Enzyme plays key role in cell fate

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The road to death or differentiation follows a similar course in embryonic stem cells, said researchers at Baylor College of Medicine in Houston in a report that appears online today in the journal *Cell Stem Cell*.

“Caspases, known as ‘killer enzymes,’ that are activated during programmed cell death, are also active in the initial phases of cell differentiation,” said Dr. Thomas Zwaka, assistant professor in the Stem Cells and Regenerative Medicine Center (STaR) at BCM.

Research into embryonic stem cells is basic to understanding differentiation, the process by which some of the earliest cells begin the process of becoming different tissues and organs. Scientists are eager to tap the potential of the pluripotent embryonic stem cells because they have the ability to become almost any kind of cell in the body. That is, however, just one of the possible fates they face. They are also capable of almost infinite self-renewal made possible by an autoregulatory loop including several key transcription factors (e.g., Oct4, Nanog). (Transcription factors bind to DNA to control the transfer of genetic information into RNA.)

The involvement of caspases in differentiation came as a surprise, said Zwaka. However, it makes a certain kind of sense.

“From a more philosophical point of view, programmed cell death (apoptosis) is a specialized form of differentiation,” said Zwaka. (Cells undergo apoptosis or programmed cell death for a variety of reasons –

most of them related to keeping organisms or tissues healthy.)

In studies in his laboratory, he and his colleagues at BCM found an "overlap between the pathways that drive cell death and cell differentiation" in a group of enzymes called caspases.

"Caspases trigger differentiation," he said. "If you remove specific caspases, stem cells have a differentiation defect. When we artificially increase caspase activity, the cells differentiated. When we increased the enzyme activity even more, the cell went into programmed cell death."

In studying how caspases achieve this activity, he noted that the enzyme is a protease or molecular scissors that cleave or cut proteins at specific points. In particular, they found that caspase cleaves Nanog, one of the transcription factors key to maintaining the embryonic stem cells in their self-renewal state.

"This is a proof of concept study," said Zwaka. "It shows a strong link between cell death and differentiation pathways. We hope this is a general concept that we can apply in other kinds of stem cells."

The finding has implications for other kinds of studies. One is that manipulating programmed cell death pathways and caspase targets could help to revert a somatic or already differentiated cell into an embryonic stem cell-like fate. For instance manipulating Nanog at the caspase cleavage site might improve the effectiveness of this technique and enable elimination of the use of viruses, which can contaminate cell lines.

Source: Baylor College of Medicine