Gen Med (Los Angel) icine: Open Access

Review Article Open Access

Congenital and Acute Kidney Disease: Translational Research Insights from Zebrafish Chemical Genetics

Shahram Jevin Poureetezadi and Rebecca A Wingert*

Department of Biological Sciences, University of Notre Dame, Notre Dame, IN 46556, USA

Abstract

Today, acute kidney injury (AKI) and congenital anomalies of the kidney and urinary tract (CAKUT) represent major issues in healthcare. Both AKI and CAKUT can lead to end stage renal disease (ESRD) that requires life-long medical care with renal replacement therapy. Renal replacement by dialysis is intensive, and kidney transplantation is restricted by organ availability. These limitations, along with the growing epidemic of patients affected by kidney disease, highlight the significant need to identify alternative ways to treat renal injury and birth defects. Drug discovery is one promising avenue of current research. Here, we discuss zebrafish chemical genetics and its latent potency as a method to rapidly identify small molecule therapeutics to accelerate recovery after AKI. Specifically, we review two groundbreaking studies that have recently provided a template to screen for compounds that expand the renal progenitor field in development that were capable of treating AKI in both the zebrafish and the mouse. These new findings demonstrate that drug discovery using zebrafish can be used for relevant translational research to identify clinical interventions for renal conditions in humans.

Keywords: Kidney; CAKUT; AKI; Zebrafish; Chemical genetics; Histone deacetylase; HDAC inhibitor

Introduction

The kidney is critical for a number of important bodily functions, including metabolic waste excretion and electrolyte homeostasis. Among vertebrates, the kidney is composed of functional units called nephrons that are generally made up of a renal corpuscle (a blood filter), a tubule, and a duct (Figure 1) [1,2]. Kidney disease can be a product of conditions such as birth defects or acute injury. Congenital anomalies of the kidney and urinary tract (CAKUT) represent 20-30% of all prenatal anomalies, and occur in 1 in 500 live births [3]. CAKUT occurs when there is a disruption in the normal development of either the kidney or urinary tract and can result in absent kidneys, diminished kidney size or incorrectly formed nephrons [3,4]. Acute kidney injury (AKI) accounts for 2-7% of inpatient hospital admissions and afflicts 5-6% of patients who become critically ill, with a 60% mortality rate [5]. AKI can be initiated from toxins, ischemia or sepsis, and is defined by an immediate loss of kidney function [6]. Both CAKUT and AKI can lead to end stage renal disease (ESRD), a state of kidney failure in which renal replacement therapy is necessary to maintain life.

Although dialysis is effective as a renal replacement therapy for patients suffering from kidney failure, it can be a demanding and exhaustive regimen over time, and it is an expensive treatment. Further, dialysis is the only medically available option to patients on ever lengthening transplant wait-lists [6]. Unfortunately, patients that do receive kidney transplants often face a multitude of health issues, with 40% of recipients either dying or losing graft function within ten years [7]. Thus, there is a dire need to identify new preventative and curative treatments for defects in renal development and adult kidney disease. One appealing avenue is the stimulation of more robust renal regeneration following injury, while other possibilities include the generation of cell-based therapies using stem cells [8].

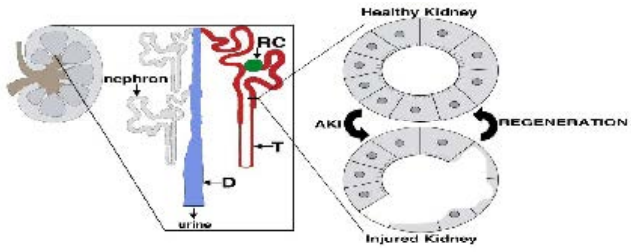

Figure 1: The kidney is comprised of nephron functional units that have some capacity to regenerate after epithelial injury. (Left) Schematic of the adult mammalian kidney, with (enlargement) depicting individual nephrons attached to the collecting duct drainage system. Each nephron is comprised of a renal corpuscle (RC) (green), tubule (T) (red) and attaches to the collecting duct (D) (blue).

In recent years, the zebrafish (*Danio rerio*) has received more and more attention as a prominent and unique model organism in the field of nephrology [9]. Zebrafish are freshwater vertebrates that share both major organs and important developmental pathways with mammals, including humans [10,11]. The large degree of gene conservation between zebrafish and mammals is only one of the many reasons why zebrafish are fast becoming widely used in translational settings [12]. There are a growing number of zebrafish mutants and transgenics that enable intricate questions to be investigated and answered. Adult zebrafish generate large clutches of embryos that develop externally, making them ideal for high-throughput studies. Furthermore, zebrafish embryos are transparent, which allow organ development and gene expression to be simply and easily observed. In particular, zebrafish are an attractive model to study the kidney because of the conserved nature of their nephron composition with mammals [13,14]. They share similarities in the composition of the renal corpuscle as well as the nephron, which is comprised of a series of proximal and distal tubule segments that reabsorb and secrete metabolites and assorted ions [13,14]. These reasons, coupled with the ability to regenerate nephrons as adults [15-18], make zebrafish an exceptional model to study kidney development and disease [19,20].

***Corresponding author:** Rebecca A Wingert, Department of Biological Sciences, University of Notre Dame, 100 Galvin Life Sciences, Notre Dame, IN 46556, USA, Tel: (574)-631-0907, Fax: (574)-631-7413; E-mail: rwingert@nd.edu

Received July 15, 2013; **Accepted** August 20, 2013; **Published** August 27, 2013

Citation: Poureetezadi SJ, Wingert RA (2013) Congenital and Acute Kidney Disease: Translational Research Insights from Zebrafish Chemical Genetics. Gen Med (Los Angel) 1: 112. doi: 10.4172/2327-5146.1000112