ImmunoTools *special* Award 2016

Lara Valiño Rivas, Ph.D.-student

Supervisor: Ph.D. María Dolores Sánchez Niño

Hospital Universitario Fundación Jiménez Díaz, Avda. Reyes Católicos, nº 2, 28040 Madrid, Spain

The Search for new therapeutic targets in renal damage by transcriptomics

The recent study "Global Burden of Disease" (GBD 2010) has identified Chronic Kidney Disease (CKD) as the second among the top 20 leading causes of death after HIV (1).

The prevalence of CKD in Spain is about 11% of the population (> 4,500,000 patients) (2). CKD can progress to end-stage renal disease (ESRD), which requires dialysis or transplantation. The ERSD has a lot of economic and human cost: the treatment of 40,000 Spanish people with kidney disease accounts for 5% of the budget for health care and the mortality of patients with chronic renal failure can be 100 times more than that of healthy patients of the same age (1). Moreover, the CKD is an independent risk factor for cardiovascular disease and it is the main predisposing factor for acute kidney injury (AKI). AKI mortality is over 50% and AKI promotes the progression of CKD (3). To date, there is still no therapy for AKI apart from the replacement of renal function.

Current treatment of CKD, based on the nephroprotective action of angiotensin converting enzyme inhibitors (ACEI) and the use of blockers of angiotensin II receptor (ARB), slows down the process, but does not prevent its progression (4). Because of the serious consequences of kidney disease and the shortage of therapeutic approaches, the CKD is considered a priority for research in the United States. Only a better understanding of the pathogenic processes that initiate, maintain and aggravate renal injury, will allow the design of successful and individualized therapeutic approaches that ideally act on pathways not modulated by angiotensin II, as well as new methods for determining the disease stage, identifying patients most likely to respond favorably to specific therapeutic interventions and to monitor response to treatment.

AKI and CKD are closely related and are considered today part of the same spectrum of disease (3). AKI predisposes to CDK and AKI can accelerate the progress of CDK. Among the processes that share both AKI and CKD, its fond loss of

renal parenchymal cells (due to an imbalance between death and cell proliferation), inflammation and fibrosis.

Therefore, the hypothesis would be that AKI and CDK could share mediators that regulate key processes, although AKI has less duration (it is especially transient) and also the seriousness of the activation of AKI molecular pathways, may differ from the CDK. This hypothesis is supported by studies on different biomarkers which are increased in tissue and in urine samples from patients with CDK and from patients with AKI, although changes were most impressive in AKI samples.

-Omics approaches to identify new mediators and markers of kidney disease

-omics approaches have provided valuable information about new molecules and pathways that contribute to tissue injury (5). The research group, which will develop this research, has been involved for some time in research projects of the European Union. This has led to the identification and characterization of potential therapeutic targets (6). Among the things that have been carried out previously in the research group are the crossroads between transcriptomics databases with databases of cDNA overexpression (7) and the creation of databases of kidney proteins (8).

Recently, the research group has been carried out crosses between a database of murine AKI and a database of human CDK, in order to find molecules that would be potential candidates for contributing both to AKI and CDK, and also that would be relevant to human and murine kidney injury. This establishes a series of priorities when characterizing molecules that may be relevant to human kidney disease and also it allow the preclinical characterization of kidney damage in animal models. We have identified some potential candidates which could use one set including as a therapeutic target or as tool and / or biomarker in kidney disease and it is potentially relevant to both humans and animal models of experimentation.

BIBLIOGRAPHY

1. Ortiz A et al. Epidemiology, contributors to, and clinical trials of mortality risk in chronic kidney failure. Lancet 2014

2. Otero A et al. Epidemiology of chronic renal disease in the Galician population: results of the pilot Spanish EPIRCE study. Kidney Int Suppl. 2005

3. Chawla LS et al. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 2012

4. Fernandez-Fernandez B et al. Therapeutic approaches to diabetic nephropathy-beyond the RAS. Nat Rev Nephrol 2014

5. He JC et al. Systems biology of kidney diseases. Kidney Int 2012

6. Sanchez-Niño MD et al. The MIF receptor CD74 in diabetic podocyte injury. J Am Soc Nephrol 2009

7. Sanchez-Niño MD et al. BASP1 promotes apoptosis in diabetic nephropathy. J Am Soc Nephrol 2010

8. Husi H et al. A combinatorial approach of Proteomics and Systems Biology in unravelling the mechanisms of acute kidney injury (AKI): involvement of NMDA receptor GRIN1 in murine AKI. BMC SystBiol 2013