Karolinska Institutet

Department of Medical Biochemistry and Biophysics

Expression Profiling of Blood Vessels in Pericyte Deficiency and Diabetes

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ABSTRACT

The kidney glomerulus is essential for the filtration of waste products from the blood into the urine and in controlling the volume and composition of body fluids. Injury to the glomerulus can lead to altered glomerular filtration rate, proteinuria, thickening of the glomerular basement membrane (GBM) and accumulation of mesangial cell matrix. The injuries can occur due to primary kidney diseases or as a secondary effect of other diseases such as diabetes mellitus. The blood-brain barrier (BBB) differs in many ways from of the glomerular filtration barrier. While glomerular endothelial cells are fenestrated and highly permeable, the endothelial cells of the blood-brain barrier are continuous and held together by tight junctions. Passage across the BBB is tightly controlled and serves to protect the neuronal tissue of the central nervous system from fluctuations in hormones, nutrients, metabolites and other substances in the blood.

The targeted deletion of either platelet-derived growth factor-B (PDGF-B) or PDGFR- β is embryonic lethal due to cardiovascular complications and lead to a failure in recruiting pericytes to the developing vasculature and mesangial cells into the glomerulus. In paper I we investigated the role of endothelium-derived PDGF-B in the recruitment of pericytes and mesangial cells using a mouse model with a targeted conditional deletion of PDGF-B in endothelial cells. We found that the phenotype mimics that of the null mutation, but is much milder. Thus the endothelium appears to be the main source of PDGF-B in the vasculature. In the kidney, the initial deficiency of glomerular mesangial cells normalized soon after birth and later led to a very light albuminuria and enlargement of the glomeruli. To increase our knowledge of the glomerular transcriptome we constructed a cDNA array from isolated mouse glomeruli.

In paper II we used it to identify a number of novel glomerular transcripts. In a series of experiments these transcripts were assigned to specific cell types and characterized as podocyte or mesangial cell/juxtaglomerular markers. Further study on podocyte marker Foxc2 revealed a role in podocyte differentiation and glomerular development.

In paper III we used several pericyte deficient mouse models to elucidate the role of pericytes in the integrity of the BBB. We found a correlation between the degree of pericyte deficiency and the extravasation of injected tracers across the BBB via macromolecular trancytosis, for the first time *in vivo* demonstrating the importance of pericytes in maintaining the BBB function.

To gain insight into the transcriptional changes behind diabetes-related glomerular injury, we analyzed kidney function and gene expression in the db/db mouse, a model of type 2 diabetes. We found increased expression of genes relating to the infiltration of monocytes/macrophages into the glomerulus, changes in expression of genes involved in the composition of the GBM and the extracellular matrix, as well as in signal transduction and growth factor expression. We also noted strong and consistent upregulation of Ym-1, a marker for alternatively activated macrophages (aaMac). Further analysis of our data set revealed that expression of several markers for aaMac were upregulated, while markers for classically activated macrophages remained unaltered.

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