**OPUS 27**

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**CD147 as a novel multifunctional modulator of podocyte metabolism and exosome**

**biogenesis: Identification of new molecular pathways and therapeutic targets in diabetic**

**kidney disease.**

Hyperglycemia is a primary factor that disturbs podocyte function in the glomerular filtration process. This disturbance leads to the development of diabetic nephropathy and, ultimately, renal failure. Podocytes, with their foot processes, form an important cellular layer of the glomerular barrier involved in the regulation of glomerular permeability. The retraction of podocyte foot processes forming the slit diaphragm is a common feature of proteinuria.

Currently, the correlation of retraction with the development of proteinuria is not well understood. A key question is whether podocyte foot processes are able to regulate slit diaphragm permeability and glomerular ultrafiltration. It is now known that the slit diaphragm protein complex does not only serve as a static molecular sieve but is rather a highly dynamic functional protein complex. Although the critical role of signaling at the slit diaphragm for active actin remodeling is highly conceivable, little is known about the effectors of slit diaphragm proteins involved in transmitting these signals to the actin cytoskeleton.

CD147 is a transmembrane glycoprotein involved in various physiological and pathological processes by interacting with several partners such as monocarboxylate transporters, Caveolin-1, and integrins. It is widely recognized as a strong activator of extracellular matrix metalloproteinases and also plays a significant role in mediating inflammatory and immune responses. Moreover, elevated levels of CD147 have been associated with the development of several diseases, including diabetes. However, its mechanism of action in podocytes has not been explored. Therefore, the primary aim of this project is to investigate the role of CD147 in the pathological changes in the glomerular filtration barrier formed by podocytes in diabetes, which ultimately leads to diabetic nephropathy and kidney failure.

The experiments will be focused on investigating the cellular and molecular mechanisms of CD147 interaction with multiple partners in podocytes, exosome biogenesis and release, podocyte migration, permeability to albumin across the podocyte monolayer, and glomerular permeability to albumin. The major part of this project will involve searching for new biomarkers of early diabetic nephropathy and podocyte damage in urine samples from the Zucker diabetic fatty (ZDF) rat model, which displays type 2 diabetes progression. An important part of this project will investigate the role of CD147 in the biogenesis and urinary secretion of exosomes, which may also be a potential marker of kidney damage. The realization of this project might help to understand the molecular mechanism of proteinuria and further develop novel diagnostic markers to test early diabetic nephropathy and podocyte damage in diabetes.