

Molecular perspectives on glomerular cell physiology in chronic kidney disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentlig försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg
Fredagen den 14 juni 2019, klockan 09:00

Av Emelie Lassén

Fakultetsopponent:

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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 provides insight into mesangial cell function in IgA nephropathy**
Liu P, Lassén E, Nair V, Berthier C, Suguro M, Sihlbom C, Kretzler M, Betsholtz C, Haraldsson B, Ju W, Ebefors K and Nyström J. *J Am Soc Nephrol (2017) 28:2961-2972*
- III. Cytoskeleton-associated protein 4 (CKAP4), a new player in the regulation of mesangial cell proliferation**
Lassén E, Liu P, Chaudhari A, Khramova A, Müller-Lüthloff S, Granqvist A, Buvall L, Ebefors K and Nyström J. *In manuscript*
- IV. Cytoskeleton-associated protein 4 (CKAP4) is essential for podocyte integrity**
Lassén E, Cocchiari P, Sánchez Vidaña D, Chaudhari A, Liu P, Buvall L, Müller-Deile J, Schiffer M, Ebefors K and Nyström J. *In manuscript*

Molecular perspectives on glomerular cell physiology in chronic kidney disease

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Abstract

Glomerulonephritis is one of the most common causes of chronic kidney disease (CKD) in the world. Recent establishment of guidelines for classification of CKD in five stages has led to increased awareness of the risks of comorbidity and mortality, also in patients with early stages of disease, and the need to further advance our understanding of their pathogenic mechanisms. Many glomerular diseases are complex and curative treatment options are currently lacking, in part due to the difficulties to identify new molecular targets for treatment. The work included in this thesis focuses on physiological and pathophysiological mechanisms in glomerular mesangial cells and podocytes, especially in the disease IgA nephropathy (IgAN). Through analysis of mesangial cells derived from IgAN patient biopsies we found that patient cells proliferated more than healthy control cells in response to pathogenic IgA or PDGF-BB. They also released more PDGF-BB and IL-6 into the growth medium than control cells in response to the same stimuli, suggesting an increased sensitivity and thereby susceptibility for disease in the patient cells. A subsequent study of the glomerular transcriptome from patients with IgAN and healthy kidney donors was done by microarray and bioinformatics analysis. It demonstrated that differential expression of mesangial cell specific standard genes was prominent in IgAN, while podocyte standard genes were less significant in this context. The mesangial cell standard genes also correlated to patients' clinical parameters after z-score transformation. Finally, we identified potential functions for the protein CKAP4 in glomerular cells, where it appears to be involved in regulation of proliferative signaling in mesangial cells through association with the PDGF pathway, and in maintenance of the podocyte structural stability through effects on the actin cytoskeleton.

In conclusion, our findings support previous knowledge about the central role of mesangial cells in IgAN, as well as suggest that these cells can have an altered susceptibility to disease. We also identified glomerular transcriptomic and mesangial cell proteomic pathways relevant for further research into development and progression of IgAN. We also found that CKAP4 is involved in disease mechanisms of mesangial cells and podocytes, warranting further investigation into the functions of the protein in health as well as in different forms of glomerular disease.

Keywords: Chronic kidney disease, IgA nephropathy, mesangial cell, podocyte, CKAP4

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