

The glomerular filtration barrier is composed of the fenestrated endothelium of the glomerular capillaries, the fused basal lamina of the endothelial cells and podocytes, and the filtration slits of the podocytes. The structures of the layers determine their permeability. Podocytes are highly specialized cells that cover the glomerular capillaries and constitute a key part of the glomerular filtration barrier. Disturbance of podocytes function has a central role in the development of proteinuria in diabetic nephropathy. Retraction and effacement of the podocyte foot processes, which form a slit diaphragm, is a common feature of proteinuria. At present, the correlation of the retraction of foot processes with the development of proteinuria is not well understood; therefore, unraveling the peculiarities of podocyte energy metabolism, notably in diabetic conditions, may provide a novel insights into the pathogenesis of diabetic nephropathy. Glycolysis and oxidative phosphorylation are the two major cellular pathways to produce energy. Most cells switch between these pathways in order to cope with changing energy demands. It is known that the intracellular metabolism in the cortical area of podocytes is regulated by glycolysis, whereas an energy balance in the central area is controlled by oxidative phosphorylation and glycolysis. Recently, it has been reported that high glucose concentration forced podocytes to switch from mitochondrial oxidative phosphorylation to glycolysis, resulting in lactic acidosis.

In addition to the role of lactate as a metabolite and energy substrate, it was demonstrated that it is a signaling substance. The lactate selectivity of the orphan receptor GPR81 was discovered in adipose tissue. To our knowledge, there are no reports that this receptor is expressed in podocytes. We suppose, that the lactate metabolic sensor GPR81 may contribute importantly to the control of podocyte functions in health and disease. Further investigation is required to elucidate how podocytes take up or extrude lactate, and to define the importance of GPR81-dependent signaling pathway, especially in diabetes. The principal goal of the project is to define the role of lactate and lactate receptor GPR81 in the development of pathological changes in renal filtration barrier observed in type 2 diabetes, which eventually lead to diabetic nephropathy and kidney failure.

The research project is divided into two parts: *in vivo* and *in vitro*. In *in vivo* study, we will use ZDSD rat model, which displays type 2 diabetes progression similar to the human disease – prediabetes (8-16 weeks of age), through overt diabetes (>16 weeks of age), to diabetic complications (24 weeks of age). In experiments *in vitro*, we will use kidney glomeruli and podocytes isolated from Wistar rats. Recently, we have showed that podocytes incubated for 5 days in high glucose became insulin resistant. Therefore, podocytes for the different experiments will be cultured in media with either normal or high glucose concentration for 5 days. The experiments of the *in vitro* part will be focused on: 1) the assessment of the degree of podocytes monolayer and glomerular permeability to albumin, and 2) evaluation of the cellular and molecular mechanisms of lactate metabolism and GPR81-dependent signaling pathways in podocyte.

The experiments will provide a new data concerning the role of lactate homeostasis and the regulation of metabolic sensor GPR81 in biology of podocytes. Moreover, we will identify and describe a potentially important novel mechanisms that may be injurious in the course of diabetes affecting podocytes and the permeability of the filtration barrier.