PROGETTO

Supervisore::	Luca Rampoldi
Titolo/*Title*:	Dissecting the heterogeneous effects of renin mutations associated with Autosomal Dominant Tubulointerstitial Kidney Disease
Curriculum:	Biologia Cellulare e Molecolare
Link alla pagina personale del sito web di Ateneo o del polo ospedaliero di riferimento:	*https://research.hsr.it/en/divisions/genetics-and-cell-biology/molecular-genetics-of-renal-disorders.html*

Descrizione del progetto (max 3.000 caratteri spazi inclusi)

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, a pro-segment and the mature protein. Renin plays a key role in blood pressure and fluid balance regulation. Originally reported ADTKD-*REN* mutations map in renin leader peptide and affect renin co-translational insertion in the endoplasmic reticulum (ER) (2). Recent studies showed that ADTKD-related mutations in *REN* can also be found in the pro-segment and in the mature part of the protein, with different effects on protein trafficking: mutations in the pro-segment lead to accumulation in the ER to Golgi compartment, while mutations in the mature part lead to ER retention (3,4). We recently demonstrated that mutations in the leader peptide and pro-segment lead to full or partial mistargeting of mutated renin to mitochondria inducing mitochondrial fragmentation and affecting mitochondrial import (5). Thus, the cellular phenotype correlates with clinical findings, since mutations associated with ER retention lead to a late onset disease, while mutations leading to mitochondrial mistargeting lead to an early onset disease (3 ,4). This suggests that while converging to a common endpoint (i.e inflammation and fibrosis), *REN* mutations could have different primary effects. Of note, 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.

The main objective of this project is to identify pathogenetic pathways induced by mutant renin expression. 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 localized in the different protein domains indicate the Integrated Stress Response (ISR) as a common convergent point for all types of mutants. We will carry out studies to understand the role of the ISR in ADTKD-*REN* pathogenesis, i.e adaptive or maladaptive, by assessing the consequences of its activation or inhibition on cell viability and induction of pro-inflammatory molecules. A second aim will be to analyse mitochondrial defect induced by mutant renin mistargeting to mitochondria.

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.

Competenze che deve acquisire lo studente (Max 600 caratteri spazi inclusi):

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)

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

Bibliografia (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., Dominant renin gene mutations associated with early-onset hyperuricemia, anemia, and chronic kidney failure. Am J Hum Genet, 2009. 85(2): p. 204-13.

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. 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.

5.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.