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Translational value of animal models of kidney failure

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ABSTRACT

Acute kidney injury (AKI) and chronic kidney disease (CKD) are associated with decreased renal function and increased mortality risk, while the therapeutic armamentarium is unsatisfactory. The availability of adequate animal models may speed up the discovery of biomarkers for disease staging and therapy individualization as well as design and testing of novel therapeutic strategies. Some longstanding animal models have failed to result in therapeutic advances in the clinical setting, such as kidney ischemia–reperfusion injury and diabetic nephropathy models. In this regard, most models for diabetic nephropathy are unsatisfactory in that they do not evolve to renal failure. Satisfactory models for additional nephropathies are needed. These include anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, IgA nephropathy, anti-phospholipase-A2-receptor (PLA2R) membranous nephropathy and Fabry nephropathy. However, recent novel models hold promise for clinical translation. Thus, the AKI to CKD translation has been modeled, in some cases with toxins of interest for human CKD such as aristolochic acid. Genetically modified mice provide models for Alport syndrome evolving to renal failure that have resulted in clinical recommendations, polycystic kidney disease models that have provided clues for the development of tolvaptan, that was recently approved for the human disease in Japan; and animal models also contributed to target C5 with eculizumab in hemolytic uremic syndrome. Some ongoing trials explore novel concepts derived from models, such TWEAK targeting as tissue protection for lupus nephritis. We now review animal models reproducing diverse, genetic and acquired, causes of AKI and CKD evolving to kidney failure and discuss the contribution to clinical translation and prospects for the future.

1. Introduction

Acute kidney injury (AKI) and chronic kidney disease (CKD) represent the most severe manifestations of kidney injury. The recent availability of consensus definitions of both AKI and CKD has contributed to increase awareness and to provide an objective estimate of the magnitude of the problem (KDIGO, 2012, 2013). AKI was previously termed acute renal failure and is associated with increased mortality and accelerated CKD (Siew and Davenport, 2015). The main criterion to diagnose AKI is an increase in serum creatinine of 0.3 mg/dl over baseline values over 48 h, a manifestation of decreased glomerular filtration rate (GFR) (KDIGO, 2012). The increasing incidence of AKI is potentially

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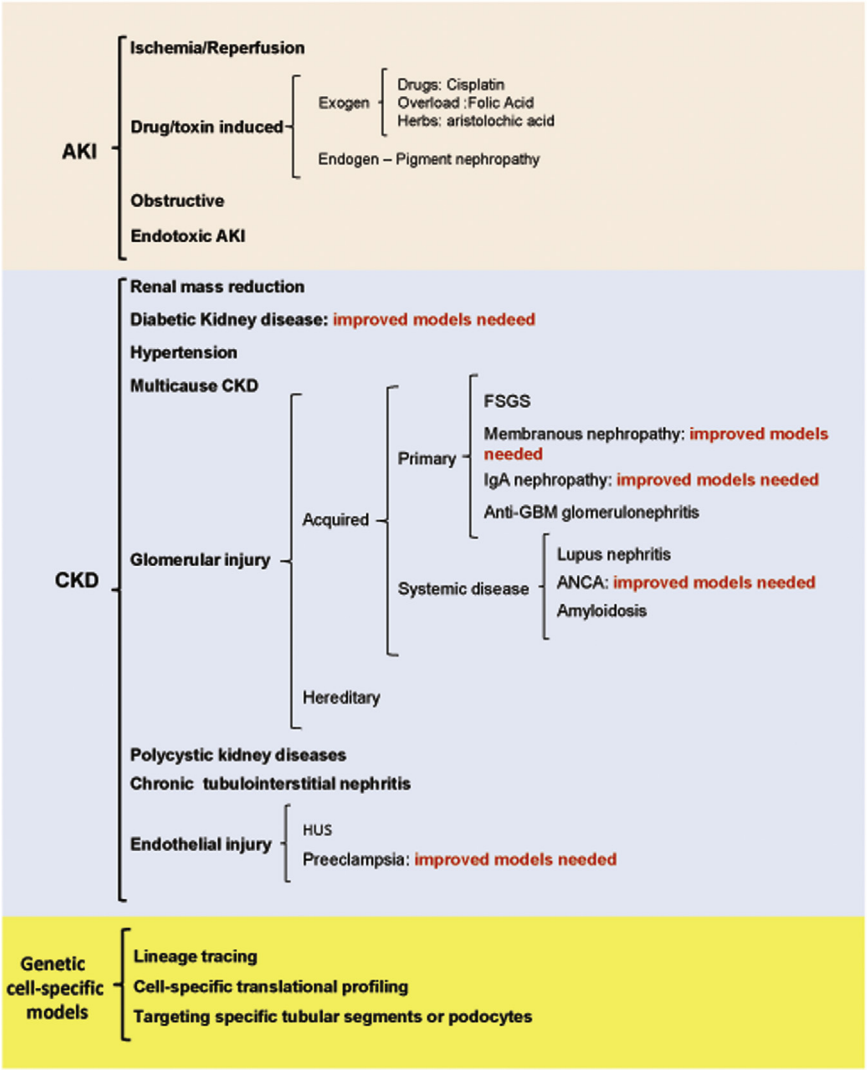

Fig. 1. Experimental animal models of acute kidney injury (AKI), chronic kidney disease (CKD) and novel genetic models that allow to address research questions on specific cell types during kidney injury. Areas in which available models have more significant shortcomings are indicated. FSGS: focal segmental glomerulosclerosis, GBM: glomerular basement membrane, ANCA: anti-neutrophil cytoplasmic antibody-associated vasculitis, and HUS: hemolytic uremic syndrome.

related to both a more fragile population and the existence of a consensus definition of AKI (Siew and Davenport, 2015). CKD is usually diagnosed by the presence of albuminuria (>30 mg/day or >30 mg/g creatinine) or a GFR estimated from serum creatinine below 60 ml/min/1.73 m^2 (KDIGO, 2013). CKD is one of the three fastest growing causes of death worldwide (Lozano et al., 2012). Indeed, CKD is associated with increased mortality, incidence of AKI and risk of progression to chronic kidney failure, defined by an eGFR <15 ml/min/1.73 m^2 (KDIGO, 2013). The mortality of patients with chronic kidney failure is 10–100 fold that of age- and sex-matched controls (Ortiz et al., 2014). The most cost-effective method to decrease the incidence of chronic kidney failure and associated mortality and morbidity is through a better understanding of the pathogenesis of kidney injury that allows the development of novel therapeutic approaches. Thus, we have focused the present review on animal models of AKI, with emphasis on progression to CKD, as well as on animal models of CKD that are associated with decreased GFR (Fig. 1). A detailed characterization of these models may provide clues for the design of novel therapeutic approaches to AKI and CKD (Chawla et al., 2014).

2. Pathophysiology of the AKI–CKD relationship

AKI is characterized by the acute and usually transient loss of kidney function. The main processes involved in AKI are tubular cell death and subsequent compensatory proliferation, and inflammation. Tubular cell death is the main histological feature in the early stages of AKI. During AKI there are two waves of tubular cell death. The first, early wave consists of apoptosis, necroptosis or necrosis and contributes to or causes damage (Linkermann et al., 2013; Sanz et al., 2008b). A second wave of tubular apoptosis contributes to the final regulation of renal regeneration, removes excess regenerated cells and facilitates remodeling and recovery of normal tissue structure. Inhibitors of apoptosis have successfully protected from AKI in animal models (Sanz et al., 2008b; Ucero et al., 2013a). After the initial wave of injury, the surviving tubular cells proliferate to regenerate tubular epithelium and recover renal function. Proliferation is dependent on the release of growth factors. Both sublethal and lethal tubular injury promote the release of inflammatory mediators from tubular cells and the generation of signals that promote kidney fibrosis (Izquierdo et al., 2012a; Ortiz et al., 2010; Sanz et al., 2008a). Inflammation further amplifies the extent of

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