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Development of a Novel Therapeutic Strategy to Prevent the Progression of Chronic Kidney Disease Induced by High Salt Intake via Lysosomal Damage Response

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Summary

Lysosomes are essential organelles for cellular homeostasis, responsible for the degradation and recycling of intracellular components. In renal tubular epithelial cells, salt overload and metabolic stress can induce lysosomal damage, leading to the leakage of hydrolytic enzymes, activation of inflammatory and senescence pathways, and ultimately the progression of chronic kidney disease (CKD).

While canonical lysosomal quality control mechanisms—such as macroautophagy, TFEB-dependent biogenesis, and ESCRT-mediated membrane repair—are well-characterized, little is known about more rapid and selective repair pathways. This study focused on a novel process called microlysophagy, in which damaged portions of the lysosomal membrane are internalized via intraluminal vesicle (ILV) formation.

We identified the AGC kinase STK38 and autophagy-related protein GABARAP as essential regulators of microlysophagy. STK38 was found to localize to damaged lysosomes in a calcium-dependent manner and phosphorylate the adaptor DOK1, which is necessary for recruiting the ESCRT disassembly factor VPS4. Independently, GABARAPs were shown to interact with ALIX, a key ESCRT-I adaptor, facilitating the assembly of the ESCRT machinery.

Loss-of-function studies revealed that depletion of STK38 or GABARAPs impairs microlysophagy, as evidenced by reduced EGFP-TRPML1 cleavage and diminished ILV formation in electron microscopy. These defects led to increased cellular senescence markers and lysosomal damage accumulation in human cells, and reduced lifespan in C. elegans models.

Collectively, these findings define a new lysosomal repair axis—STK38–DOK1–VPS4 and GABARAP–ALIX–ESCRT—which acts independently of canonical autophagy pathways. This mechanism protects cells from lysosomal damage and delays the onset of senescence.

Importantly, in the context of high-salt conditions that exacerbate CKD, promoting microlysophagy may serve as a novel therapeutic strategy to maintain lysosomal integrity in renal tubular cells. Future studies will explore whether targeting this pathway can prevent kidney injury and disease progression under salt stress.