

KIDNEY

CONTROL OF HOMEOSTASIS

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Kidney—Control of Homeostasis

is a Swiss research initiative, headquartered at University of Zurich, which brings together leading specialists in experimental and clinical nephrology and physiology from the universities of Bern, Fribourg, Geneva, Lausanne, and Zurich, and corresponding university hospitals.

ION TRANSPORT ACTIVITY AND TUBULAR METABOLISM ARE LINKED IN KIDNEY DISEASE



Transport and metabolism are closely linked in the kidney. The movement of large amounts of water and solutes by tubular epithelial cells generates a huge demand for ATP. In chronic kidney disease (CKD), the increased oxygen consumption by remnant nephrons may lead to activation of hypoxia sensing mechanisms. This in turn could cause downregulation of normal metabolic processes, like fatty acid metabolism and gluconeogenesis, whilst activating pro-inflammatory and pro-fibrotic pathways. Understanding the exact nature of these changes could reveal new targets for intervention to slow the progression of CKD.

The major function of the kidney tubule is to reabsorb vast amounts of water and solutes filtered by glomeruli, to maintain body homeostasis. This is an energy-expensive process, and as a result, tubular epithelial cells have to produce a lot of ATP, the molecular currency of energy within most biological systems. The majority of this then consumed by the enzyme Na^+/K^+ -ATPase, also known as the “Na-pump”, which is highly expressed along the basolateral membrane of tubular cells. The Na-pump uses one ATP molecule to actively extrude three intracellular sodium ions, while simultaneously taking in two extracellular potassium ions. The resulting electrochemical gradients are then leveraged to drive the activity of various co-transporters, antiporters and ion channels.



Andrew Hall

As anyone who has ever accidentally put diesel into a petrol car will know, even the most sophisticated transport machinery won't work without the right fuel. And so it is in the kidney, where the numerous different cell types along the tubule are dependent on specific metabolic pathways to optimally perform their specialized solute transport functions. Historically, the study of renal transport and metabolism has largely proceeded in parallel, but the two are in fact hugely interdependent. For example, patients with mitochondrial diseases present with tubular transport defects, whilst metabolites themselves need to be transported in and out of cells. However, by harnessing newer technologies some recent studies—including within the NCCR—are at last bringing these previously distinct fields together, to reveal the complex interplay between transport and metabolism in the kidney, and how this changes and evolves in disease states and compensatory remodeling. Crucially, this work is not only providing a more holistic understanding of kidney physiology, but is also identifying exciting new targets for therapeutic intervention. A good example is the metabolic co-factor NAD, which plays a vital role in tubular metabolism, and NAD supplements are now being evaluated in clinical trials in patients with acute kidney injury. Although there is still a long way to go, it seems that the distant dream of powering up faltering kidneys is slowly starting to become a reality.

In this manner, the active transcellular transport of sodium is directly coupled to that of many other solutes, including chloride, phosphate, glucose, and amino acids. Moreover, by generating transepithelial potential differences and concentration gradients, it is also essential for promoting paracellular ion and fluid reabsorption.

In total, active ion transport by renal epithelial cells consumes about 3 kg of ATP per day in humans. Intense cellular metabolism is needed to meet this demand, and the kidney ranks second only to the heart for mitochondrial density and oxygen consumption. However, each specific tubular segment relies to a greater or lesser extent on different metabolic pathways. For example, proximal tubule cells—which perform the bulk of solute transport—mainly depend on oxidative metabolism of fatty acids, whilst glycolysis is more active in distal segments. The efficiency of tubular sodium transport is an index of the overall metabolic cost of solute reabsorption. It is calculated as the ratio between oxygen consumption rate and the number of sodium ions transported per unit of time. Efficiency levels progressively decrease from the proximal to the distal tubules, reflecting the fact that beta oxidation of fatty acids provides the biggest yield of ATP per molecule of fuel. It is also worth mentioning that proximal tubular cells use other reabsorbed metabolites (such as lactate, glycerol and some amino acids) to make glucose, by a process called gluconeogenesis. In fact, the kidneys contribute about one third of the body's glucose production, something which is often overlooked.

In both acute kidney injury (AKI) and CKD, major changes in tubular metabolism have been found to occur. For example, when acutely damaged by insults like ischemia, proximal tubular cells undergo a dramatic shift from fatty acid oxidation to glycolysis, presumably as a protective mechanism to maintain ATP levels and minimize oxidative stress when the normal oxygen supply is compromised. Crucially, in our recent studies in patients with AKI, we have also demonstrated that proximal tubules lose the ability to produce glucose. This leads to major systemic consequences, such as hypoglycemia, which might in turn explain the high levels of morbidity and mortality seen in such patients (Legouis et al., *Nature Metabolism*). Such metabolic changes in the proximal tubule are accompanied by a downregulation of master regulators of mitochondrial biogenesis and fatty acid oxidation, such as PGC1 α . Moreover, substantial decreases in the critical metabolic co-factor NAD⁺ have been documented and NAD⁺ replenishment in animals restores mitochondrial function and ATP generation, leading to better outcomes. Clinical trials of NAD supplementation are now underway to see if these exciting findings can translate to humans.

Following an acute insult to the kidney, patients are often left with fewer remaining nephrons, which have to increase their workload accordingly to compensate. Some individuals then develop a syndrome of progressive loss of kidney function, known as CKD. This is characterized histologically by increasing interstitial immune cell infiltration and fibrosis, which gradually destroys and replaces the tubules. Recent studies suggest that fatty acid metabolism also becomes downregulated in proximal tubules in CKD, and that the resulting lipid overload stimulates pro-inflammatory and pro-fibrotic signaling, thus mechanistically linking these events. What actually causes this apparently adverse metabolic switch remains unclear, but it is likely to represent a chain reaction of events, with rises in active electrolyte transport increasing the rate of oxygen consumption, potentially leading to a decrease in tissue oxygen content and the triggering of hypoxia sensors. Indeed, we have recently shown that stimulating sodium transport in the kidney tubule directly increases oxygen usage and activates hypoxia inducible factor (HIF), a master metabolic regulator that co-ordinates a myriad of adaptive responses. We are now exploring whether this activation of the HIF pathway may drive the shift away from oxidative metabolism of fatty acids to glycolysis in proximal tubules, and if so, whether this could thus represent an upstream target for intervention to prevent fibrosis.

In summary, our past and recent works are aiming to explore the potential role of metabolic switches in kidney tubular cells as a causative event in the pathogenesis of progressive renal failure. These studies could help to find promising therapeutic targets in the race to halt the progression of CKD.



Eric Feraille is an Associate Professor of Fundamental Medicine at the Department of Cell Physiology and Metabolism of the University of Geneva. He was one among the initial team members who successfully built the NCCR Kidney.CH along with Prof. François Verrey.



Sophie de Seigneux is an Assistant Professor of Nephrology at the Department of Internal Medicine of the University Hospital of Geneva. She is recipient of Swiss National Foundation professorship. She has also served as co-leader of the NCCR's "Work Package: Oxygen" for almost 6 years as of now.

PROF. RUXANDRA BACHMANN-GAGESCU



Ruxandra Bachmann-Gagescu is a medical geneticist who recently joined the NCCR Kidney.CH.

Ruxandra Bachmann-Gagescu is an SNF assistant professor at University of Zurich, and one of the newest members of the NCCR Kidney.CH. She currently heads a research group at the institute of medical genetics with a focus on ciliopathy modelling. We asked her about her current research and plans for the future.

WE'RE DELIGHTED TO HAVE YOU AS PART OF THE NCCR! WHAT PROJECTS ARE YOU PLANNING TO PURSUE AS A MEMBER?

The main aim of our project within the scope of the NCCR Kidney.ch is the development of renal organoids derived from human induced pluripotent stem cells (hiPSC). This model system will be applied to studying the role of primary cilia in renal tubular cells and cystogenesis. In addition, the establishment of kidney organoids can be of interest to all researchers of the NCCR Kidney.CH, and can serve as a platform for future collaborations.

A second contribution to the NCCR Kidney.CH will be my participation in the genetic analysis of data from the Swiss Kidney Stone Cohort.

WHAT LED YOU TO YOUR CURRENT LINE OF RESEARCH?

A combination of interests and fate... While I was searching for a research topic for my fellowship in medical genetics at the University of Washington in Seattle, my former mentor Cecilia Moens (a developmental biologist studying hindbrain development) and my mentor-to-be Dan Doherty (who has one of the largest cohort of patients with Joubert syndrome, a ciliopathy characterized by a specific hindbrain malformation) were starting a collaboration to study a newly identified Joubert gene in zebrafish. Based on my interests and skills, I was the obvious candidate to take on this project; so I suppose I was in the right place at the right moment!

YOUR WORK FOCUSES ON CILIOPATHIES, PARTICULARLY IN THE KIDNEY AND THE RETINA. WHAT DO YOU FIND INTERESTING ABOUT CILIA?

Primary cilia are like the cell's antenna; they're responsible for sensing outside signals and for regulating their transduction into the cell, whereby the type of signal depends on the cell type and on the developmental stage. Examples include such different signals as light in retinal photoreceptors or transduction of key developmental signaling pathways, including hedgehog and Wnt signaling. Consequently, cilia are involved in a very wide range of developmental and biological processes. The study of primary cilia provides a research focus at the crossroads between genetics, developmental biology and molecular biology, which I find fascinating. From a genetics point of view, the disorders caused by ciliary dysfunction (collectively termed "ciliopathies") are perfect models to study key open questions in human genetics, such as the mechanisms underlying phenotypic variability in monogenic disorders.

WHAT ORGANISMS DO YOU USE FOR MODELING?

Besides the hiPSC-based models we are currently establishing in the lab, our main research model is the zebrafish, which is an excellent model for ciliopathies. We have generated a collection of zebrafish mutants in ciliary genes, and we combine techniques such as live imaging of tagged proteins of interest in a whole tissue context (favored by the transparency of the larvae) with modern -omics approaches.

WHERE DO YOU HOPE THIS RESEARCH WILL LEAD?

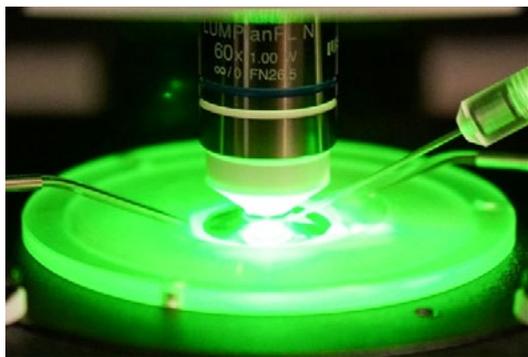
As a medical geneticist, my overarching goal is to understand the path leading from genetic variation to human disease, in order to provide patients with more accurate predictions of

their disease course and hopefully to develop therapies to alleviate or cure their symptoms. To achieve this goal, I believe that a combination of models has the highest chance of providing relevant insights. The combination of approaches allying human genetic studies, animal models such as the zebrafish, and now in vitro models on human cells appears to be a promising path that will hopefully lead to a deeper understanding of the pathomechanisms underlying these diseases. In the end, I hope to be able to bring back to the patients the insights we have gained in order to provide better care.

WHAT DO YOU LIKE TO DO WHEN YOU'RE NOT IN THE LAB?

Being an outdoor-oriented person, I love hiking, camping, skiing or cycling with my husband and three children. When allowed to do so (...), we above all enjoy traveling the world to discover wild animals, forests, mountains, rivers, lakes and seas in remote places. Besides this, I enjoy a good book, a play or dance performance, a good movie or a nice documentary, to travel at least mentally.

NEW ELECTROPHYSIOLOGY PLATFORM LAUNCHED



In a joint effort of the Department of Molecular Life Sciences of UZH and the Institute of Anatomy, as well as the Clinic of Endocrinology, Diabetology and Clinical Nutrition from the USZ and the National Center of Competence in Research (NCCR) Kidney.CH, we have launched the Electrophysiology Facility (e-phac).

Ion channels are vital for all living cells and organisms. In-vitro electrophysiological techniques (e.g. Patch-Clamp) are the gold standard to measure bioelectrical currents from single channels and cells. Unfortunately, most of the conventional in-vitro electrophysiological techniques require very costly and bulky equipment in addition to highly trained staff; hence, it is not affordable for many individual research groups. The newly launched e-phac facility combines powerful in-vitro electrophysiology with image-based techniques in order to offer a comprehensive approach to study bioelectrical signaling in cells and tissues. In the future, the facility plans to extend their services towards high-throughput automated patch clamp, an essential platform to search for novel therapeutic approaches in the context of personalized medicine. The facility is open to discussing new projects, and can be found at the Irchel Campus of UZH, Department of Molecular Life Sciences, room Y13 K52.

Email: ephac@mls.uzh.ch

WebLink: <https://www.e-phac.uzh.ch/en.html>

NCCR-SPONSORED IPAHK+ TRIAL GETS "POSH"

The IPAHK+ ("Incidence of Primary Aldosteronism in Patients with Hypokalemia") study was launched by the Endocrinology Clinic at the Zurich University Hospital's in October 2019, with the goal of investigating the incidence of primary hyperaldosteronism in a hypokalemic population. Since then, a hypokalemia registry specially set up for this purpose, which records all outpatients at the University Hospital Zurich with hypokalemia ≤ 3.0 mmol/l, has been growing continuously. The evaluation of the first 100 reported patients is currently underway and a corresponding publication is expected in spring 2021.

In parallel, an exciting new sub-study has been developed called POSH: effects of Potassium Supplementation on blood pressure in patients with Hypokalemia. More than just an acronym, the name POSH is apt because the study is charmingly elegant in its design, procedures and scientific question. The "POSH" study is a prospective interventional trial examining the short-term effects of a one-week oral potassium

NCCR SCIENTIST WINS STERN-GATTIKER PRIZE



Sophie de Seigneux

The Swiss Academy of Medical Sciences (SAMS) recently announced the winners of the 2020 Stern-Gattiker Prize, a biennial award recognizing outstanding women in academia. The NCCR's own Sophie de Seigneux was one of two women recognized this year.

Sophie de Seigneux is an SNF professor and a senior physician at the Nephrology Division of Geneva University Hospital (HUG), and is currently leading a project on "nephron loss and hypoxia" with the NCCR Kidney.CH. She and her fellow winner, Prof. Sara Meyer of Basel University Hospital, were selected by the SAMS jury for their outstanding contributions to the field of medical research.

The nomination submissions and the two scientists' CVs testify to outstanding careers: after graduating in medicine, they both undertook postdoctoral studies abroad and secured third-party funding amounting to several million Swiss francs for their research projects. Their talents were recognised by the Swiss National Science Foundation through its Ambizione and Eccellenza programmes. Both of the prizewinners are now around 40 and have a family. They are involved in teaching and mentoring activities and have already received other awards.

Congratulations to both winners!

EVENTS

10TH KIDNEY.CH RETREAT 2021

15 January 2021

Virtually (via Whova/Zoom)

WORLD KIDNEY DAY

11 March 2021

Global campaign

58TH ERA-EDTA CONGRESS

5–8 June 2021

Virtually

10TH INTERNATIONAL KIDNEY.CH SYMPOSIUM 2021

18 June 2021

Location TBA

ISN FRONTIERS MEETING 2021 "COMPLEMENT RELATED KIDNEY DISEASES: CLASSIFICATION, GENETICS AND TREATMENT"

1–3 July 2021

Bergamo, Italy

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