ROLE OF THE NON-CANONICAL NOTCH LIGAND DLK1 IN EXPERIMENTAL RENAL DAMAGE

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Introduction

The Notch pathway is an evolutionarily conserved mechanism. The activation of Notch signaling is produced when a canonical ligand bounds to the extracellular part of the receptor. This triggers a first activating cleavage mediated by the disintegrin and metalloproteinases (ADAMs) and then the γ-secretase complex is responsible for the second proteolytic event that leads to the release of Notch receptor intracellular domain (NICD) which migrates towards the nucleus and forms a nuclear complex with the transcriptional activator RBP-Jk *(Recombination Signal-binding Protein 1 for J-kappa).* This activates the transcription of the target genes, the hairy and enhancer of split (*hes*) and the Hes-related proteins (hey).

Previous studies have demonstrated that Notch pathway is activated in human and experimental renal damage, and Notch-1/Jagged-1 levels have been suggested as potential biomarkers of renal damage. Moreover, in experimental studies blockade of Notch activation by γ-secretase inhibitors ameliorated renal disease progression.

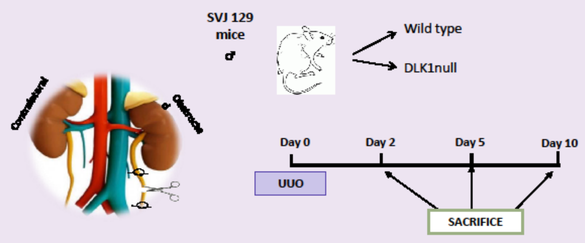
The non-canonical ligand Dlk1 has been shown to act as an inhibitor of Notch signaling *in vitro.* However, information about the role of non-canonical Notch ligands in renal injury is scarce.

Our principal aim was to study the role of the non-canonical ligand DLK1 in experimental renal injury

Materials and methods

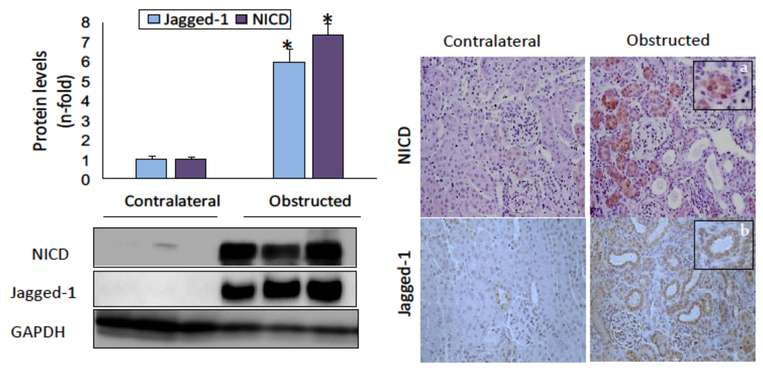
In the unilateral ureteral obstruction (UUO) the role of Notch activation was evaluated by treatment with the gamma-secretase inhibitor DAPT (0,1 mg/mouse). The animals were sacrificed five days after the injury.

To evaluate the role of DLK1, the UUO model was carried out in mice with a deletion in DLK1 gene (DLK1null) comparing with their corresponding littermates. The animals were sacrificed after two, five and ten days after the injury.

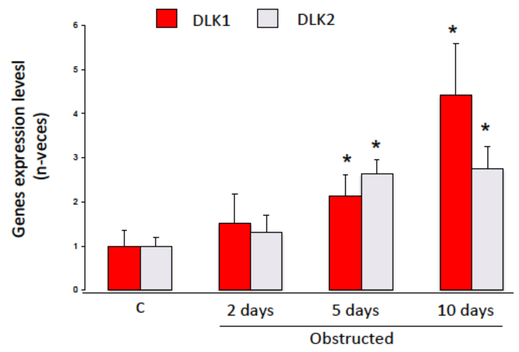


Results

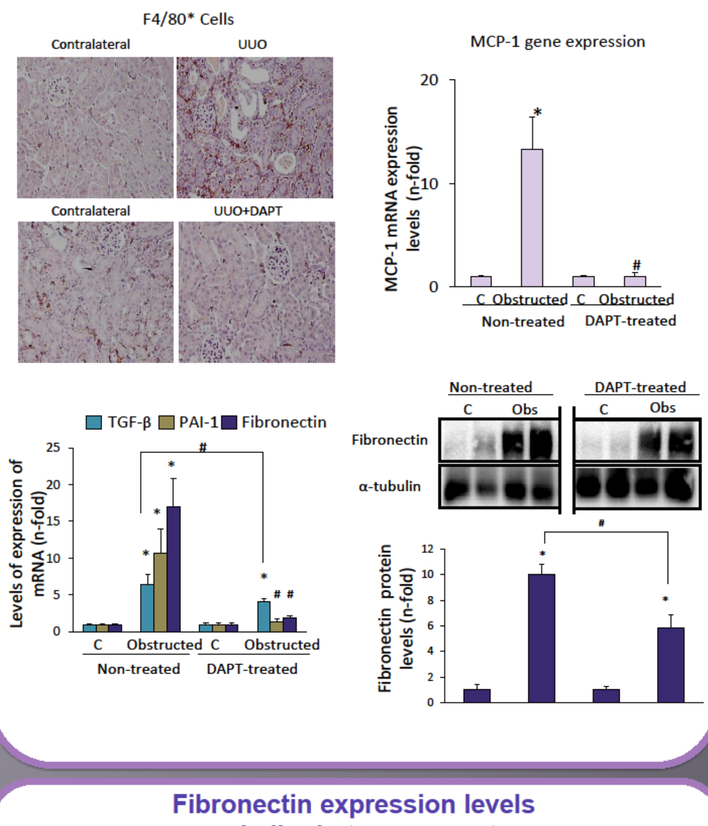
The Notch pathway is activated in experimental renal injury following UUO



Gene expression levels of DLK1 and DLK2 are augmented in obstructed kidneys of wild type animals

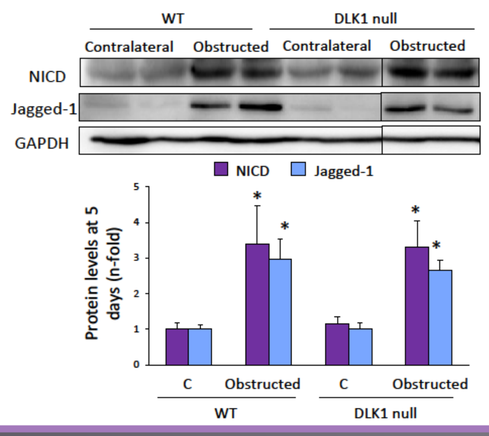


The treatment with DAPT ameliorated the inflammatory and fibrotic response in the model of UUO

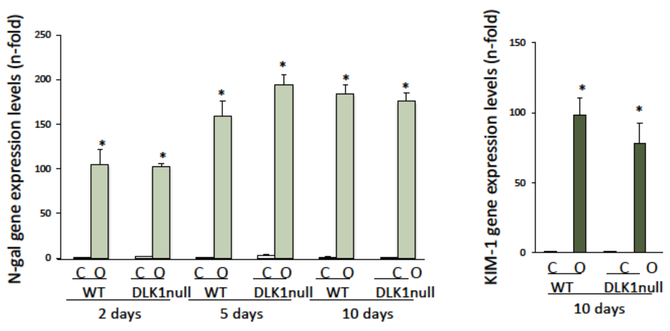


Studies in DLK1 Knockout mice in the UUO model

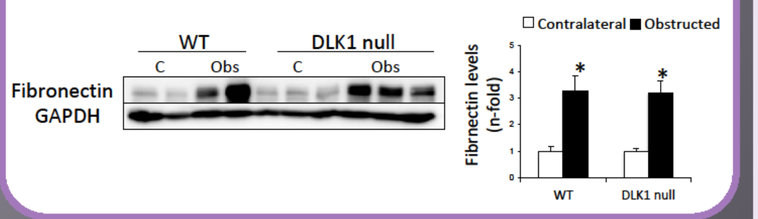
The activation of the canonical Notch pathway: There were no differences between obstructed kidneys of wild type and DLK1 null genotypes



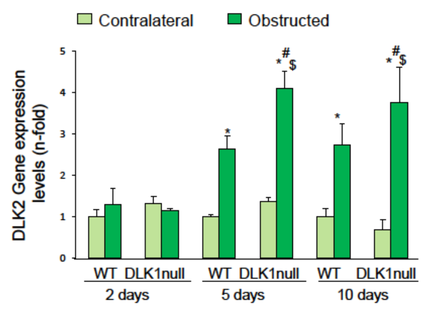
Gene expression levels of renal damage markers Showed no differences between genotypes



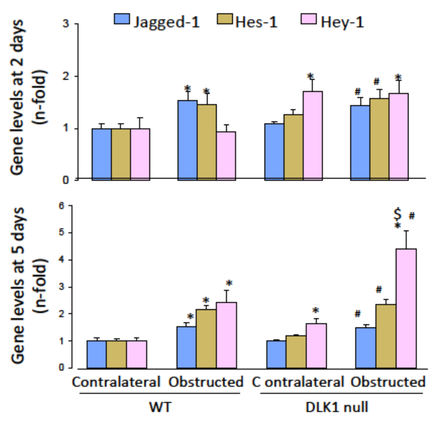
Fibronectin expression levels were similar between genotypes



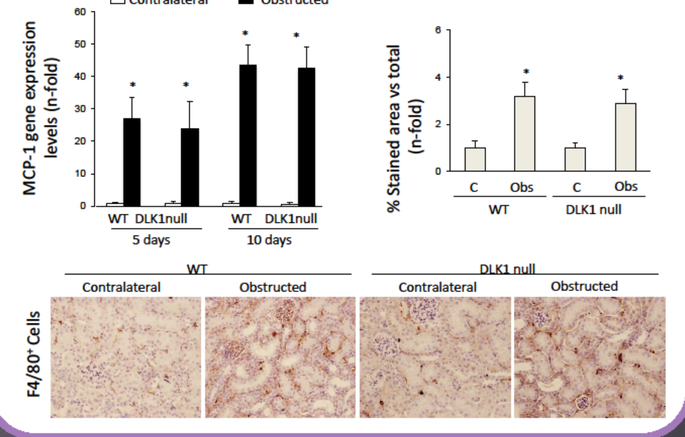
DLK2 gene expression levels was augmented in injured kidneys of DLK1 null mice when compared to wild type animals at 5 and 10 days



Hey-1 expression levels were increased in KO animals with a significant difference between obstructed kidneys of wild type and DLK1null animals



There were no differences on renal inflammation between genotypes



Conclusions

1. The canonical Notch pathway is activated in response to UUO.
2. The blockade of this pathway by the pharmacological inhibitor DAPT ameliorated the experimental renal injury, diminishing inflammation and fibrosis.
3. The deletion of DLK1 gene do not modifies the progression of the renal damage caused by UUO.

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