The role of bile acid receptor TGR5 in insulin-dependent regulation of podocyte function and glomerular filtration barrier permeability

The gut microbiota is recognized as a distinct organ that, apart from facilitating the absorption of nutrients and energy storage, also participates in the production of secondary bile acids (BAs) in the host's body. Changes in the composition and homeostasis of the gut microbiota resulting in the alterations in the overall pool of BAs undergo significant modifications in pathological conditions associated with insulin resistance, such as obesity or type 2 diabetes. Imbalances in the gut-kidney axis contribute to the pathogenesis of kidney diseases, including diabetic kidney disease The experimental findings indicate that insulin influences the morphology and functioning of podocytes that surround the glomerular capillaries, determining the impermeability of the filtration barrier to plasma proteins. In diabetes, insulin signaling disruption leads to the development of insulin resistance that impairs podocyte function, resulting in the disintegration of the glomerular filtration barrier and increased permeability to albumin, known as albuminuria.

As signaling molecules, BAs interact with the membrane G protein-coupled bile acid receptor (GPBAR1 commonly known as TGR5). TGR5 is involved in regulating insulin sensitivity, glucose metabolism, and glucose tolerance. However, these mechanisms have not been investigated in podocytes until now, despite previously demonstrated reduction in TGR5 expression in these cells exposed to high glucose concentrations and in the kidneys of diabetic patients. Therefore, the main goal of this project is to determine the involvement of TGR5 in podocyte damage mechanisms that negatively affect the filtration function of the renal glomerulus and ultimately lead to diabetic kidney disease and kidney failure.

The project will include in vitro and in vivo experiments. In the in vitro part, cellular and molecular mechanisms between TGR5 activity and insulin-dependent podocyte functioning will be investigated, including albumin permeability through a monolayer of podocytes and the permeability of the isolated glomeruli to albumin. An important part of this project will also include studies on the effect of BAs and the TGR5 receptor on kidney function in ZDF rats (Zucker Diabetic Fatty rats), which are characterized by type 2 diabetes.

The obtained results may contribute to understanding the pathomechanisms of glomerulopathy and, consequently, could be the first step toward designing new pharmacological therapies and therapeutic targets in kidney disease treatment.