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EDITORIAL

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Charles E. Alpers

Department of Pathology, University of Washington Medical Center, 1959 NE Pacific Street, Box 356100, Room NE110, Seattle, WA 98195, USA. Email: (calp@uw.edu)

The value of animal models for studies of the pathogenesis and natural history of kidney disease is beyond question. Recreating the complexity of mammalian organ structure and function, as well as the perturbations which lead to organ-specific or systemic diseases, cannot be adequately captured in more limited and somewhat artificial systems such as cell culture or *in silico* settings. Animal models allow us to envision how perturbations in metabolism or host exposure to external pathogenic stimuli such as microbes or other elements of a hostile environment lead to disease or modified expression of disease.

An ideal animal model of any specific disease category would reproduce most or all of the lesions of the human disease and would be susceptible to genetic analysis. For practical reasons such an animal model should be cheap to maintain and be widely available. These last requirements generally preclude consideration of nonhuman primates, dogs, and swine as widely utilizable animal species for model development. Although there are examples where investigators have used lower order model systems such as fruit flies and zebrafish to gain mechanistic insights into renal injury, the greatest amount of information on renal diseases available comes from mammalian models, and this is reflected in the discussion of relevant disease models in this compilation of reviews. The focus is largely on rodent (mouse and rat) disease models, for reasons that include their wide availability, their low cost relative to higher order mammals, and the technological ease with which genetic mutations can be introduced, that allow cell fate tracking and testing of specific molecules as mediators of disease.

There are a multitude of animal model systems to study kidney development, and genetic and congenital disease such as polycystic kidney, immune mediated diseases, acute toxic and ischemic injuries, progressively fibrotic injuries, and aging. In this set of reviews, leading animal models of specific classes of disease (IgA nephropathy, lupus nephritis) and common pathways that determine clinical and structural manifestations and outcome of diseases of the kidney arising

Charles Alpers is a Professor of Pathology and Adjunct Professor of Medicine at the University of Washington, Seattle, WA, USA, where he also serves as Vice-Chair of Pathology. At the University of Washington, he directs a large renal biopsy pathology service, and his research interests are focused on models of diabetic nephropathy and mechanisms that promote progressive glomerular injury in experimental models of glomerulonephritis. He received his undergraduate education at Yale University, and his M.D. degree from the University of Rochester in 1978. His postgraduate training included two years of training in internal medicine at Boston University, four years of training in anatomic and clinical pathology at the University of California, San Francisco, and two years of clinical and research training at the Brigham and Women's Hospital in Boston, before he assumed a faculty position at the University of Washington in 1986. He has served as councilor and president of the Renal Pathology Society. Recently, he has been the founding chair of the Glomerular Disease Advisory Group of the American Society of Nephrology, and has co-organized and co-directed the courses in renal pathology at the World Congress of Nephrology meetings in 2007, 2009, 2011, and 2013. He has authored or co-authored 266 original research papers, 34 review/editorial articles, and 33 book chapters, and is co-author of the textbook *Fundamentals of Renal Pathology* (2014).

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from a multiplicity of inciting events (inflammatory injury, dysregulation of complement) and disease evolution (integrins in injury and repair, pathways of progressive renal injury) will be presented and compared. The goal is to provide a comprehensive and useful guide to currently available model systems for investigators seeking relevant models that can be used to identify and test therapeutic targets that will be clinically relevant to kidney disease patients. In these considerations of animal models of disease, we should keep in mind those features that model initiation of disease, that focus on mediators that influence chronology and severity of onset and influence progression, and focus on factors that influence repair. In this regard, we call particular attention to a consideration that is a central point of each of the following reviews: What are the features of a human disease or the injury processes that determine the manifestations of this disease that should be present in an animal model of the disease, and to what extent are they indeed present? The answers to these questions ultimately determines the potential of a given animal model to yield translational insights from basic biologic research, and its value for testing the therapeutic efficacy of new drug regimens.

The absolute limitations of animal models are also a crucial issue that is addressed in these reviews. Even if we restrict consideration of disease models to mammalian systems, we have learned that use of inbred mouse strains can result in limited reproducibility of pathogenic stimuli and disease manifestations from one strain to another. Certain inbred strains are particularly suited to the introduction of genetic mutations that are powerful tools for analysis of pathophysiologic events. However, the different susceptibilities of mouse strains for specific diseases (a noteworthy example is the conclusion of the Animal Models of Diabetes Complication Consortium than mice of the C57Bl/6 strain are particularly resistant to developing the structural alterations characteristic of diabetic nephropathy [1]) can severely limit the generalizability of studies in one strain to the more complex, outbred human condition. Accordingly, as the preponderance of mouse mutations are introduced and propagated in C57Bl/6, FVB, and 129S strains, there can be substantial further limits to reproducibility and generalizability of key findings when only a limited number of strains with these mutations can be studied. This important issue is not a principal focus of the invited reviews, but nonetheless must be kept in mind in assessing the utility of any animal model of disease.

The first review in this series, by Suzuki et al., focuses on IgA nephropathy, widely acknowledged to be the commonest form of glomerulonephritis encountered worldwide. Major advances in our understanding of the pathogenesis of this disorder have come from the laboratory of Jan Novak, one of the authors of this review. These particular studies have identified the role of aberrant glycosylation of IgA molecules, which then may become an antigenic target of autoantibodies leading to immune complex formation and deposition in the kidney glomeruli. This then incites a series of acute or chronic inflammatory and/or fibrosing sclerosing injuries, which necessarily involve some of the disease pathways considered in the reviews by Holderied et al., Zent et al. and Lim et al. on inflammation, integrins, matrix, and disease progression.

Development of model systems of IgA nephropathy that closely mimic the human disease has proven to be especially challenging. Suzuki et al. point out that only humans and nonhuman primates have an antibody repertoire that includes the IgA1 subclass which is the pathogenic antibody of IgA nephropathy; this has been a major barrier to developing a useful model of this disease. Undeterred by this obstacle, they detail how a spontaneous model of IgA deposition in the ddY mouse strain was modified through a lengthy breeding/phenotyping program to develop a mouse model with a predictable disease course, from which genetic susceptibility data could be obtained and from which studies of aberrant glycosylation could be performed. Their studies lead to a conclusion that while rodent models cannot recapitulate some key aspects of IgA nephropathy without substantial genetic manipulation, they can be enhanced to model enough key aspects that they can be useful for studies of those additional aspects that contribute to disease. These additional attributes, when identified, can be used for preclinical identification of new therapeutic targets.

Animal models of systemic lupus, and specifically of lupus nephritis, have been studied for several decades. Such models are complex, as lupus nephritis is the result of pathogenetic events that take place both in the kidney and systemically. Therefore, the utility of animal models that inform us of pathophysiologic mechanisms, and identify new therapeutic targets, will depend in part on the ability of such models to encompass both systemic and kidney-specific mechanisms of disease, and recognize that unique and valuable opportunities for kidney therapeutics may come from targeting disease pathways occurring outside the kidney.

McGaha and Madaio review the very complex interactions of immune dysregulation and engagement of inflammatory pathways that converge in the development of lupus nephritis in humans. They focus on the development of an immune complex deposition process in the kidney, and the development of systemic autoimmunity and subsequent inflammatory events within the kidney. They provide a cogent description of the leading genetic and inducible rodent models of lupus, and review some of the key genetic mutations in immune pathways identified in rodent models that have been the basis of current paradigms of lupus nephritis pathogenesis.

A particularly valuable component of their review is a comparison of clinical, histologic, and immunologic features

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