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Role of selective autophagy in cellular homeostasis and neurodegenerative disease

Proteomes are highly dynamic and undergo remodeling under a variety of conditions, ranging from cellular and organelle stress to developmental changes in state. We are exploring mechanisms by which organelles, protein complexes and signaling pathways are altered in response to activation of pathways to promote selective forms of autophagy and role of these pathways in disease. In one series of experiments, we are using quantitative proteomics to understand how assembly of ubiquitin chains on the mitochondrial outer membrane of damaged mitochondria by the PARKIN ubiquitin ligase promotes its recognition by autophagy receptors, pathways that are specifically mutated in familial forms of Parkinson's Disease. These autophagy receptors bind ubiquitin chains assembled by PARKIN and recruit the core autophagy machinery for targeting to the lysosome, a process called mitophagy. In order to facilitate these studies, we have created a facile human embryonic stem cell system that allows us to make mutations in key mitophagy regulators and also convert these cells into neurons in amounts suitable for biochemical studies. In parallel, we are also studying additional forms of selective autophagy, including the recent identification of a previously unstudied ER membrane protein that we have found is a receptor for degradation of ER in response to amino acid withdrawal, reflecting the cells response to nutrient stress. Control of ER degradation by this pathway relies on the association of this novel protein with the core autophagy machinery, including ATG8 proteins. Finally, we are studying the mechanisms by which ribosomes are regulated by nutrient stress signals, and have developed a model that integrates measurements of ribosome abundance, ribosome assembly, and effects on ribosomal subunit expression in response to nutrient stress. This work seeks to provide a molecular inventory of ribosome number and state through quantitative proteomics and ribophagy flux reporters. Recent advances in these studies will be discussed.