Heme metabolism in blood vessel wall - the influence on abdominal aortic aneurysm formation

One in one hundred men over 60 years old will develop abdominal aortic aneurysm (AAA), and only 15-35% of people survives the aneurysm rupture. The risk of developing AAA is increased by aging and endothelial dysfunction. However, the exact mechanism of aneurysm development is still unclear. Recent studies show that heme, which is a cofactor of many enzymes and crucial element of mitochondrial electron transport, is required for healthy endothelium.

Indeed, we observed that mice lacking heme oxygenase-1 (HO1), heme-degrading enzyme, have lower incidence of AAA than wild-type animals. **Therefore, we hypothesize that increased availability of heme in endothelial cells reshapes cellular metabolism and thus makes blood vessels less prone for injury.** The main aim of this project is to verify this hypothesis.

Using mice with cell-type specific deletion of a HO1 gene, we will check which blood vessel cells are responsible for the observed protective effect of decreased heme degradation. In human primary endothelial cells with decreased heme degradation we observed no changes in **total heme** levels but decreased expression of key enzymes for heme synthesis. To evaluate levels of **free heme**, we will use novel fluorescence-based detection system, which allow us to understand better the production and trafficking of heme in endothelial cells. We will also generate **new transgenic mouse model** that will allow us to study free heme levels in living animals. The analysis of the transcriptome profile and metabolites in cells with decreased heme degradation, will help us to evaluate the **fine-tuning of cellular metabolism by heme**. Changes in metabolites and gene expression will be further confirmed in functional assays. Primary murine endothelial cells lacking HO1 showed **altered pathways that regulate cellular quiescence.** Using human primary endothelial cells and murine aortas we will further analyse the impact of low heme degradation on both endothelial quiescence and senescence.

Finally, we will test if heme and its precursors could prevent developing the aneurysm in a murine model. Knowledge of the mechanisms that underlie the disease will allow developing new therapies for the life-threatening condition.