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EDITORIAL

Frontiers in the pathogenesis of kidney disease

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Worldwide, approximately 10% of the population suffer from chronic kidney disease (CKD), as defined by an abnormal urinary protein excretion and/or a decrease in glomerular filtration rate. CKD is associated with two significant and competing risks: (1) an increase in cardiovascular morbidity and mortality, and (2) a progressive loss of renal function [1]. The incidence of end stage kidney disease requiring renal replacement therapy is steadily increasing and poses a tremendous burden on health care budgets, even for highly developed countries. CKD is frequently associated with elevated blood pressure and increasing evidence indicates that also the so-called essential hypertension, which affects more than 30% of the population, is caused by abnormal renal sodium handling [2].

Despite the recognized importance of disorders in kidney function, the understanding of the underlying mechanisms and opportunities for specific therapeutic intervention remain very limited. Less funding options exist for kidney research than for other fields of medicine. At the same time, the anatomical complexity of the kidney with more than 30 different cell types, the interplay between large trans- and pericellular fluid shifts and renal hemodynamics, and the multifactorial pathogenesis of renal disease create significant hurdles for the understanding of renal pathophysiology [3]. These challenges can only be met with a comprehensive approach combining modern cell biology with sophisticated animal experiments and ongoing attempts of translation into the human situation.

In this special issue, five concise reviews outline a spectrum of current frontiers in renal research. By focusing on topic areas which go beyond the established areas of inflammation and fibrosis research, these articles aim to draw attention to a diversity of different aspects that may open novel opportunities for diagnosis and therapy. Several aspects of the work presented have implications also for other organs and diseases. Four of these articles are related to projects that are part of a Collaborative Research Center funded by the German Research Foundation at the University of Erlangen-Nuremberg in Germany, one of only few research consortia in Europe with a special focus on kidney disease (Sonderforschungsbereich 423 der Deutschen Forschungsgemeinschaft).

Several lines of evidence indicate that predisposition to kidney disease is highly variable. In addition to genetic factors, external influences during fetal life appear to have an important impact on kidney structure, function, and disease predisposition. Dötsch et al. review evidence indicating that structural aspects determined during fetal life include the total number of nephrons and that this number is inversely related to the risk for development of arterial hypertension and CKD during later life [4]. There is also experimental and clinical evidence suggesting that influences during the early postnatal period impact on the outcome of alterations induced during fetal life. The findings reported in this article indicate that much closer links probably need to be established between physicians combating the late manifestations of cardiovascular diseases and pediatricians as well as developmental biologists

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in order to identify individuals at high risk and establish truly effective preventive strategies.

The integrity of the filtration barrier, which is formed by endothelial cells of the glomerular capillaries and podocytes, a layer of specialized epithelial cells covering the outer surface of the endothelia, together with a common basal membrane between them, is crucial for kidney function. Subtle disturbances in the structure–function relationship between these cells can lead to large protein losses in the urine (nephrotic syndrome) with devastating consequences for affected individuals. In many instances, identification of single gene defects in infants with congenital nephrotic syndrome has led to the discovery of molecules that play an important role in the formation of the intact filter. Zenker et al. summarize recent developments in this field which have led to the concept that the glomerular filter is a highly dynamic structure [5]. Both the multiprotein slit diaphragm complex between podocyte extensions and the integrin receptor complexes that mediate podocyte binding to the basement membrane convey outside–inside signaling which alters the cytoskeleton. While rare congenital abnormalities serve as important disease models, similar disturbances are probably of major relevance also in the pathogenesis of much more common acquired proteinuric diseases.

As in the pathogenesis of other diseases, inflammation plays a central role in both acute and chronic kidney injury. There is increasing interest in how local inflammation is influenced by blood supply and innervation. Due to extensive shunt diffusion between arterial and venous intrarenal vessels, the kidney is highly dependent on a comparatively high blood flow to maintain sufficient tissue oxygenation. Acute reductions in renal blood flow are an important cause of acute kidney injury. Jang et al. outline how ischemia–reperfusion triggers both innate and adaptive immune responses in the kidney [6]. These findings have clinical implications for a variety of settings, including renal transplantation. Early graft dysfunction, caused by ischemia–reperfusion injury is associated with the development of chronic allograft nephropathy, so that understanding the initial processes of ischemia-induced inflammation may lead to strategies that prolong graft function.

The concept that autonomous innervation can modulate disease processes provides exciting perspectives for a link between the central nervous system and organ dysfunction. Despite the recognized complexity of renal innervation and its role in blood pressure regulation, its interaction with renal inflammation has so far not been appreciated. Ditting et al. report recent findings on the impact of mechanical denervation and pharmacological interference with neurotransmitter release in different animal models of kidney disease [7]. These findings suggest that in particular yet unrecognized peptidergic sensory neurons play an important role, since they can induce local neurogenic inflammation via paracrine effects of their transmitters and also increase sympathetic outflow of the kidneys. Nerval outflow in turn can promote inflammation and contribute to the adverse systemic consequences of CKD.

While renal glomeruli provide the structural backbone for formation of the ultrafiltrate, the renal tubules are essential for net reabsorption of most of the ultrafiltrate and its continuous adaptation to body composition. Irrespective of the variable differentiation of tubular epithelial cells along the nephron, their growth needs to be tightly controlled. Proliferation is essential to replace cell losses resulting from acute injury, but excessive growth can result in cyst formation or kidney cancer. While these processes have so far been considered as largely independent, recent findings outlined by Wiesener et al. indicate that there may be common link, with an important role of the von Hippel Lindau (VHL) protein [8]. Among a variety of functions VHL is essential for degradation of hypoxia-inducible transcription factors; the respective syndrome, caused by germ-line VHL mutations, is characterized by an abnormal activity of hypoxia-inducible gene expression in a variety of tissues.

Clear cell renal carcinoma, the most frequent type of renal cancer, is also characterized by VHL inactivation, and more recent data indicate that VHL interacts with primary cilia on renal epithelial cells. While the precise function of these cilia and their possible role in sensing urine flow are still not completely understood, it is striking that genetic defects leading to cystic kidney disease usually affect proteins that influence structure or function of the cilia. Unraveling the complex role of VHL in renal epithelial cells is therefore likely to shed further insight into mechanisms of epithelial growth control, epithelial differentiation, and tumor development.

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