**Human blood vessel organoids provide new insights into diabetes**

With 422 million people worldwide, the number of people with diabetes has quadrupled since 1980. As reported recently in a global WHO report, diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputations, and thus one of the major public health challenges today. In fact, all these devastating diabetic complications can be attributed to changes in blood vessels that lead to their dysfunctionality. Despite extensive research on diabetic vascular complications we still don’t have a full picture of how these blood vessel changes develop. One major obstacle is the difference between the physiology of human and mouse, the most widely used model organism for pre-clinical research, as common diabetic mouse models only poorly recapitulate the blood vessel changes of diabetic patients.

We recently were able to generate human blood vessels from pluripotent stem cells in a petri dish. These lab-grown blood vessels mimic to a great extent the architecture of human capillaries; an inner endothelial lining that forms the vessel lumen, pericytes covering the endothelium and a vascular basement membrane that encloses the vessel. Further we found a similar molecular composition compared to real human blood vessels. Most importantly, if we transplant human blood vessels into mice, they connect to the mouse circulation and are able to transport blood and show normal physiological parameters. Thus, the stem cell derived blood vessels are truly functional. We culture the human blood vessels as 1-2 mm large spheres and named them: Human blood vessel organoids.

With this new technology in place, we asked what would happen if we make the human blood vessel organoids diabetic. For this, we increased the sugar concentration in our culture media and added a low dose of inflammatory cytokines, a condition often found in diabetic patients. Excitingly, we indeed observed similar blood vessel changes as in diabetic patients. The most important one was that the vascular basement membrane became massively enlarged, which is a major reason why in patients blood vessels become dysfunctional in terms of delivering oxygen and why they die off eventually. Also, when we transplanted the human blood vessel organoids in diabetic mice, we observed the same vessel changes; vascular basement membrane thickening and a loss of vessels. Interestingly, these changes could only be observed on the human-derived vessels but not the endogenous mouse blood vessels, at the time point of analysis.

We then used our human blood vessel organoid platform for testing various compounds and found that a γ-secretase inhibitor (DAPT) that abrogates Notch signalling, could prevent the diabetic vascular basement membrane thickening. To evaluate this finding, we treated diabetic mice carrying human blood vessels with DAPT and could show that DAPT prevents vascular basement membrane thickening and loss of the human blood vessels. γ-secretase inhibitors were previously used in clinical trials for cancer and Alzheimer disease but showed massive side effects because they block all four Notch receptors that have diverse functions in various tissues. To identify the right Notch receptor and ligand, we used blocking antibodies/peptides and gene editing methods on our human blood vessel organoids. Notch3 on pericytes turned out to be the major Notch receptor, responsible for the diabetic vascular basement membrane thickening, with Dll4 as its main ligand on endothelial cells. Finally, we went into patients and found elevated Notch3 signalling in the diabetic blood vessels, indicating that altered Notch3 activity might indeed contribute to the vascular changes in diabetes.

As a next step, we will investigate whether we can not only prevent, but reverse the diabetic vascular complications. And as Notch3 is an important protein on blood vessels it is questionable whether blocking Notch3 would be the right strategy in diabetic patients. Certainly, our human blood vessel organoids provide the opportunity to screen for a multitude of compounds, with the hope to identify targets that are more suitable for directly moving into clinical trials.

Beyond diabetes, human blood vessel organoids have a broad applicability, for example to study genetic vascular diseases using patient-derived iPS cells, preclinical toxicology or even for tissue regeneration, and will hopefully contribute to the development of new medications for vascular diseases in the future.