PROJECT

Supervisor:	Luca Rampoldi
Title:	Role of uromodulin as a risk factor for hypertension and related kidney damage
Curriculum:	Clinical and Experimental Medicine
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)

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, and 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 that this mechanism is relevant also in humans.

The aim of this project is to 1) characterize the molecular mechanisms that are associated with increased uromodulin expression levels; 2) investigate the interplay between uromodulin gene dosage with dietary salt, sodium handling and BP regulation; 3) characterize the molecular events linking uromodulin expression, hypertension-mediated organ damage (HMOD) and kidney aging.

We will combine hypothesis-driven and multiomics experiments in already available mouse models with different Umod gene dosage (knock-out, control, transgenic).

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

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

- 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, microsurgery)

- Analysis of data from multi-omics characterization of kidney tissue

References (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.