Nephrology Dialysis Transplantation 33 (Supplement 1): i100–i110, 2018
doi:10.1093/ndt/gfy104

G. AKI. EXPERIMENTAL

FP204 **BET FAMILY MEMBER BRD4 DEPENDENT ENHANCER AND SUPER-ENHANCER DYNAMICS PROMOTE KIDNEY REPAIR AND PROGRESSION TO FIBROSIS**

Julia Wilflingseder[4,1,5], Michaela Willi[4], Chaochen Wang[4], Hannes Olauson[3], Takaharu Ichimura[2], Reinhold Erben[5], Todd Valerius[2], Lothar Hennighausen[4], Joseph Bonventre[2]

[1]Nephrology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [2]Renal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [3]Clinical Sciences, Intervention and Technology, Karolinska Institute, Stockholm, Sweden, [4]Laboratory of Genetics and Physiology, National Institute of Health, NIDDK, Bethesda, MD, United States and [5]Physiology, Pahtophysiolgy and Endocrinology, University of Veterinary Medicine, Vienna, Austria

INTRODUCTION AND AIMS: The endogenous repair process of the mammalian kidney allows rapid recovery after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. There is currently limited understanding of which transcriptional regulators activate these repair programs and how transcriptional deregulation leads to maladaptive repair. Here we investigate the existence of enhancer dynamics in the regenerating mouse kidney.

METHODS: RNA-Seq and CHIP-Seq (H3K27ac, H3K4m3, BRD4, MED1, POL2) were performed on samples from repairing kidney cortex 4 hours and 2 days after ischemia/reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and super-enhancers associated with kidney repair. Further we investigated the role of super-enhancer activation in kidney repair through pharmacological BET inhibition via the small chemical compound JQ1 in vitro and in three kidney injury models in vivo.

RESULTS: We have established the enhancer and super-enhancer landscape associated with kidney injury and repair. Furthermore, we identify key transcription factors, which cooperate with BRD4 at enhancer sites, likely activating repair programs in tubular epithelial cells. Loss of BRD4 function before injury by BET inhibitor JQ1 (50 mg/kg/day) leads to increased kidney failure between days 2 and 3 after the insult. By contrast, inhibition of prolonged transcriptional responses after injury, through blockade of Brd4 at enhancer sites with JQ1 from day 2 to day 7 after the initiation of injury, ameliorates interstitial fibrosis in unilateral ureter obstruction (UUO), unilateral IRI and aristolochic acid (AA) kidney injury models at day 10 and day 21, respectively.

CONCLUSIONS: These results are the first demonstration of BRD4 enhancer and super-enhancer function in the repairing kidney, providing a critical link between AKI and CKD. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET proteins that are already being tested in clinical trials in cancer patients who are at risk for AKI. Our comprehensive analysis of epigenetic changes after kidney injury in vivo has the potential to identify new targets for therapeutic intervention.