

CCPG1-Mediated ER-Phagy Facilitates Gastric Epithelial Reprogramming Following Injury

Thanh Nguyen¹, Iris Li¹, Sophia Terez¹, Charles J Cho², Jason C Mills^{1,3}

¹Department of Medicine, Baylor College of Medicine, Houston, TX

²Department of Medicine, Emory University, Atlanta, GA

³Department of Molecular and Precision Medicine, Penn State College of Medicine, Hershey, PA

Introduction

Tissue repair requires differentiated cells to transiently relinquish specialized functions and adopt regenerative states following injury. In the gastric corpus, mature chief cells undergo this reprogramming by dismantling their secretory machinery, activating injury-associated gene programs, and re-entering the cell cycle. Because chief cells contain an extensive rough endoplasmic reticulum (ER), we hypothesized that selective ER remodeling through ER-phagy facilitates their transition to a regenerative state.

Methods

Acute gastric epithelial injury was induced in adult mice using high-dose tamoxifen, a reversible model of epithelial regeneration. Gastric tissues were analyzed across the regenerative time course by molecular, histologic, and ultrastructural approaches. ER-enriched fractions were subjected to RNA sequencing and protein analyses, and autophagy-associated cargoes were identified by p62/SQSTM1 immunoprecipitation coupled with mass spectrometry. The functional role of ER-phagy was evaluated using *Ccpgl*-deficient mice.

Results

Gastric injury induced rapid cellular stress responses accompanied by extensive remodeling of the chief cell ER. Transmission electron microscopy revealed ER fragmentation and sequestration within autophagic vesicles, followed by progressive ER clearance during regeneration. RNA sequencing of ER-enriched fractions showed induction of stress-response, inflammatory, and tissue-remodeling programs together with loss of transcripts associated with mature secretory function. p62/SQSTM1-associated proteomic analysis identified multiple ER-localized proteins as autophagy-associated cargoes following injury. Importantly, CCPG1 deficiency resulted in persistent ER accumulation, impaired organelle remodeling, attenuated regenerative responses, and significantly reduced epithelial proliferation. These findings indicate that CCPG1-dependent ER-phagy facilitates progression through injury-induced epithelial reprogramming.

Conclusion/Significance

Our findings identify ER remodeling as an integral component of gastric epithelial regeneration. CCPG1-dependent ER-phagy facilitates removal of differentiated secretory architecture as chief cells transition toward a regenerative state, linking selective organelle remodeling to epithelial plasticity, proliferation, and tissue repair.