PROGETTO

Supervisore::	Luca Rampoldi
Titolo/*Title*:	Role of uromodulin as a risk factor for hypertension and related kidney damage
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)

Uromodulin is the most abundant protein in the urine in physiological conditions. It is exclusively expressed and secreted by renal epithelial cells lining the thick ascending limb of Henle's loop (TAL) segment of the nephron. Its biological function is not fully elucidated, though it has been associated with protection against urinary tract infections and renal stone formation, immunomodulation, regulated salt absorption in the TAL.

Multiple genome-wide association studies (GWAS) have identified common variants in the promoter of the UMOD gene, which encodes uromodulin, associated with independent susceptibility to chronic kidney disease (CKD) and hypertension. Interestingly, several genetic studies showed that the association of UMOD and CKD is age-dependent and is particularly increased over 65 years of age.

We previously demonstrated that UMOD risk variants, mostly located in the gene promoter, are associated with increased UMOD expression in vitro and in vivo. We modelled such effect in transgenic mice (TgUmodwt) and showed that Umod overexpression leads to salt-sensitive hypertension and to the presence of age-dependent renal lesions similar to those observed in elderly individuals homozygous for UMOD promoter risk variants. Also, we showed that increased blood pressure (BP) in TgUmodwt mice is due to overactivation of the sodium cotransporter NKCC2, operating in the TAL. We demonstrated the relevance of this mechanism in humans by showing that pharmacological inhibition of NKCC2 was more effective in lowering BP in hypertensive patients who are homozygous for UMOD promoter risk variants than in other hypertensive patients.

The aim of this project is to 1) characterize the molecular mechanisms that link uromodulin to the signaling cascade resulting in NKCC2 activation and sodium handling; 2) investigate the

interplay between uromodulin gene dosage with dietary salt and BP regulation; 3) characterize the molecular events linking uromodulin expression and hypertension-mediated organ damage (HMOD).

Results from these lines of investigation will help to identify targets/pathways related to hypertension and renal damage, whose translational relevance could be further validated in vivo.

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

- Several molecular biology, biochemistry and cell biology techniques
- Ex vivo studies (e.g. microdissection of nephron segments from mouse kidneys)
- *In vivo* studies (e.g. analysis of kidney function, blood pressure measurement, histology)
- Generation and analysis of data from multi-omics characterization of kidney tissue

Bibliografia (max. 15)

1) Kottgen et al, Nat Genet 41(6):712-7, 2009.

2) Padmanabhan et al, PLoS Genet, 6, e1001177, 2010.

3) Trudu et al, Nat Med 19(12):1655-60, 2013.

4) Devuyst et al, Nat Rev Nephrol 13(9):525-544, 2017.

5) Schaeffer et al, Annu Rev Physiol 83:477-501, 2021.