AAP China Scholarship Council - CSC 2024

PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : Hnf1b regulation in the context of renal development and regeneration

DIRECTION de THESE

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Ecole doctorale de rattachement : ED515 - Complexité du vivant

Nombre de doctorants actuellement encadrés : 0

CO-DIRECTION de THESE (HDR) ou CO-ENCADREMENT (Non HDR) :

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Ecole doctorale de rattachement Sorbonne Université : Sélectionner ou autre :

Nombre de doctorants actuellement encadrés :

CO-TUTELLE INTERNATIONALE envisagée : ☐ OUI ☒ NON

DESCRIPTIF du PRD :

*Ce texte sera affiché en ligne à destination des candidates et candidats chinois : il ne doit pas excéder **2 pages** doit être rédigé en **ANGLAIS***

Heterozygous mutations in HNF1B (Hepatocyte nuclear factor 1 β) are the most commonly identified genetic cause of developmental kidney disease in human. They have been associated with several disorders such as the Renal Cysts and Diabetes Syndrome (RCAD), a multi-organ disease characterized by kidney and genital tract abnormalities, pancreas hypoplasia and early onset of diabetes. More than 150 HNF1B heterozygous mutations are described, ranging from intragenic mutations to whole-gene deletions. The phenotype of HNF1B mutant carriers is highly variable between and within families. This variability is also observed in a novel mouse model that we have generated (1), carrying an identified human mutation at the intron-2 splice donor site and exhibiting decreased HNF1B protein levels from the normal allele.

HNF1B encodes a transcription factor involved in kidney development in vertebrates. HNF1B is expressed throughout renal development and its inactivation in mouse models leads to drastic renal developmental defects. Hnf1b coordinates transcriptional networks involved in nephrogenesis and epithelial differentiation. It controls proximal-intermediate nephron segment identity, which function is conserved in the Xenopus tadpole kidney, the pronephros. The Xenopus pronephros therefore offers an attractive and valuable model system to study nephrogenesis and explore mechanisms causing renal developmental defects in humans (2). Besides its role during renal development, Hnf1b is also involved in tissue maintenance and injury response of renal tubules. Loss of function experiments have already led to the identification of many HNF1B target genes. In contrast, genetic networks involved in the control of HNF1B expression in the different embryonic renal compartments are still poorly understood. We propose to use Xenopus to identify the regulatory networks involved in the control of Hnf1b expression during renal development as well as regeneration.

Specific objectives are: 1/to identify and characterize functional Hnf1b enhancers in the developing pronephros 2/ to identify the putative TFs acting through these enhancers and analyze their function during pronephric development 3/ to identify Hnf1b enhancers and associated TFs involved in pronephros regeneration

We will combine phylogenetic footprinting and epigenetic profiling to identify potential regulatory sequences implicated in Hnf1b regulation. In order to identify functional enhancers, the ability of these sequences to drive reporter expression in renal cell lines (MDCK, Madin-Darby canine kidney and RPTEC, human renal proximal tubule epithelial), as well as in the developing Xenopus pronephros using a powerful transgenesis assay will be tested. Candidate transcription factors acting through these enhancers will be identified according to their binding motifs present in enhancer sequence and their pronephric expression. Their function will be tested during pronephros development and regeneration using gain and loss-of function approaches. Consequences will be analyzed on the successive steps of pronephric development (renal specification, patterning of the pronephros anlage, epithelialization of the tubule, segment establishment and differentiation, morphogenesis) and of the regeneration process (sequential gene expression, proliferation). This strategy has already been used to identify Pax8 as a major regulator of hnf1b acting through an evolutionary conserved distal enhancer responsible for hnf1b pronephric expression (2).

With this project, we expect to identify critical regulators (regulatory sequences and transcription factors) acting in the yet poorly understood genetic networks involved in the control of Hnf1b expression during kidney development and regeneration. Our work will contribute to highlight cis-regulatory regions and Hnf1b transcription factor regulators that could potentially contribute to the renal pathogenesis when subjected to genetic alterations. The new knowledge about evolutionarily

conserved HNF1B enhancer regions and transcription factors could be used to screen for genetic variants in patients with genetically unexplained congenital anomalies of the kidney and urinary tract. Indeed, although more than 300 monogenic kidney disease causes have been identified in the past two decades, molecular diagnosis is only available for 20 % of the cases. Finally, characterization of Hnf1b regulation in the context of pronephros regeneration may contribute to our understanding of renal repair in mammals.

1- Niborski, L. L. et al. Hnf1b haploinsufficiency differentially affects developmental target genes in a new renal cysts and diabetes mouse model. Dis Model Mech 14, dmm047498 (2021). doi:10.1242/dmm.047498

2- - Goea L, Buisson I, Bello V, Eschstruth A, Paces-Fessy M, Le Bouffant R, Chesneau A, Cereghini S, Riou JF, Umbhauer

M. Hnf1b renal expression directed by a distal enhancer responsive to Pax8. 2022. Sci rep, 12(1):19921. doi: 10.1038/s41598-022-21171-

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