Illuminating Novel Molecular Mechanisms of Lysosomes in Cystinosis to Uncover Therapeutic Targets

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Abstract: Cystinosis is caused by genetic mutations that alter lysosomes, a specialized compartment that is essential for regulating the breakdown of proteins. While it is well-established that lysosomes are altered in cystinosis, the molecular consequences and signaling events downstream remain to be completely understood. Our studies aim to address this gap in knowledge with the goal of uncovering new insights into disease processes and molecular targets for therapeutic intervention. We utilized a combination of molecular biology tools and high-resolution microscopy and identified a novel process that was dysregulated in a cell culture model of cystinotic proximal tubule cells. We find that lysosomes showed increased levels of protein methylation compared to healthy control cells. Further, the defective accumulation of methylation could not be restored by cysteamine treatments, which suggests that this process could offer a new therapeutic target. Importantly, the increase of methylation in lysosomes was also associated by an increase level of nitric oxide synthase (NOS) activity and contributed to imbalance redox homeostasis that was specific to cystinotic cells. Additionally, altered NOS signaling also resulted in a dysregulation of glycolysis and cellular metabolism. Altogether, these findings could reveal the fundamental basis of the disease and potential new targets for correcting pathways resistant to current treatments.