SWISS NATIONAL CENTRE OF COMPETENCE IN RESEARCH

KIDNEY
CONTROL OF HOMEOSTASIS

NEWSLETTER ::: NO. 9 ::: DECEMBER 2014

Kidney – Control of Homeostasis is a Swiss research initiative, headquartered at University of Zurich, bringing together leading specialists in experimental and clinical nephrology and physiology from the Universities of Basel, Berne, Fribourg, Geneva, Lausanne and Zurich, and corresponding University Hospitals.

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DECIPHERING THE IMPORTANCE OF UROMODULIN

Manneken Pis, Brussels

Uromodulin is the most abundant protein in urine and it plays an important role in protecting against urinary tract infections and kidney stones. Recent studies have shown that the protein is also involved in rare disorders, in the control of blood pressure, and in the risk of chronic kidney disease in the general population.

Uromodulin (Tamm–Horsfall protein) is a complex protein discovered in the early 1950s by Drs Tamm and Horsfall then working at the Rockefeller Institute in New York. Uromodulin is exclusively produced by tubular cells in the loop of Henle (TAL), to be secreted into the urine at a rate of 50 to 100 mg per day. In fact, it is by far the most abundant protein in normal urine. Previous research evidenced the complex biochemical characteristics of uromodulin, as well its role as a protection against urinary tract infections and kidney stones in knock-out mice. However, the role(s) and regulation of uromodulin remained largely unknown, due to difficulties in handling the protein and assessing the cells that produce it.

Renewed interest in uromodulin has been triggered by genetic studies, focusing on rare disorders and on the population risk for chronic kidney disease (CKD)

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Robert Unwin is Professor of Nephrology and Physiology at University College London.

Credit to those who convince the world

When I first learned of the initiative for the NCCR Kidney.CH, I was both impressed and envious. The foresight and innovative approach of bringing together scientists and clinicians from major universities across Switzerland has strengthened and secured a major research programme into kidney physiology. The NCCR provides a critical mass of expertise and within its framework participants can exchange ideas, techniques and resources – an ideal environment and structure for young scientists that is rewarding and fun, as well as cost-effective!

The NCCR Kidney.CH will succeed, striving as it does to move original research findings quickly into the clinic, and at the same time drawing on patients and clinical observations to test these findings and offer new thinking. On top of that, it is not exclusively 'Swiss-centric'. Its participants engage with research groups across Europe and beyond, with their activities being publicized via scientific meetings and its newsletter.

'In science credit goes to the one who convinces the world...' (Sir William Osler), something I am sure NCCR Kidney.CH will do; and I feel privileged to have some involvement in seeing what NCCR Kidney.CH can deliver.

Robert Unwin
Member of the Advisory Board
NCCR Kidney.CH

and hypertension. The support of NCCR Kidney.CH and the International Fellowship Programme on Integrative Kidney Physiology and Pathophysiology (IKPP) at the University of Bern has been instrumental for these studies, conducted by the group of Olivier Devuyst (UZH) in collaboration with Murielle Bochud (UNIL) and the SKIPOGH network.

RARE INHERITED DISORDERS

A big surprise came with the discovery that mutations in *UMOD*, the gene that codes for uromodulin, are responsible for a set of rare, autosomal dominant disorders causing tubulo-interstitial damage, fibrosis, and renal failure. These patients also suffer from hyperuricemia and develop gout early in life, and from alteration of urinary concentrating ability. These uromodulin-associated kidney diseases invariably progress to end-stage renal disease in young adulthood.

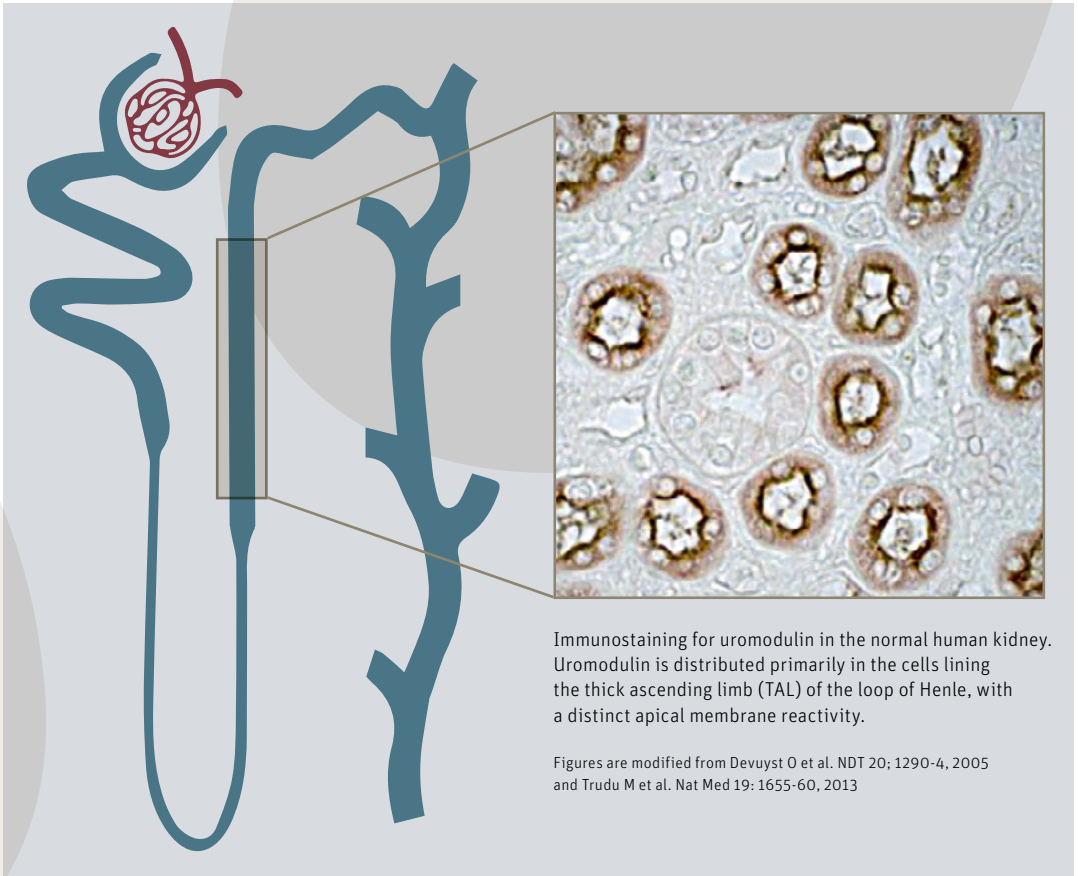
To date, more than 70 *UMOD* mutations have been described; mostly missense changes that often affect conserved cysteine residues of uromodulin. The mutations lead to defective trafficking and intracellular retention of this protein in the tubular cells, explaining the decrease in uromodulin excretion into the urine of these patients and the presence of intracellular aggregates in kidney biopsies.

RISK OF CHRONIC KIDNEY DISEASE AND HYPERTENSION

It is known that there is a significant genetic component in the risk of complex diseases such as CKD and hypertension in the general population. Genome-wide association studies (GWAS), which investigate the association of markers (single nucleotide polymorphisms, or SNPs) across the whole genome with the risk of disease in large cohorts, are increasingly used to decipher the genetic factors of complex disorders. Numerous GWAS have consistently shown that common SNPs in the *UMOD* locus are strongly associated with the risk of CKD, hypertension, and kidney stones in the general population. It has been demonstrated that the deleterious variants (which are located in the promoter of *UMOD*) lead to a two-fold increase in the transcription and urinary secretion of uromodulin. Studies of a transgenic *UMOD* mouse model proved that these variants are also associated with NaCl-sensitive hypertension and premature kidney aging. At the cellular level, the increased production of uromodulin was associated with an abnormal activation of the sodium-potassium-chloride co-transporter (NKCC2), which could be blocked by the loop diuretic furosemide. Similar defects, include abnormal response to furosemide, have been observed in humans.

PERSPECTIVES

The studies outlined above enabled the generation of tools to further address the role of uromodulin, including a robust ELISA and biochemical assays to assess uromodulin levels in well-established human cohorts; a registry of patients with *UMOD* mutations in Switzerland (in collaboration with the Gebert-Ruef Foundation); new mouse models targeting uromodulin; and a primary culture system of TAL cells. The use of these tools should give insights into the role of uromodulin in the homeostatic functions (e.g. NaCl transport, blood pressure regulation, urinary concentration, and divalent cation handling) mediated by the TAL, in line with the NCCR Kidney.CH's main objectives.

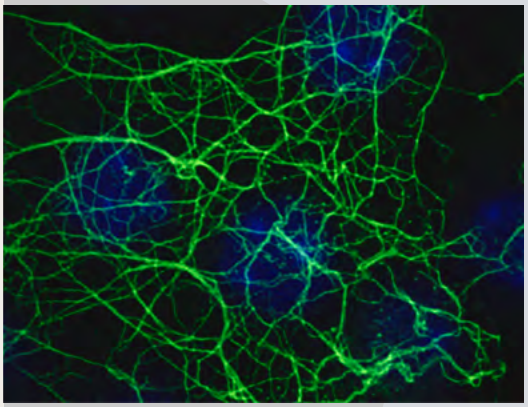


Immunostaining for uromodulin in the normal human kidney. Uromodulin is distributed primarily in the cells lining the thick ascending limb (TAL) of the loop of Henle, with a distinct apical membrane reactivity.

Figures are modified from Devuyst O et al. NDT 20; 1290-4, 2005 and Trudu M et al. Nat Med 19: 1655-60, 2013

Priority aspects will include investigation of the effect of diet, hormones, genetics and transport activity on the regulation of uromodulin. The potential value of uromodulin as a biomarker for kidney function and for kidney stone formers will also be analysed, as will the influence of the *UMOD* genotype on these functions.

Olivier Devuyst
is a nephrologist and professor at the Institute of Physiology of the University of Zurich and participant within the NCCR Kidney.CH



Uromodulin filaments (green), stained above a monolayer of primary medullary thick ascending limb (mTAL) cells

UROMODULIN

Uromodulin is a 640 amino acid protein which is glycosylphosphatidylinositol (GPI)-anchored and contains 7 N-glycosylation sites and 48 cysteine residues engaged in disulfide bonds. The protein is sorted to the apical plasma membrane of the cell, cleaved by proteases, and released into the urine to form high-molecular-weight polymers.

PORTRAIT

HOW OUR GENES INFLUENCE THE KIDNEY'S SELF-REGULATION

Disturbed kidney-related homeostasis could be inherited. However, until now its genetic factors have barely been researched. New genetic association studies will bring insights into familial heritability.

Several rare Mendelian (monogenic) disorders are characterized by disturbed kidney-related homeostasis. This underlines the functional role of selected rare mutations in human physiology. The significant heritability of homeostasis parameters evidenced in population-based cohorts implies the existence of strong genetic influences on these parameters in the general population. There appears to be a continuum between rare monogenic and common polygenic kidney-related diseases. However, the nature of these genetic factors remains poorly defined. Their discovery could yield important insights into essential homeostatic and metabolic pathways, with relevance for many common chronic cardio-metabolic diseases and as well as for some cancers. The availability of powerful genomic tools such as genome-wide association studies (GWAS) and exome sequencing, combined with existing databases in various populations with more than 10,000 samples, offers the unique opportunity to decipher such genetic pathways and to combine them with clinical parameters available within NCCR Kidney.CH.

TARGETED GENETIC STUDIES

We will conduct genome-wide association studies or genetic association studies, focusing on selected candidate genes and/or regions of interest. For example, some of this research will target the Cardio-Metabo-Chip (Illumina) in Swiss population-based studies and in international consortia with high-quality phenotypes. Phenotypes of interest include blood and urinary electrolytes. A network of international collaborations is in place to allow the replication of the most interesting findings. State-of-the-art statistical methods are being used to combine the aggregated results from multiple cohorts, while taking multiple testing and population stratification into account. Since we have access to individual-level data for two Swiss population-based groups—the Cohorte Lausannoise (CoLaus) and the Swiss Kidney Project on Genes in Hypertension (SKIPOGH)—we will be able to refine the analyses according to preliminary discoveries and to conduct selected analyses in response to findings in experimental studies, such as animal studies.

RESEARCHING THE SWISS POPULATION

CoLaus is an ongoing population-based cohort led by Professors Peter Vollenweider and Gérard Waeber (CHUV, Lausanne). For this group Olivier Devuyst and his team have measured urinary electrolytes at baseline in around 6,000 CoLaus participants. The ten-year follow-up examination (2014–2016) of CoLaus participants is currently ongoing.

SKIPOGH is a multi-centric, family-based, population-based cohort including 1,100 participants aged 18 years and over. The SKIPOGH group includes seven co-investigators and twelve research MD fellows. They are all closely involved in collecting, supervising and analysing the data. SKIPOGH is embedded within the European Project on Genes in Hypertension (EPOGH).

EXPLORING FAMILIAL HERITABILITY

As a result of this research we expect to better explore the familial aggregation and heritability of kidney-related phenotypes within the Swiss context. In collaboration with international and national partners, we expect to identify new genes, or regulatory genetic variants, involved in kidney-related homeostasis in humans including magnesium and calcium homeostasis. Numerous synergistic collaborations with the NCCR Kidney.CH research groups are possible. The potential for novel findings is elevated and the availability of human population-based data will enhance opportunities for translational research.

Murielle Bochud
holds a diploma in Medicine from the University of Geneva (1994), an MD from the University of Lausanne (2002) and a PhD in Genetic Epidemiology (2007) from Case University (Cleveland, OH, USA). She specializes in epidemiology and public health (FMH, 2010), is the principal investigator in the Swiss Kidney Project on Genes in Hypertension (SKIPOGH), and is part of the analysis group of the CoLaus cohort. She has expertise in cardiometabolic and renal epidemiology and in genetic association studies, and is currently head of the Chronic Disease division at the Institute for Social and Preventive Medicine at the CHUV, Lausanne.
Bochud has interests in the genetic determinants of blood pressure and renal function and in public health genomics. She has published more than 100 peer-reviewed scientific manuscripts.

FOCUS ON CLINICAL RESEARCH

By launching its first internal call for human/clinical and translational cooperative projects (HCPs), the NCCR Kidney.CH Clinical Study Group aims to stimulate clinical and translational research.

Three types of project proposals are covered by this call:

1. Well-controlled, small-scale studies of subjects/patients, in particular proof-of-principle studies aimed at testing ideas emanating from animal studies and involving at least two research groups.
2. Observational studies, for example using population genetics (genome-wide association studies) or biopsy material, for instance to establish new biomarkers.
3. Translational preclinical studies aimed at mechanistically understanding observations made in humans.

Besides smaller-scale projects, one larger project may be funded with up to CHF 300,000. The results of the call will be announced in February 2015.

RENOWNED SCIENTISTS JOIN ADVISORY BOARD

In October 2014 three leading international kidney specialists joined the NCCR's Advisory Board. They bring additional expertise to the now six-member board and will be involved in evaluating all the NCCR's scientific projects.

Joachim Fandrey is Full Professor of Physiology at the University of Duisburg-Essen and member of the interdisciplinary Centre of Medical Biotechnology. As managing director of the Institute of Physiology since March 1999 his research interest focuses on the oxygen-dependent gene expression and cellular oxygen sensor. A medical scientist and member of the German National Scholarship, Fandrey is also Dean for Student Affairs at the Medical Faculty of the University of Duisburg-Essen.

Pascal Houillier is Full Professor and medical practitioner at Paris Descartes University and Georges Pompidou University Hospital. He is head of the Metabolic and Renal Diseases Unit and head of the Laboratory of Metabolism and Renal Physiology at the Cordeliers Research Centre, Paris. Houillier is chairman of the Scientific Council of the Fondation du Rein and member of the Scientific Council at the French Institute of Health and Medical Research (INSERM).

Robert Unwin is Professor of Nephrology and Physiology at University College London (UCL) and honorary consultant physician and nephrologist at the Royal Free Hospital and the University College Hospital Trust. As head of the Research Department of Internal Medicine — part of the Division of Medicine — his research interest is in renal tubular physiology, renal tubular disease, and renal stones. Currently, Unwin is also a chief scientist on secondment for cardiovascular and metabolic diseases at AstraZeneca.

NEW JUNIOR GRANT

With its 5th Junior Grant, NCCR Kidney.CH will support yet another young scientist with up to CHF 60,000 per year for a maximum of three years. By enabling young researchers to start their own project, the NCCR fosters the next generation of kidney researchers. Young scientists with a PhD or an MD and who are affiliated with one of the participating or associated research groups of NCCR Kidney.CH are eligible for the Junior Grant.

After a pre-selection procedure, candidates will submit their full proposal by January 22, 2015 and the result of the final selection will be announced in February.

E-LEARNING MODULE 3 STARTED: CALCIUM AND PHOSPHATE METABOLISM

After last years' success of the e-learning modules 1 & 2 in basics in nephrology, a third, new module was created in collaboration with the Health Science eTraining Foundation (HSeT). It deals with the renal handling of calcium and phosphate and links this to pathophysiological conditions when the functioning of the kidney is disturbed.

The kick off for this new module took place on October 14, 2014 at the University of Bern and included presentations on "Mineral metabolism" (by Olivier Bonny from the University of Lausanne) and "Phosphate handling in chronic kidney disease" (by Sophie de Seigneux from the University Hospital of Geneva). Participants individually study six annotated milestone articles, which are available online via our e-learning platform. Subgroups of the participants will then each study one specific article in greater depth and will analyze it according to questions provided by the tutors. On March 12, 2015 all groups will meet to present and discuss their work in front of our panel of Kidney.CH experts. Progress will be self-assessed during the course.

Additional modules will follow to progressively build up a comprehensive education programme for a better understanding of the basics of kidney physiology and pathophysiology. Each module corresponds to 2 to 3 ECTS credit points and shall become part of an official CAS- and DAS-certified course.

EVENTS

NCCR KIDNEY.CH RETREAT 2015
February 6–7, 2015
Murten, Switzerland

ADVANCEMENT OF WOMEN: WORKSHOP "HOW TO APPLY FOR A PERMANENT ACADEMIC POSITION"
February 9–11, 2015
Zurich, Switzerland

E-LEARNING MODULE 3 FINAL MEETING
March 12, 2015
Bern, Switzerland

39. NEPHROLOGISCHES SEMINAR
March 19–21, 2015
Heidelberg, Gemany

52ND ERA-EDTA CONGRESS
May 28–31, 2015
London, UK

5TH INTERNATIONAL NCCR KIDNEY.CH SYMPOSIUM
June 11, 2015
Zurich, Switzerland

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University of Zurich[UZH]

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