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TRANSCRIPTIONAL AND POST-TRANSLATIONAL NETWORKS COORDINATE SELECTIVE AUTOPHAGY TO MAINTAIN ORGANELLE HOMEOSTASIS

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Organelle homeostasis depends on a tight balance between biogenesis and selective autophagy-mediated degradation. Dysregulation of this balance underlies neurodegenerative diseases, cancer, and resistance to chemotherapy. Our research aims to dissect the molecular mechanisms that coordinate selective autophagy with organelle biogenesis, with a focus on identifying new regulatory axes and potential therapeutic targets.

We previously identified PP2A-B55α/PPP2R2A as a master regulator of mitochondrial homeostasis. Upon mitochondrial damage, PP2A-B55α orchestrates both mitophagy induction and execution while simultaneously controlling mitochondrial biogenesis. Importantly, PP2A-B55α targeting rescued neurodegenerative phenotypes in a fly model of Parkinson's disease1.

Extending this framework to other organelles, we are now investigating the regulation of pexophagy, a selective autophagy pathway targeting peroxisomes whose dysfunction causes severe metabolic diseases. We identify a novel regulatory axis that couples a specific stress signal to key transcriptional regulators of autophagy, promoting efficient peroxisome degradation. Notably, components of this axis are altered in a subtype of kidney cancer, pointing to a previously unrecognized link between pexophagy dysregulation and oncogenesis.

Altogether, these results indicate that common regulatory nodes - including kinase-phosphatase networks and transcriptional programs - coordinate selective autophagy across distinct organelles, suggesting that targeting these convergent mechanisms may offer broad therapeutic opportunities.

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References

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