Researchers identify tumor suppressor that manages cellular cleaning and recycling proceses

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Researchers at the University of Southern California (USC) have identified a specific tumor suppressor that manages membrane traffic routes for cellular cleaning and recycling.

The study will be published in the July issue of the journal *Nature Cell Biology*, and is now available online.

"Our studies indicate that UVRAG tumor suppressor functionally connects and manages two distinct but converged membrane traffic routes for garbage cleaning and cargo recycling," says Chengyu Liang, M.D., Ph.D., assistant professor of research in the Department of Molecular Microbiology and Immunology at the Keck School of Medicine of USC.

The study identified a novel mechanism of the UVRAG tumor suppressor in regulation of autophagy, a mechanism that enables cells to digest or turn over their own contents for maintaining homeostasis (a balanced, stable condition) and responding to various stresses.

Autophagy is marked by the assembly of specialized vesicles called autophagosomes (the cellular equivalent of garbage bags) that engulf damaged proteins, organelles and invading microbes. The "bagged garbage" is then delivered to lysosomes (the cell's garbage disposal system) through autophagic trafficking that involves autophagosome-

lysosome fusion. This fusion disposes of waste with the help of lysosomal enzymes for recycling.

The findings of the study indicate that the tumor suppressor UVRAG not only facilities autophagosome formation, but also facilitates autophagosome maturation by association with the C Vps complex, a cellular machinery that facilitates membrane fusion.

In addition to identifying a novel mechanism of the UVRAG tumor suppressor in autophagy regulation, the study also identified UVRAG as an important effector protein in membrane trafficking and demonstrated the connection between endocytic and autophagic trafficking. The research conducted by Liang and colleagues with Jae U. Jung, Ph.D., professor and chair of the Department of Molecular Microbiology and Immunology at the Keck School of Medicine, suggests a functional connection and coordinated regulation of two distinct but converged membrane trafficking pathways.

"The report provides new insights into understanding some human diseases with compromised autophagic and endosomal trafficking, including cardiomyopathy (a disease of the heart muscle), myopathy (a neuromuscular disease), neuronal ceroid lipofuscinosis (genetic disorders of nerve cells) and Danon Disease)a genetic disorder characterized by heart problems)," Liang says.

The findings warrant further study into whether the UVRAG-mediated trafficking activity contributes to its tumor suppression function, she says.

Citation: Chengyu Liang, Jong-soo Lee, Kyung-Soo Inn, Michaela U. Gack, Qinglin Li, Esteban A. Roberts, Isabelle Vergne, Vojo Deretic, Pinghui Feng, Chihiro Akazawa and Jae U. Jung. "Beclin 1-binding UVRAG targets the class C Vps complex to coordinate autophagosome

maturation and endocytic trafficking." *Nature Cell Biology* (July 2008). Doi: 10.1038/ncb1740.

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