

Cellular and molecular mechanisms of kidney injury and regeneration

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, fredagen den 8 december 2023, klockan 9:00

av **Michelle Kha**

Fakultetsopponent:

Professor Benjamin D. Humphreys,

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Avhandlingen baseras på följande delarbeten

- I. **Kha M**, Krawczyk K, Choong OK, De Luca F, Altiparmak G, Källberg E, Nilsson H, Leandersson K, Swärd K, Johansson ME. The injury-induced transcription factor SOX9 alters the expression of *LBR*, *HMGA2*, and *HIPK3* in the human kidney. *Am J Physiol Renal Physiol*. 2023;324(1):F75-F90.
- II. **Kha M**, Altiparmak G, Lundgren J, Swärd K, Johansson ME. HNF4A re-expression partially restores a proximal tubular phenotype in cultured primary kidney cells. *Manuscript*.
- III. **Kha M**, Altiparmak G, Elliott K, Xie X, Larsson E, Oldfors A, Swärd K, Johansson ME. Age and injury-related changes of mitochondrial respiratory complexes in human kidney tubules. *Manuscript*.
- IV. De Luca F, **Kha M**, Swärd K, Johansson ME. Identification of ARMH4 and WIPF3 as human podocyte proteins with potential roles in immunomodulation and cytoskeletal dynamics. *PLoS One*. 2023;18(1):e0280270.

**SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICIN**



Cellular and molecular mechanisms of kidney injury and regeneration

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Abstract

The prevalence of kidney disease is constantly increasing with about 600 million people afflicted globally. Kidney disease may result in end stage renal disease, a condition that requires renal replacement therapy in the form of kidney transplantation or dialysis. However, the mechanisms behind kidney injury and regeneration are still incompletely understood. In this thesis, we aimed to study the phenotype of the scattered tubular cells (STCs), a cell population distributed throughout the proximal tubules (PT) of human kidney involved in injury and regeneration, for better understanding of the underlying mechanisms of tubular repair. In **Paper I**, we established SOX9 as an STC marker and demonstrated that SOX9 is activated in response to injury in the human kidney. Furthermore, we identified *LBR*, *HMGA2*, and *HIPK3* as potential downstream targets of SOX9 in tubular repair. In **Paper II**, we observed that the STC phenotype is induced in cultured primary PT cells and that the PT phenotype could be partially restored by re-expression of HNF4A. In **Paper III**, we showed that the STCs have a general reduction of mitochondrial markers, and we also found another cell population in the PT which displayed selective loss of mitochondrial respiratory chain complex I that increased with age. In **Paper IV**, we presented ARMH4 and WIPF3 as novel podocyte proteins possibly involved in glomerular injury and disease. Taken together, these findings elucidate potential therapeutic targets during kidney injury and regeneration.

Keywords: kidney, injury, regeneration, repair, scattered tubular cells, proximal tubular cells, podocytes, SOX9, HNF4A