AAP China Scholarship Council - CSC 2024

PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : USE OF CALCINEURIN INHIBITORS AGAINST THE PROGRESSION OF CHRONIC KIDNEY DISEASE

DIRECTION de THESE

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Unité de recherche : Code (ex. UMR xxx) et Intitulé : UMR S 1155 "MALADIES RENALES FREQUENTES ET RARES: DES MECANISMES MOLECULAIRES A LA MEDECINE PERSONNALISEE"

Ecole doctorale de rattachement : ED394 - P2T

Nombre de doctorants actuellement encadrés : 1

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

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Unité de recherche : Code (ex. UMR xxx) et Intitulé :

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***

USE OF CALCINEURIN INHIBITORS AGAINST THE PROGRESSION OF CHRONIC KIDNEY DISEASE

CONTEXT:

The rising incidence of renal diseases represents a considerable burden on the healthcare system worldwide. Glomerulonephritis remains a common cause of end-stage renal disease and encompasses a range of disorders characterized by glomerular damage, proteinuria and tubulointerstitial fibrosis leading to the progression of chronic kidney disease. Despite mechanistic advances, current treatments for glomerulonephritis remain non-specific and partially successful. Therefore, identifying novel specific therapy targets and/or proposing more efficient treatments against the progression of glomerulonephritis remains one of the major challenges of public health today.

Calcineurin is an important modulator of renal function and promotes inflammation, podocyte injury and renal disease. Calcineurin inhibitors such as cyclosporine or tacrolimus are commonly used to suppress the immune system and to avoid rejection of the transplanted kidney. However, these pharmacological inhibitors have serious various side effects such as vascular cytotoxicity. Therefore, searching for alternative calcineurin inhibitors such as endogenous inhibitors that attenuate kidney injury without having the toxicity of exogenous pharmacological inhibitors might be of great therapeutic significance.

PRELIMINARY RESULTS:

We have recently identified several endogenous agents that modulate calcineurin activity and action. Our preliminary data show that one of them displays several interesting features that can be relevant to renal pathophysiology:

1) it is expressed in the kidney under normal conditions;

2) it inhibits efficiently calcineurin activity in vitro;

3) its renal expression decreases with the progression of renal disease in an experimental model of glomerulonephritis;

4) mice with a genetic deletion for this agent and subjected to an experimental model of glomerulonephritis, show increased expression of calcineurin in the kidney and accelerated development of renal failure.

GENERAL HYPOTHESIS:

We hypothesize that this endogenous calcineurin inhibitor could oppose the pro-inflammatory cascade induced by calcineurin activation and could thus constitute an important and novel protective mechanism against the progression of kidney disease, lacking complications induced by pharmacological calcineurin inhibitors.

SPECIFIC OBJECTIVES:

1) Determine the renal cell population involved in experimental glomerulonephritis.

2) Investigate the physiopathological role of the calcineurin inhibition using single cell transcriptomics.

3) Evaluate the use of this inhibitor as a potential therapy target.

4) Explore the translational relevance of calcineurin-endogenous inhibitor interaction expression in selected biopsies of patients.

METHODOLOGY:

The nephrotoxic serum induced-glomerulonephritis will be used as model of renal disease. In this model three cell types mainly participate in the development of renal disease: podocytes, endothelial cells and macrophages. To assess the role of calcineurin inhibition in these cell types, we will use three conditional mouse lines inducing a specific gene deletion of the endogenous inhibitor in podocytes, endothelial cells or macrophages. We will evaluate and compare the impact of cell-specific inactivation on renal function, morphology, inflammation and fibrosis.

Once the above experiments identify the type(s) of renal cells involved, we will subsequently analyze the pathways involved using single cell RNA-seq on podocyte or endothelial cells or macrophages. This strategy will allow identifying factors underlying the pathophysiology of glomerulonephritis and will provide additional potential therapy targets that will be further validated in vivo using AAV vectors or antisens ODNs delivery, both frequently used in the host lab.

Next, conditional transgenic mice overexpressing the endogenous inhibitor in podocytes or endothelial cells or macrophages (depending on the previous results) will be generated using cell specific strains (available in host lab), and the nephrotoxic serum induced-glomerulonephritis model will be applied. Renal function, structure and histology will be measured as in our previous publications. Finally, the host lab has an important collection of biopsies from different types of glomerulonephritis. In these biopsies will check whether decreased expression of the endogenous inhibitor is correlated with increased expression of calcineurin and decline of renal function.

RISKS:

Most risks associated with the project are low: no side effects of the endogenous inhibitor KO mice on basal kidney function and general metabolism; cell specific animal strains are already available in the host lab. The host laboratory has a long standing experience using experimental models of renal disease and all techniques required for the successful completion of the project are already implemented and routinely used.

EXPECTED RESULTS:

In the end of this thesis, we will:

1) Demonstrate that the endogenous inhibitor displays a renoprotective effect and can be used as a new therapy approach.

2) Identify novel key mechanisms and cellular pathways that control the development of renal disease.

3) Explore the translational relevance of endogenous calcineurin inhibition in human biopsies.

AVIS de l'Ecole Doctorale :

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