

# Molecular mechanisms of the kidney in health and disease

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentlig försvaras i hörsal Hjärtat, Vita stråket 12, Sahlgrenska sjukhuset, Göteborg fredagen den 17 juni 2011 kl 09.00

av Kerstin Ebefors

Fakultetsopponent: Associate professor Mario Schiffer, Dept. Of Nephrology, University of Hannover, Hannover, Tyskland

Avhandlingen baseras på följande delarbeten:

**I. Podocyte proteoglycan synthesis is involved in the development of nephrotic syndrome**

Björnson Granqvist A, Ebefors K, Saleem MA, Mathieson PW, Haraldsson B, Nyström JS

*Am J Physiol Renal Physiol.* 2006 Oct;291(4):F722-30

**II. Role of glomerular proteoglycans in IgA nephropathy**

Ebefors K, Granqvist A, Ingelsten M, Mölne J, Haraldsson B and Nyström J

*PLoS ONE.* 2011 6(4):e18575

**III. Comparison of human and mouse glomerular transcriptomes by Affymetrix gene array analysis**

Sun Y, Ebefors K, Haraldsson B, Katayama M, Lal M, Patrakka J, Pikkarainen T, He L, Tryggvason K, Nyström J and Betsholtz C

*manuscript*

**IV. Mesangial cell matrix production in IgA nephropathy**

Ebefors K, Sun Y, Elvin J, Levan K, Fridén V, Tryggvason K, Betsholtz C, Haraldsson B and Nyström J

*manuscript*



UNIVERSITY OF GOTHENBURG

# Molecular mechanisms of the kidney in health and disease

Kerstin Ebefors

Department of Molecular and Clinical Medicine, Institute of Medicine  
The Sahlgrenska Academy at University of Gothenburg, Sweden

## ABSTRACT

In 2010, 307 Swedish patients received a new kidney through transplantation, and the first of April 2011, 603 patients were on the kidney transplant waiting list. In Sweden over 8000 patients are presently in active uremic care with about half in dialysis and the other half with a functional kidney graft. The numbers of patients in need of active uremic care are escalating and so are the costs for renal health care, in Sweden as in most of the western world. For patients with end stage renal disease active uremic care is the last option for survival since there is no cure or specific treatment for most renal diseases. The lack of treatment options often leaves steroids and chemotherapy as the only available choices. In order to find more specific treatment and to cure or delay the progress of renal disease we need to learn more about the molecular background of these diseases.

To increase our understanding of the molecular mechanisms behind renal disease we have studied the gene expression in both an animal model of the nephrotic syndrome in rat as well as in human material in form of renal biopsies and cell cultures. The most common renal diseases all start in the glomerulus, the capillary tuft in the nephron where the ultrafiltration of blood takes place, and therefore we have focused on gene expression in the glomerulus.

When investigating the gene expression in glomeruli from healthy kidney donors and from mice we found a core cluster of conserved, highly glomerulus-specific genes. Normal function of some of these genes in the glomerulus is already known to be of importance to the filtration barrier and mutations in certain of them are tightly connected to proteinuria. The discovered core cluster also contained genes that so far has not been coupled to renal function and disease, and can therefore be used as a new source of kidney glomerular-specific genes and biomarkers.

By studying gene expression in rats with nephrotic syndrome and in patients with renal disease we found that expression of a special family of extracellular matrix proteins, called proteoglycans, was changed in renal disease compared to healthy controls. Proteoglycans are multifunctional proteins with functions ranging from holding and releasing signal molecules to making up part of the extracellular matrix structure. In patients with IgA nephropathy we found that the proteoglycan perlecan had an increased gene expression compared to control, and that the gene expression correlated to the excretion of protein in the urine and even to the progress rate of the disease. This suggests that perlecan could likely be used as a molecular marker for IgA nephropathy and as such help us to further understand the progression of the disease. In addition we have developed a unique method of culturing cells from patients with renal disease and we believe that this will give us new information about the molecular mechanism of this disorder and help us develop more specific and individualized treatment for patients with kidney failure.

**Keywords:** gene expression, kidney, glomerulus, nephrotic syndrome, IgA nephropathy, proteoglycans