

Functional and molecular mechanisms behind glomerular kidney disease

Akademisk avhandling

Som för avläggande av medicin doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg
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Avhandlingen baseras på följande delarbeten

- I. **Mesangial cells from patients with IgA nephropathy have increased susceptibility to galactose-deficient IgA1**
Ebefors K, Liu P, Lassén E, Elvin J, Candemark E, Levan K, Haraldsson B and Nyström J.
BMC Nephrology (2016) 17:40
- II. **Transcriptomic and proteomic profiling reveal insights of mesangial cell function in patients with IgA Nephropathy**
Liu P, Lassén E, Sihlbom C, Nair V, Berthier C, Katayama M, Kretzler M, Betsholtz C, Ju W, Ebefors K and Nyström J.
Manuscript
- III. **A potential receptor of IgA is involved in mesangial proliferation and development of IgA nephropathy**
Liu P, Lassén E, Müller-Lüthloff S, Candemark E, Wallentin H, Hultenby K, Sihlbom C, Buvall L, Ebefors K and Nyström J.
Manuscript
- IV. **Podocytes regulate expression of a specific glomerular basement membrane protein via micro-RNA in glomerular disease**
Müller-Deile J, Dannenberg J, Schröder P, Miner J, Chen R, Bräsen J, Thum T, Liu P, Nyström J, Haller H, Lorenzen J and Schiffer M.
Manuscript

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Abstract

Glomerulonephritis (GN) is one of the most common causes of chronic kidney disease (CKD). In our studies, we investigated the molecular mechanisms behind GN on both transcriptomic and proteomic levels using a combined *in vivo* and *in vitro* approach. By doing so, our aim was to find new possible candidates for therapeutic intervention in CKD. IgA nephropathy (IgAN) is the most common type of GN worldwide. It is a proliferative glomerular kidney disease in which galactose-deficient IgA (gd-IgA) is deposited in the mesangial area of the glomeruli. Previous studies have pointed out that gd-IgA is not the only factor inducing the disease. Our hypothesis is that the mesangial cells are of great importance in IgAN development and that patients with IgAN have more susceptible mesangial cells to gd-IgA compared to healthy individuals. The deposition of gd-IgA is likely caused by interaction with a receptor on the mesangial cell leading to proliferation and inflammation. To study these mechanisms, we cultured primary human mesangial cells from IgAN patient biopsy samples and healthy controls. Our results showed that patient mesangial cells had a significantly increased release of the growth factors PDGF, TGF β 1 as well as the cytokines IL-6 and CCL5, when treated with gd-IgA. These cells also had a significantly higher proliferation rate compared to control cells. We investigated the mesangial cell transcriptomic and proteomic function in patients with IgAN using microarray and mass spectrometry techniques. We demonstrated that many inflammatory pathways were significantly regulated both in the glomeruli and in the gd-IgA treated mesangial cells. By using cell-type specific positive standard genes we found a dominant role in IgAN of the mesangial cell compared to the podocytes. The transformed z-scores based on mesangial cell standard genes showed significant correlation with patient clinical data (eGFR and serum creatinine). In order to know how gd-IgA is deposited in the mesangium, we investigated receptors from the mesangial cells interacting with gd-IgA. Interestingly, a transmembrane receptor was identified to be associated with gd-IgA and it also regulated mesangial cell proliferation. Additionally, we investigated micro-RNAs in glomerular disease using a screening technique. MiR-x7 was found to regulate a specific podocyte protein and the level was correlated to disease. Since it is a small molecule, miR-x7 can be detected in urine samples and may be used as a diagnostic marker for CKD.

In conclusion, we have verified the importance of mesangial cells in IgAN. The correlation of mesangial cell standard genes with clinical data can potentially explain the progression of the disease. A specific receptor was found to regulate the proliferation of the mesangial cells and it may potentially be involved in the deposition of gd-IgA. Micro-RNAs are found to be promising markers for CKD and thus disease-specific micro-RNAs should be further investigated.

Keywords: Glomerular kidney disease, IgA nephropathy, mesangial cell, micro-RNA