FHL1 helps build muscle mass

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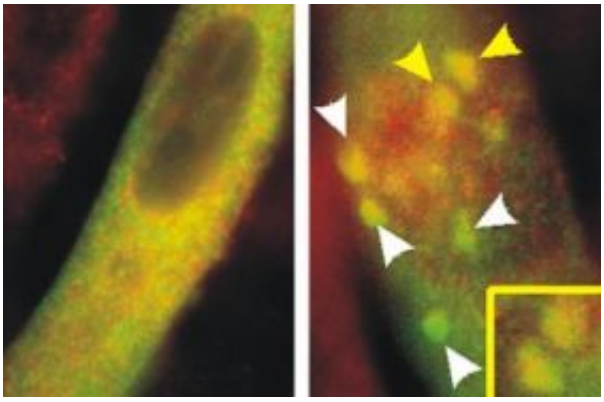

Unlike the wild-type protein (left), mutant FHL1 (right, green) forms cytosolic aggregates (arrows) that sequester NFATc1 (red). Credit: J. Cell Biol.

Cowling et al. report how to build muscle mass with FHL1. The protein partners with and activates the transcription factor, NFATc1. Encouraging this partnership might provide a possible treatment for muscle wasting disorders. The article will appear in the December 15, 2008 issue of *The Journal of Cell Biology (JCB).*

Mutations in FHL1 are present in several myopathies, including reducing-body myopathy (RBM), but until now, both the molecular mechanisms causing the disease, and the regular function of FHL1 in healthy tissue, remained unknown.

To address this, Cowling et al. overexpressed FHL1 in both transgenic mice and cultured myoblasts. The mice developed skeletal muscle

hypertrophy, and showed increased strength and endurance. Overexpression in myoblasts also increased cell fusion, resulting in hypertrophic myotubes. These phenotypes are similar to those caused by the calcineurin/NFAT pathway and, indeed, inhibiting calcineurin blocked the effects of FHL1 overexpression in vitro. The authors showed that FHL1 binds to and enhances the transcriptional activity of NFATc1 in vitro and in vivo.

So what goes wrong when FHL1 is mutated? In RBM, mutant FHL1 accumulates in cytoplasmic aggregates called reducing bodies, probably as a result of misfolding. When these mutants were expressed in cultured myoblasts, they also aggregated, and did not induce hypertrophy. Cowling and colleagues found that NFATc1 was sequestered to the aggregates, and was therefore unable to activate its target genes.

More info: Cowling, B.S., et al. 2008. J. Cell Biol. doi:10.1083/jcb.200804077. www.jcb.org

Source: Rockefeller University