Cystinosis Research Foundation

Lay Abstract Template for Awardees

Please complete this lay-oriented grant abstract form which will be published on the CRF web site, in CRF Star Facts and in the CRF magazine when we announce your grant award. *Please do not exceed 400 words (no more than 1-1/4 page total).* Please submit this form electronically to nstack@cystinosisresearch.org as a Word document.

Title: "Role of nutrient sensing and mTORC1 signaling in cystinosis" CRFS 2022-003

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Objective/Rationale: Cystinosis is a lysosomal storage disease caused by loss-of-function mutations in the *CTNS* gene coding for the proton-driven transporter cystinosin (CTNS) that exports cystine out of lysosomes. The loss of CTNS results in the lysosomal cystine storage, causing early manifestations of kidney proximal tubule (PT) dysfunction followed by multi-systemic complications and kidney failure.

Lysosomal alterations in cystinosis lead to defective autophagy-mediated clearance of damaged mitochondria, which triggers a signaling cascade driving cell proliferation and apical dedifferentiation, as evidenced by multiple transport defects. However, the mechanisms linking CTNS loss and the resulting cystine storage to imbalances in metabolism and differentiation remain unknown.

A crucial step in nutrient sensing is the recruitment of an evolutionarily conserved protein kinase named mechanistic target of rapamycin complex 1 (mTORC1) to the surface of lysosomes. In presence of nutrients, such as amino acids, glucose, and lipids, the activation of mTORC1 pathway initiates anabolic programs that boost anabolic growth and proliferation while inhibiting autophagy and lysosome biogenesis. The functional interactions between CTNS function, lysosomal cystine levels, mTORC1 signaling, and maintenance of differentiation in PT cells remain to be characterized.

Project Description: In this project, we will take advantage of established disease model organisms and physiologically relevant PT cellular systems, in combination with cutting-edge cell biology tools, developed with the support of the CRF, to: (i) investigate whether the loss of CTNS disrupts metabolic homeostasis and differentiation by constitutively activating the mTORC1 signaling at the surface of lysosomes; (ii) dissect how the absence of CTNS and the resulting cystine storage shape the response of mTORC1 signaling in PT cells; (iii) assess the potential effect of targeting mTORC1 pathway by dietary and pharmacological approaches to rescue the lysosome and PT function in cystinosis cells.

Relevance to the Understanding and/or Treatment of Cystinosis: These studies will shed new light on how the lysosome controls homeostasis in the context of normal and diseased PT of the kidney- taken as a paradigm of highly differentiated epithelial cell system. Insights into the cellular coordinators linking lysosomal deficits to epithelial dysfunction may provide new druggable targets relevant for nephropathic cystinosis.

Anticipated Outcome: The combination of knowledge target-driven approach with phenotypic screening in disease relevant model organisms and cellular systems will address the translatability gap and accelerate drug discovery and development of transformative therapeutics in cystinosis.