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EDITORIAL

From genetics to personalized nephrology: kidney research at a tipping point

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Introduction

Technologies for genetic analysis continue their evolution at an amazing pace, including advances in whole genome sequencing, total RNA sequencing and single cell genomics. Complementary to these, total sequencing and analytical services are increasingly becoming commercial with rapid and high quality service provision. These developments have led to the full availability of genetic analysis to ever wider research communities and consequent advances in a variety of research areas, while the fundamentals have not changed: with all of the novel tools that are becoming available, critical thinking and alertness shown by well-trained clinicians working seamlessly together with scientists remain the key to success.

The technical advances are, furthermore, changing the value of discovery research and the way that it integrates into the further development of solutions for direct patient benefit: the biopharmaceutical and diagnostic industries need to cooperate with the best producers of discovery data, which usually come from universities and research institutions. These developments also call for increasing adherence to quality standards in genetics, patient data and massive sample repositories with repercussions in legal and commercial issues. We can fairly state that, in many ways, the traditional research concepts are at crossroads and must re-adjust. The research community working on kidney diseases has been early to adapt and, consequently, has benefitted hugely from the new technologies and approaches.

In this special issue of Cell and Tissue Research, called "Genetic Kidney Diseases", we present the leading edge of research achievements, novel approaches and prospects for the future so that we can better anticipate the next level of research into hereditary and acquired kidney diseases.

Genetics of kidney diseases

Genetic kidney diseases account for a considerable fraction of end stage renal kidney disease. Novel monogenetic causes, genetic modifiers and new risk gene variants for kidney diseases have been discovered at an amazing pace in recent years. This knowledge is currently being translated into a much deeper understanding of the pathophysiology of many renal diseases.

In his article "New structural insights into podocyte biology", Florian Grahammer (2017) highlights the latest advances in light- and electron-microscopic techniques and shows their skilful application in revealing the remaining controversies in

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the assembly of key elements composing the glomerular filtration barrier. Notably, the novel imaging approaches have led to a new understanding of the way that the congenital nephrosis gene product NEPHRIN together with NEPH1 forms the slit diaphragm, an advance that will hopefully translate into a better understanding of proteinuric diseases.

In his article "Role of primary cilia in non-dividing and post-mitotic cells", Gerd Walz (2017) describes yet another intriguing aspect, namely the role of primary cilia in differentiated post-mitotic cells in the regulation of, for example, DNA damage responses, autophagy and mitochondrial functions. By integrating these different cellular functions, primary cilia in non-dividing cells seem to form a signalling hub controlling cell homeostasis.

Apoptosis is a known regulatory process in the development of the polycystic diseases in the kidney. In their article "Role of apoptosis in the development of polycystic kidney diseases", Peintner and Borner (2017) summarize key factors affecting the balance in the polycystin-1- and polycystin-2–based multiprotein membrane complex and its consequences for regulating cell survival, proliferation, differentiation and autophagy in polycystic kidney disease.

The article "Insights into autosomal dominant polycystic kidney disease by quantitative mass spectrometry-based proteomics" by Diedrich and Dengjel (2017) shows the power of advanced mass-specrometry (MS) methods in revealing the complex of proteins and their respective associations with intracellular structures and pathways in autosomal polycystic kidney disease. More generally, their review shows that the leading edge technical approach to protein analytics can be of immense help in understanding disease pathogenesis, protein modifications and protein-protein interactions in general. Notably, the prospect of MS-based technologies for disease diagnostics and monitoring is discussed, paving the way for their future use as a support in clinical disease management.

Fabry disease is a lysosomal storage disease with often devastating kidney manifestations. In their article "Pathomechanisms of renal Fabry disease", Eikrem et al. (2017) summarize the genetic background and pathophysiologic details of this glycosphingolipid disorder. Of note, next to the enzyme replacement therapy that is used as clinical routine, novel chaperone-mediated therapies have recently entered the clinical arena. Therefore, Fabry disease represents a "model disease" of the way that genetic and pathophysiologic discovery are providing novel clinical treatment strategies.

Skin and kidney share not only some basic structural molecular components but also distinct overlapping diseases. In their review article "Renal-skin syndromes", Has and He (2017) provide a comprehensive overview highlighting this previously underrecognized disease group. Diseases shared by the skin and the kidney are related to defects in cell-matrix adhesion and the key molecular players at the shared sites and experimental models are introduced by these authors. Furthermore, distinct types of epidermolysis bullosa are reviewed in depth with a description of their respective renal involvement.

Mechanisms, consequences and the regulation of the epigenetic machinery have rapidly been unfolded, with an increasing understanding of the way that DNA methylation and histone modifications affect disease progression. In their article "Epigenetics of kidney disease", Wanner and Bechtel-Walz (2017) summarize current knowledge of the renal cell epigenome in development, maintenance and kidney disease thereby offering a novel basis for comprehending renal disease initiation and progression. Furthermore, the promise of epigenetics for biomarker discovery and emerging new treatments are discussed.

In his article "Advances in renal genetic diagnosis", Bergmann (2017) highlights the benefits that recent technical advances of next-generation sequencing (NGS) has provided in disease diagnosis and the identification of the pathophysiology of hereditary nephropathies. The increasing knowledge of the genotype-phenotype correlation not only provides the basis for genetic counselling, risk assessment and clinical management but also offers new therapeutic concepts for several genetic diseases.

Disease modeling in genetic kidney diseases

The advances in identifying causal gene mutations or gene variants associated with kidney diseases offer new opportunities for basic research and the development of therapeutic compounds. In recent years, scientists have been creating models of human genetic disease by using organoids, worms, flies, zebrafish, frogs, mice and other animals to gain novel insights into the molecular mechanisms of many renal diseases.

In their article "Genetic kidney diseases: *Caenorhabditis elegans* as model system", Ganner and Neumann-Haefelin (2017) review the possibilities of fully utilizing the simple nematode for studies of disease and developmental aspects of the kidney. The abundance of genetic similarities between human species and *C. elegans* allows the study of slit diaphragm biology, ciliopathies, tubulogenesis and general mechanisms of cellular homeostasis.

Helmstädter and Simons (2017) review the experimental uses, advantages and limitations of *Drosophila* in studying human kidney disease in "Using *Drosophila* nephrocytes in genetic kidney disease". The high conservation of human podocyte and proximal tubular cell functions by *Drosophila* nephrocytes make them a highly valuable kidney model as evidenced by recent work. Because of the easy genetic accessibility of *Drosophila*, this model can be a game changer in future studies aimed at distinguishing disease-causing sequence variants from functional gene variants present in the human genome.

Schenk et al. (2017) review the recent advances in zebrafish models with regard to studying kidney diseases in "Disease modeling in genetic kidney diseases: zebrafish". The major benefits of using zebrafish are the relative simplicity in inducing genetic manipulations and in monitoring renal functions, even in real time. Recently developed high-throughput screening and genome editing techniques offer tremendous opportunities to model kidney diseases in zebrafish.

Getwan and Lienkamp (2017) discuss the implications of the *Xenopus* tadpole: "Toolbox in a tadpole: *Xenopus* for kidney research". With the obvious benefits of the rapid embryonic development of *Xenopus* and the availability of targeted injections, the tadpole offers obvious benefits for studying, in particular, organogenesis and genetic diseases. In this article, the authors review the variety of methods employed so far and those coming increasingly into use, including those for gene editing. As the authors point out in the article, the use of the tadpole system has provided instrumental insight into the molecular mechanisms of human kidney disease.

For decades, mice with engineered genomes have been most extensively used for targeted studies of kidney pathophysiology and genetics. In their article "Disease modeling in genetic kidney diseases: mice", Andreas F. Hofmeister and colleagues (2017) now provide a comprehensive survey to the methods currently in use and the results obtained for a better understanding of the biology of the respective disease-causing genes.

Ganna Reint and coworkers (2017) in their article "Kidney development and perspectives for organ engineering" provide intriguing views of alternative developments for future kidney replacement. In particular, they highlight the emerging techniques of using decellurized and three-dimensional bioprinting strategies.

In their article "Engineering the kidney: novel approaches towards reprogramming and directed differentiation of renal cells", Kaminski et al. (2017) review the most recently developed techniques for generating renal cells and tissues by either directed differentiation or transcription-factor-based reprogramming. These novel tools offer exciting possibilities for modeling inherited and acquired kidney diseases from patient-derived cells, for performing nephrotoxicity testing, or for potentially developing novel kidney replacement therapies.

New aspects of cell metabolism, soluble factors, biomarkers and cell quantification in kidney disease

In recent years, the cell metabolism of renal cells, the soluble factors mediating glomerular diseases, the previously underappreciated cell compartments such as parietal epithelial cells and novel biomarkers have all entered the center stage of kidney disease discovery research.

As has been known for a long time, metabolic signaling and energy metabolism play a critical role in genetic and acquired kidney disease. In their article "Metabolism and homeostasis in the kidney: metabolic regulation through insulin signaling in the kidney", Kuczkowski and Brinkkoetter (2017) show that the kidney is not just a passive target of systemic metabolic changes but that renal cell intrinsic metabolic signaling pathways are main drivers of renal disease. With the emphasis on insulin signaling, the authors provide a comprehensive review of the current understanding and the link between insulin signaling and mitochondrial function contributing importantly to the pathogenesis of kidney disease.

The kidney is either an active participant or an innocent bystander suffering from collateral damage of immunological actions. The manner in which the kidney interacts in molecular terms with other tissues and cross talks with the immunological system has seen substantial advances in recent years, especially in the form of circulating factors tentatively identified in the pathogenesis of idiopathic nephrotic syndrome. In their review article "Extrarenal determinants of kidney filter function", Hahm et al. (2017) provide comprehensive insight into the derivation of suPAR (from the bone-marrow), its regulation and its promise not only as a target, but also as a potential high-value diagnostic biomarker for the management of this devastating kidney disease.

These ubiquitous vehicles of cell-to-cell communication and other fundamental biological functions are reviewed by Barreiro and Holthofer (2017) in their article "Urinary extracellular vesicles. A promising shortcut to novel biomarker discoveries". Whereas the re-discovery of these vesicles of various size categories and overlapping physico-chemical properties is highlighted by results indicating their value in changing our understanding of many of the biological pathways involved, the lack of standardization results in partially misleading and overenthusiastic interpretations. Nevertheless, extracellular vesicles are increasingly relevant for kidney research because of the new and efficient methods of harvesting them from urine.

Loss of podocytes appears to be the pacemakers of most progressive kidney diseases. In their article "Quantifying podocyte depletion: theoretical and practical considerations", Victor Puelles and colleagues (2017) provide valuable insights into podocyte depletion in disease pathogenesis by introducing currently available methods for quantifying podocyte depletion. These methods include, for example, the analysis of their number from glomerular cross-sections, stereological methods and new techniques allowing glomerular analysis in optically cleared samples. The review provides a balanced evaluation in all of these techniques suitable for podocyte quantitation and will be of practical help in the selection of methods for use.

Whereas glomerular visceral epithelial cells (podocytes) have long been considered as cornerstones in many

proteinuric kidney diseases, the role of glomerular parietal epithelial cells (PECs) of the Bowman's capsule has remained enigmatic and controversial. In their review article "Parietal cells-new perspectives in glomerular disease", Laura Miesen and coworkers (2017) provide a comprehensive new understanding of this cell type. By reviewing the evidence regarding their important roles as a reservoire for the replacement of lost podocytes and as the site of extracapillary proliferative lesions in glomerular disease, their true pathogenetic role becomes evident. We expect to see future aspects of their role revealed by the use of targeted experimental models and more accurate techniques of imaging. Future developments of targeted therapeutics aimed at PECs can also be expected.

We feel that the leading edge researchers with their very high quality contributions in this special issue provide an excellent observation point enabling us to see the direction from which the field has come and the route along which kidney research and drug development is now heading.

We warmly thank all the contributors for sharing their time, commitment and special expertise in research-intensive nephrology with our readers. The outcome of this special issue speaks for itself and we hope that this special issue paves the way to future discoveries for the benefit of our kidney patients.

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