Binding sites for LIN28 protein found in thousands of human genes

September 4 2012

This is Gene Yeo, Ph.D. Credit: UC San Diego School of Medicine

A study led by researchers at the UC San Diego Stem Cell Research program and funded by the California Institute for Regenerative Medicine (CIRM) looks at an important RNA binding protein called LIN28, which is implicated in pluripotency and reprogramming as well as in cancer and other diseases. According to the researchers, their study – published in the September 6 online issue of *Molecular Cell* – will change how scientists view this protein and its impact on human disease.

Studying embryonic stem cells and somatic cells stably expressing

LIN28, the researchers defined discrete binding sites of LIN28 in 25 percent of human transcripts. In addition, splicing-sensitive microarrays demonstrated that LIN28 expression causes widespread downstream alternative splicing changes –variations in gene products that can result in cancer or other diseases.

"Surprisingly, we discovered that LIN28 not only binds to the non-coding microRNAs, but can also bind directly to thousands of messenger RNAs," said first author Melissa Wilbert, a doctoral student in the UC San Diego Biomedical Sciences graduate program.

Messenger RNA or mRNA, are RNA molecules that encode a chemical "blueprint" for the synthesis of a protein. MicroRNAs (miRNAs) are short snippets of RNA that are crucial regulators of cell growth, differentiation, and death. While they don't encode for proteins, miRNAs are important for regulating protein production in the cell by repressing or "turning off" genes.

"The LIN28 protein is linked to growth and development and is important very early in human development," said principal investigator Gene Yeo, PhD, MBA, of the Department of Cellular and Molecular Medicine, the Stem Cell Research Program and the Institute for Genomic Medicine at UC San Diego. "It is usually turned off in adult tissue, but can be reactivated, for instance, in certain cancers or metabolic disorders, such as obesity."

Using genome-wide biochemical methods to look at the set of all RNA molecules across the transcriptome, the researchers found that LIN28 recognizes and binds to a known hairpin-like structure found on the let-7 family of miRNA, but surprisingly, this same structure is also found on mRNAs, allowing LIN28 to directly regulate thousands of targets.

"One of these targets actually encodes for the LIN28 protein itself. In

other words, LIN28 helps to make more of itself," said Yeo. This process, known as autoregulation, helps to maintain a so-called "steady-state" system in which a protein positively regulates its own production by binding to a regulatory element of the mRNA for the gene coding it.

"Since these mRNA targets include those known to be involved in gene splicing, we also implicate LIN28 in the regulation of alternative splicing ," said Wilbert, adding that abnormal variations in splicing are often implicated in cancer and other disorders.

In the splicing process, fragments that do not typically code for protein, called introns, are removed from gene transcripts, and the remaining sequences, called exons, are reconnected. The splicing factor proteins themselves, as well as the location where these proteins bind, dictate which pieces of the RNA are included or excluded in the final gene transcript – in much the same way that removing and inserting scenes, or splicing, can alter the plot of a movie.

The discovery of thousands of precise binding sites for LIN28 within human genes offers a novel look at the role this protein plays in development and disease processes. For example, scientists had looked at targeting a particular miRNA called let-7 to halt cancer growth. "But we now see that LIN28 can, in essence, bypass let-7 and find many, many other binding sites – perhaps with the same adverse effect of uncontrolled cell overgrowth," said Yeo. "This suggests that LIN28 itself should be the therapeutic target for diseases, rather than let-7 or other miRNAs."

Provided by University of California - San Diego