PROJECT

Supervisor:	Luca Rampoldi
Title:	Molecular mechanisms of pathogenesis in Autosomal Dominant Tubulointerstitial Kidney Disease due to renin mutations
Curriculum:	Cell and Molecular Biology
Link to the personal page of the University or relevant hospital site website:	https://research.hsr.it/en/divisions/genetics-and-cell-biology/molecular-genetics-of-renal-disorders.html

Description of the Project (max 3,000 characters including spaces)

Autosomal Dominant Tubulo-interstitial Kidney Disease (ADTKD) is a rare genetic disorder characterized by progressive chronic kidney disease and renal tubulo-interstitial fibrosis. Identified ADTKD-associated genes are UMOD (uromodulin), MUC1 (mucin-1), HNF1B (HNF1-beta), REN (renin) and SEC61A1 (alpha1-subunit of translocon 61) (1). REN encodes for renin, a secreted aspartyl protease that contains a leader peptide allowing its insertion in the endoplasmic reticulum (ER), a pro-segment regulating its protease activity, and the mature part. It plays a key role in blood pressure and fluid balance regulation.

The localisation of REN mutations correlates with different clinical phenotypes (2). Mutations in the leader peptide and pro-segment are associated with onset of the disease in childhood or adolescence, while mutations in the mature protein lead to a milder, adult-onset form. We recently demonstrated that these different clinical pictures correlate with different cellular effects. While mutations in mature renin lead to ER retention of mutant protein (3), mutations in the pre- or pro-sequence lead to full or partial mistargeting of mutated renin to mitochondria, inducing mitochondrial fragmentation and affecting mitochondrial import (4). This suggests that while converging to a common endpoint (i.e. kidney inflammation and fibrosis), REN mutations have different primary effects.

The main objective of this project is to dissect the molecular pathogenesis of ADTKD-REN. Genetic data strongly suggest a gain-of-function mechanism for REN mutations. Indeed, loss-of-function REN mutations are associated with a recessive disease, renal tubular dysgenesis, characterized by perinatal mortality, and heterozygous carriers of such mutations do not have any kidney phenotype, excluding haploinsufficiency as a mechanism of ADTKD-REN mutations.

We aim at understanding if/how cellular pathways activated by mutant renin expression converge to a common gain-of-toxic-function effect, while raising from different trafficking defect and organelles. Preliminary results obtained from transcriptional profiling performed in cell models of inducible expression of different mutations indicate the Integrated Stress Response (ISR) as a common convergent point for all types of mutants. By combining transcriptomics, proteomics and metabolomics data on innovative cell and animal models, we aim at identifying the stress signal(s) emerging from ER and mitochondria and at understanding how these are linked with ISR activation and the role of the ISR in ADTKD-REN pathogenesis.

This project will lead to a significant step forward in the understanding of the main molecular mechanisms of pathogenesis associated with different renin mutations and will allow to single out potential targets for therapeutic intervention.

Skills that the student should acquire (max. 600 characters including spaces):

The student will acquire skills in:

- molecular and cellular biology and biochemistry techniques (as cloning, transfection, protein and RNA extraction, immunoprecipitation, Western blot, quantitative real time PCR)

- in vivo studies (e.g. analysis of kidney function, blood pressure measurement, histology)

- bioinformatics analysis of omics data and use of large-scale sequencing databases (e.g. Genome Aggregation Database (gnomAD) (https://gnomad.broadinstitute.org))

References (max. 15)

1. Devuyst, O., et al., Autosomal dominant tubulointerstitial kidney disease. Nat Rev Dis Primers, 2019. 5(1): p. 60.

2. Zivna, M., et al., An international cohort study of autosomal dominant tubulointerstitial kidney disease due to REN mutations identifies distinct clinical subtypes. Kidney Int, 2020. 98(6): p. 1589-1604.

3. Schaeffer, C., et al., Autosomal Dominant Tubulointerstitial Kidney Disease with Adult Onset due to a Novel Renin Mutation Mapping in the Mature Protein. Sci Rep, 2019. 9(1): p. 11601.

4. Schaeffer, C., et al., Leader peptide or pro-segment mutants of renin are misrouted to mitochondria in autosomal dominant tubulointerstitial kidney disease. Dis Model Mech, 2023. 16(6):dmm049963.