of cells. The cell types themselves are created well before they are "wired together" to create functional organs and bodily systems.

The same basic process takes place in humans, scientists say. In fact, the process is so important and fundamental to life that it has been conserved through millions of years of evolution, and is largely the same among vertebrate animal species, whether they are fish, horses, mice or humans.

Once the process is more fully understood, it should be much more feasible to influence and control it, researchers say. If the task were spinal cord repair, for instance, the goal would be to influence cells to become certain types of spinal cord cells. This area of "molecular medicine" is one of the fastest growing fields of research today, and may ultimately lead to cures or treatments for conditions now thought to be incurable.

"You can't attempt to cure a disease or repair a problem if you don't know what molecular players are involved," Gross said. "That's what we're moving towards. We now have a better idea of some of the key components in this process."

Source: Oregon State University