Study explores 'garbage disposal' role of VCP and implications for degenerative disease

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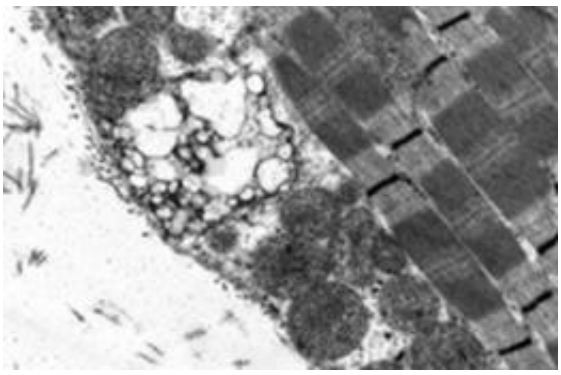

Membranous vacuoles corresponding to nondegradative autophagosomes accumulate in muscle expressing mutated VCP. Credit: Ju, J.-S., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200908115.

It's important to finish what you start, say Jeong-Sun Ju and researchers from Washington University School of Medicine, St. Louis. In the December 14, 2009 issue of the *Journal of Cell Biology*, Ju et al. reveal how a mutant ATPase blocks autophagy partway through to cause a multi-tissue degenerative disease.

Mutations in VCP, a member of the AAA ATPase family, cause inclusion body myopathy, Paget's disease of the bone, and frontotemporal dementia (IBMPFD), a rare disorder that mainly affects skeletal muscle, brain, and bone. Patient muscle contains aggregates of

membrane and proteins called rimmed vacuoles, which accumulate and disrupt cellular architecture. This pileup of membranous trash is inconsistent with VCP's known involvement in proteasome-mediated protein degradation. Ju et al. thus wondered whether the ATPase might also be involved in garbage disposal via the autophagy pathway.

Knocking down or expressing mutated VCP in cells increased levels of the autophagy markers p62 and LC3. Microscopy revealed that although autophagosomes containing these two proteins formed, they failed to mature into autolysosomes capable of degradation. VCP mutant mice and IBMPFD patients also accumulated p62 and LC3 in their muscle, and the two proteins localized to rimmed vacuoles, suggesting that the membrane-protein aggregates arise from frustrated autophagosomes. Indeed, injecting wild-type mice with a drug that blocks autophagosome maturation also produced rimmed vacuoles, as well as inducing other markers of IBMPFD myopathy.

The researchers now want to determine the mechanism by which VCP promotes the final stages of autophagy and how this is perturbed in IBMPFD patients. However, senior author Chris Weihl points out that many therapies being developed to treat degenerative diseases attempt to rescue cells by stimulating autophagy. In the case of IBMPFD, this could make matters worse, as autophagy has no problem initiating—it's the failure to finish that causes the problem.

More information: Ju, J.-S., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200908115

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