# Molecular background of microvascular complications in *HNF1A*-MODY patients: induced pluripotent stem cells as disease modeling tool

Maturity onset diabetes of the young (MODY) is caused by a mutation in a single gene and leads to diabetes under the age of 25. The most common form of MODY is caused by a mutation in the hepatocyte nuclear factor-1 alpha (*HNF1A)* gene. In every fourth patient with *HNF1A*-MODY microvascular complications, like diabetic retinopathy or nephropathy, have been observed. Even though hyperglycemia is considered as a major factor contributing to endothelial dysfunction in diabetic patients, studies have also shown that in a significant number of patients, even though hyperglycemic, there are no microvascular complications. This data suggests that these patients can have endogenous protective factors that can neutralize the adverse effect of hyperglycemia. Contrary, mutations in different genes were found to be risk factors for developing diabetic complications. Therefore, identification of novel candidate genes associated with diabetic vascular complications will further contribute to our understanding of the mechanisms underlying disease progression.

Recently we have shown that *HNF1A* mutation in endothelial cells (ECs) could sensitize these cells to vascular complications under normal glycemic conditions. We found that in *HNF1A* heterozygous mutated cells there is an increased vascular permeability, which is one of the first observable alteration in diabetic retinopathy. The results were obtained with isogenic pairs of disease-specific and control induced pluripotent stem cells (iPSCs) lines that differ exclusively at the disease-causing mutation. It is worth mentioning that the combination of iPSCs and genome editing provides an unprecedented opportunity to study the fundamental principles of cell biology. In the current project, we would use the same disease model to dissect the molecular background of the increased vascular permeabilization in endothelial cells with *HNF1A* mutation and additionally we will validate the significant results in *HNF1A*-MODY patient-specific cells. Our hypothesis, based on current preliminary results, is that mutations in the *HNF1A* gene, as occurring in patients with *HNF1A*-MODY, can cause weakening of cell-cell contacts in ECs, through imbalanced intracellular reactive oxygen species (ROS) production and alteration in the calcium signaling. Therefore, the impairment in the interconnection between ROS production, calcium signaling, mitochondrial physiology, and cell junctional proteins, will be checked. If our hypothesis would be proven, that *HNF1A* could be considered as a significant risk factor for endothelial dysfunction, new prevention strategies for *HNF1A*-MODY patients could be considered. Knowing the exact molecular basis of such alterations would allow for more precise target-based prevention or therapy.