MedicalXpress

Alternative splicing proteins prompt heart development

December 8 2008

Just as the emotions it represents are dynamic, the heart's development requires dynamic shifts in proteins that prompt alternative spicing, a mechanism that allows a given gene to program the cell to make several proteins, said a group of researchers at Baylor College of Medicine in a report that appears online today in the journal *Proceedings of the National Academy of Sciences.*

Using a technique called splicing sensitive microarrays or gene chips that help identify genes, the researchers from BCM, Massachusetts Institute of Technology in Cambridge and Rosetta Inpharmatics, LLC in Seattle identified two proteins (CUGBP and ETR-3-like factors called CELF and muscleblind-like protein called MBNL1) that reprogram alternative splicing in the developing hearts of mice, affecting how the heart grows during the pre-birth, immediately post-birth periods.

There is a rapid decrease in the amount of CELF proteins (more than 10-fold) and a concomitant increase in MBNL1 proteins (nearly 4-fold) during the first two weeks after birth. The finding has implications for a muscle-wasting ailment called myotonic dystrophy as well as for normal heart development.

"These are physiologically important times," said Dr. Thomas Cooper, professor of pathology and molecular and cellular biology at BCM and the senior author of the report. "Before birth, the heart is getting ready for a complete change in function. After birth, it needs to work harder to accommodate the demands of moving about."

"It is now clear that there's a new level of regulation during development," he said. "It's not just turning genes on and off. It is changing the composition of the proteins expressed from this one set of genes."

In fact, half of the alternative splicing changes that occur during heart development are controlled by the CELF and muscleblind-like factors, said Cooper.

Most of the changes in alternative splicing found in mouse heart development were also found in chicken heart development strongly suggesting that the changes are very important for normal heart. It is very likely that the same changes are needed for normal human heart development as well.

Alternative splicing is a fairly common occurrence that is crucial to enabling an estimated 25,000 genes in humans to make the 100,000 or more proteins needed to carry out the functions of cells throughout the body. Genes, made up of DNA, have exons that carry the coding sequences for amino acids that make up proteins (the "genetic code"). However, before the proteins are made, messenger RNA (mRNA) must be made from the DNA. The mRNA then carries the code to the protein-building structures of the cell. The mRNA can contain all or just some of the exons or coding sequences of the gene. The protein that is made varies, depending on which exons are included in the mRNA. This variation in the mRNA is called alternative splicing because the mRNA splices in different coding sequences.

Now Cooper and his colleagues have identified two factors that are crucial in switching the alternative splicing, depending on the stage of heart development. "This work is the first to identify specific sets of exons that are regulated only by CUGBP1 or MBNL1", said Dr. Auinash Kalsotra, lead author of the paper and postdoctoral fellow in the

department of pathology at BCM.

In myotonic dystrophy, the alternative splicing pattern is disrupted by the disease, switching from an adult to an embryonic pattern, said Cooper. The presence of embryonic rather than adult forms of proteins cause major symptoms of the disease. Myotonic dystrophy is the most common form of muscular dystrophy that begins in adulthood. Understanding normal modes of alternative splicing regulation will aid in identifying pathways that are disrupted in the disease which are considered to be potential targets for therapy.

Source: Baylor College of Medicine