Researchers find level of special protein is critical to proper formation of muscles

April 24 2007

Proper formation of the proteins that power heart and skeletal muscle seems to rely on a precise concentration of a "chaperone" protein known as UNC-45, according to a new study.

This basic discovery may have important implications for understanding and eventually treating heart failure and muscle wasting elsewhere in the body resulting from burns, brain trauma, diabetes, cancer and the effects of aging, the senior author of the paper said. The finding resulted from experiments using tiny, genetically engineered worms at the University of Texas Medical Branch at Galveston (UTMB), and is reported in a paper featured on the cover of the April 23, 2007, issue of the *Journal of Cell Biology*.

Chaperone proteins (known to biologists simply as chaperones) guide other newly formed proteins into the shapes that enable them to perform their specific functions.

In muscle cells, UNC-45 acts as a chaperone for myosin proteins, helping them fold into long, thin stable structures which clump together to form the thicker filaments that give heart and skeletal muscle its striated appearance. Chemical signals cause these myosin filaments to contract -- producing a heartbeat, for example, or an arm movement.

Scientists already knew that a shortage of UNC-45 disrupted myosin formation, leading to muscle paralysis. The reason: when there's not enough UNC-45 to go around, myosin proteins not yet in their final,

stable form fall victim to a cellular cleanup squad called the ubiquitin/proteasome system (UPS), which breaks unstable (and presumably malfunctioning) proteins down into their amino acid components.

But the UTMB study, done using worms of the species Caenorhabiditis elegans (also known as C. elegans), showed that an over-supply of UNC-45 is also a problem.

"What we saw was that too much UNC-45 interfered with myosin accumulation and assembly," said Dr. Henry Epstein, chairman of UTMB's Department of Neuroscience and Cell Biology and senior author of the Journal of Cell Biology paper. "It now looks as though precise levels of UNC-45 are critical during myosin formation."

Epstein's group made the discovery using C. elegans worms genetically engineered to produce more UNC-45 than do normal worms. (C. elegans is often employed in lab experiments because it possesses many of the same cell types as more complicated animals do, but it is simple enough to make extremely detailed study and genetic manipulation more convenient.)

The problem with having too much UNC-45, the researchers found, is that it also allows the UPS to interfere with myosin assembly. Apparently, being "over-chaperoned" by extra UNC-45 prevents the myosin proteins from binding into thick filaments and leaves them free-floating and vulnerable to the UPS. The result is a partially paralyzed worm whose muscles show visibly smaller fibers.

"This kind of process that we're seeing in our worms is likely to be important in both the building up and tearing down of heart and skeletal muscle in humans," Epstein said. "So we predict that the regulation of UNC-45 will be important in heart failure as well as muscle wasting

elsewhere in the body, which is significant to people suffering from burns, brain trauma, diabetes, cancer and the effects of aging."

Source: University of Texas