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A Podocyte view on RhoGTPases and actin cytoskeleton regulation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats Aula, Sahlgrenska Universitetssjukhuset, Göteborg,
Fredagen den 4 september 2020, klockan 09:00

Av Lovisa Bergwall

Fakultetsopponent:

Christian Faul, PhD, Associate Professor

University of Alabama at Birmingham, Birmingham, USA

Avhandlingen baseras på följande delarbeten

I. Amplification of the Melanocortin-1 Receptor In Nephrotic Syndrome Identifies a Target for Podocyte Cytoskeleton Stabilization

Bergwall L, Wallentin H, Elvin J, Liu P, Boi R, Sihlbom C, Hayes K, Wright D, Haraldsson B, Nyström J and Buvall L. *Scientific Reports (2018) 8 (1), 15731*

II. Podocyte Geranylgeranyl transferase type I is essential for maintenance of the glomerular filtration barrier function

Bergwall L, Boi R, Akula M.K, Ebefors K, Bergo O. M, Nyström J, Buvall L. *In manuscript*

III. The role of βpix in podocyte Rac1 activation and cytoskeleton rearrangement

Bergwall L, Wallentin H, Boi R, Svensk S, Lövljung V, Sihlbom C, Weins A, Ericsson A, William-Olsson L, Granqvist B. A, Ebefors K, Nyström J, Buvall L. *In manuscript*

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A Podocyte view on RhoGTPases and actin cytoskeleton regulation

Lovisa Bergwall

Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Proteinuria is a hallmark symptom of chronic kidney disease, that if left to persist constitutes a risk for progression of disease. Symptomatic treatment aiming at decreasing proteinuria is therefore standard practice. Curative treatments for the underlying cause of disease are however lacking and treatments currently in use to induce disease remission are associated with unfavorable side effects. Dysregulation of the podocyte actin cytoskeleton underlies the pathological process called foot process effacement (FPE), which is one of the leading causes of proteinuria. The studies included in this thesis have focused on podocyte actin cytoskeleton regulation and a group of proteins called RhoGTPases, known to be involved in actin cytoskeleton regulation in podocytes. In the first study, glomerular microarray analysis showed an increase in the expression of the melanocortin 1-receptor (MC1R) in renal diseases focal segmental glomerulosclerosis and membranous nephropathy. Subsequent mass spectrometry analysis in combination with pathway and biochemical analysis revealed the podocyte protective effects of MC1R stimulation *in vitro*. Activation of MC1R proved to be stabilizing the podocyte actin cytoskeleton through inhibition of the epidermal growth factor receptor (EGFR) and maintenance of the actin associated protein synaptopodin. In the second study, the depletion of the prenylation enzyme Geranylgeranyl transferase type I (GGTase-I) in podocytes led to the development of proteinuria and FPE in mice due to an imbalanced RhoGTPase activity and disruption of the actin cytoskeleton. These findings suggest that GGTase-I activity is essential for podocyte function. In the last study, a guanine nucleotide exchange factor (activator of RhoGTPases) named βpix was identified to be modulated in podocytes following treatment with a renal stressor, using mass spectrometry analysis. Gene silencing of βpix protected against actin cytoskeleton remodulation in a model of podocyte injury, demonstrating the importance of βpix for podocyte actin cytoskeleton regulation.

In conclusion, the results in this thesis confirm the importance of actin cytoskeleton regulation for podocyte integrity. Further on, the results provide new information on actin cytoskeleton regulatory pathways involving RhoGTPases in podocytes, which can be of importance for future attempts in finding targeted treatments of proteinuria and chronic kidney disease.

Keywords: Podocyte, RhoGTPases, actin cytoskeleton regulation

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