RING finger protein 5 may guide treatment for muscle disease in older adults

April 4 2008

Researchers at the Burnham Institute for Medical Research (Burnham) have discovered a new player in the development of a disorder called Sporadic Inclusion Body Myositis (sIBM). sIBM is a muscle disease that affects predominantly older men, causing muscles to gradually weaken and waste away. The number of people living with sIBM is unknown, but it is the most common muscle disease among those over the age of 50, and due to its unfamiliarity, it is probably underdiagnosed. This discovery provides a potential avenue for future diagnostic and therapeutic opportunities for this disease.

In muscles, proteins are continuously made and broken down by the endoplasmic reticulum (ER), a “protein factory” in the cell. To assure that proteins produced pass quality control, a set of ER-based inspectors identify and remove those proteins that are not properly folded. Ubiquitin ligase RNF5 (or RING Finger Protein 5) acts much like one of these quality-control inspectors at the end of the assembly line by tagging defective protein products so that they can be recycled.

Burnham scientists have found that RNF5 plays a key role in the progression of IBM. While the causes of sIBM or how it progresses are still mostly unknown, and there is no cure or standard treatment, this finding offers a new understanding for the mechanism underlying development of sIBM and points to possible use of new markers for diagnosis and mouse models to test for novel therapeutics. The results of this study appeared in *PLoS ONE* on February 13.

The Burnham research team was led by Ze'ev Ronai, Ph.D., and included Agnes Delaunay, PhD., and P. Lorenzo Puri, M.D., Ph.D., with Diane Shelton, D.V.M. Ph.D of UCSD and international collaborators from Japan and Italy. Dr. Ronai had previously shown that RNF5 is important for muscle maintenance in the worm model C. elegans; now the team discovered that RNF5 is up-regulated in biopsies from sIBM patients.

Following this discovery, the team developed three mouse models: one knockout model in which the RNF5 gene was missing, and two in which cells could be triggered to overproduce RNF5, with expression either limited to skeletal muscle, -or within muscle and a variety of other organs.

A comparison of normal and knockout mice exposed to muscle-damaging toxin showed slower healing in the knockouts compared with the normal mice, demonstrating the importance of RNF5 in muscle repair.

Pathologic changes within muscles of the transgenic models with RNF5 overexpression were similar to those found in muscle biopsies from patients with sIBM. Overproduction of RNF5 caused a rapid and significant muscle degeneration, weight loss and muscle weakness. Followed by extensive muscle regeneration. Similar to what is often seen in patients with IBM, muscle specimens from RNF5 overexpressing animals revealed the presence of structures known as rimmed vacuoles and congophilic inclusions, hallmarks of this disease.

The researchers also found increased levels of markers characteristic of ER stress, a phenomenon that has been linked with a variety of human diseases, including sIBM. It is believed that ER stress is a response to misfolded-protein buildup; sensing the backlog, the ER recruits helpers through the Unfolded Protein Response (UPR)—chaperonins that increase the export of misfolded proteins to enable their breakdown and

recycling. But, with prolonged stress, the UPR eventually fails to handle the overload, resulting in the accumulation of misfolded proteins in the cytoplasmic vacuoles, structures within the cell cytoplasm which are characteristic of sIBM patients.

Whether RNF5 is the primary cause for sIBM, or an important contributor in the development of this muscle disorder is yet to be determined. Dr. Ronai, lead author of the study, says the link established between ER stress, RNF5 and sIBM strengthen one theory stating that ER stress is causative for the disease and will now allow further study of the mechanisms underlying this disabling and all too common muscle disease.

“We now have a great mouse model that can be used to screen for drugs that might alleviate symptoms of sIBM,” says Dr. Ronai. But questions about what may interact with RNF5 in the cell to cause the symptoms of sIBM, he explains, still need to be addressed. “We know the substrates for this ubiquitin ligase in C. elegans, but not yet in human muscle.”

Source: Burnham Institute