Ronin recruits protein 'allies' to sustain embryonic stem cell growth

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Ronin, crucial to the self-renewal of embryonic stem cells, and a co-regulator called Hcf-1, binds to a small strand of DNA called a hyperconserved enhancer element to control a gene "program" that stimulates growth of the stem cells and may even play a role in cancer, said a group of researchers led by Baylor College of Medicine in a current report in the journal Genes and Development.

Dr. Thomas P. Zwaka, associate professor in the Stem Cells and Regenerative Medicine (STaR) Center at BCM and others in his laboratory first identified Ronin and its role in maintaining stem cells in their undifferentiated state. Now he and his colleagues from the University of Houston, The University of Texas MD Anderson Cancer Center and Massachusetts Institute of Technology (MIT) in Cambridge, Mass., have identified the tiny strand of DNA that enables the protein with its co-regulator Hcf-1 to maintain the rapid growth that characterizes embryonic stems cells.

Finding this small DNA strand required determining the genetic sequence of the site to which Ronin binds in the genome, he said. They used high tech, extremely rapid sequencing methods (high throughput, massively parallel sequencing) to identify the appropriate sequences and determine their genetic code. They analyzed 866 potential binding sites and found a similar motif in 844.

As chance would have it, this genetic sequence had been previously identified in a pure bioinformatics study of genetic sequences that are

present in most mammalian species. Because such sequences are conserved throughout evolution, they are believed to play a fundamental role in cellular processes. In a list of 100 most conserved genetic regions, this DNA sequence ranked fourth in frequency. In this case, researchers believe that the small DNA strand bound to a transcription factor that they had not identified. (A transcription factor governs translation of the DNA message in a gene into RNA, which can then be used by the cell's machinery as a template for a protein.)

"Ronin is that factor," said Zwaka. "Ronin binds to the 'hyperconserved enhancer element' sequence and then recruits Hcf-1. Only if it recruits Hcf-1 do we get activation of the special gene growth program."

With this highly conserved enhancer element, the Ronin/Hcf-1 combination controls a specific growth program of genes that are required in the early formation of an embryo, stem cells and maybe in some tumor cells, he said.

"When you look at the target genes of Ronin/Hcf-1, all are in the category of protein metabolism," he said.

Embryonic stem cells are characterized by rapid growth and renewal.

"Graduate students complain that they have to split and feed the cells every day. If you don't supply them with fresh medium, they die because they use it all up. It is important to understand what underlies this prolific growth," he said.

Understanding that could help scientists growth the cells better in the laboratory. Cancer growth, in many ways, simulates that of embryonic stem cells, he said. Understanding the growth program made up of 1,000 or more genes regulated by Ronin/Hcf-1 could help determine new strategies for fighting tumors.

Provided by Baylor College of Medicine