Diabetic endotheliopathy is the main cause for impaired angiogenesis and reduced neovascularization that lead to microvascular injury and vascular complications. The pathogenic basis for vascular complications arising from diabetes is complex. Elucidation of key underlying mechanisms will help the development of novel therapies and the discovery of potential biomarkers. The ability to generate functional endothelial cells (ECs) from induced pluripotent stem cells (iPSCs) from small amounts of blood is a novel and powerful tool for cell-based therapies. Human iPSC-derived ECs (iPS-ECs) have a broad range of clinical applications including cell-based therapy, disease modelling and drug screening; they can be used in mechanistic studies towards the development of novel therapies and in the discovery of new biomarkers to be applied in regenerative medicine and treatment of diabetic vasculopathy. Here we utilize transcriptomic and proteomic technologies to assess patient-specific iPSCs from diabetic (DiPS-ECs) and non-diabetic (NiPS-ECs) donors in order to investigate the mechanisms driving endotheliopathy in diabetes. Our in vitro and in vivo models recapitulate the effects of hyperglycaemia on the vasculature in the clinical setting. RNA-seq data showed that genes and proteins involved in angiogenesis and EC function were significantly downregulated in DiPS-ECs compared to NiPS-ECs (n=3, p<0.05). Specific epsins regulating VEGF-mediated angiogenesis were downregulated in DiPS-ECs, leading to increased signalling VEGF pathway activation. Moreover factors involved in E-cadherin signalling, endothelial-to-mesenchymal transition and fibrosis were increased in DiPS-ECs. We detected abnormal capillary permeability and barrier integrity in DiPS-ECs using xCELLigence®. DiPS-ECs significantly reduced barrier integrity and barrier recovery (n=3, p<0.001, ±SEM) and also displayed impaired tube formation in vitro (n=3, ±SEM, p<0.05). DiPS-ECs displayed impaired function demonstrated by decreased blood flow recovery (BFR) compared to NiPS ECs (n=3) when injected to the hindlimb of mice following femoral artery ligation. Finally, our proteomic and transcriptomic analysis confirmed imbalances in several angiogenic genes including endothelial specific Roundabout protein 4 (ROBO4) that is highly involved in pathways related to angiogenesis, barrier stability and endothelial health. Expression of ROBO4 was found to be impaired in DiPS-ECs and transcriptomic analysis along with in vitro and in vivo studies revealed its importance in vascular development and angiogenesis. Our data support the impaired angiogenic functionality of DiPS-ECs cells in vitro and in vivo and show that DiPS-ECs carry an imprint of the diabetic milieu which is reflected in their dysfunction. To the best of our knowledge, we have identified a novel disease-specific signature in diabetic iPS-ECs, therefore our human iPS-EC model may serve as a valuable tool to study biological pathways and identify new treatments for diabetes-induced endotheliopathy.

Conflict of Interest None