iPSC-derived endothelial cells reflect accelerated senescence and increased inflammatory response in a CVD-risk stratified manner

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Background: Cardiovascular disease (CVD) remains the leading cause of death worldwide and its multifactorial nature is recognized, with both an individual's genetic background and lifestyle strongly impacting on its course. On a molecular level, accelerated cellular aging and increased inflammation interact to drive the severity of the disease. We have used patient-derived induced pluripotent stem cells (iPSC) to investigate the impact of a patients' genetic background on (epi-)genetically determined functionality, telomere attrition and inflammatory response.

Purpose: The purpose of this study is to investigate differences on the cellular level between iPSC-derived endothelial cells from risk-stratified CAD patients (both ACS and stable CAD) in both functionality, inflammatory response and ageing rate.

Methods: iPSCs were generated from participants with similar lifestyle but different disease progression (healthy >65 y/o, stable CAD >65 y/o, ACS <65y/o) and differentiated into endothelial cells (iPS-EC). After quality control, iPS-EC were exposed to inflammatory stimulation via TNF-α under static and pro- vs. anti-atherogenic flow conditions (laminar vs. disturbed flow, high vs. low shear stress) and their gene and protein expression of adhesion molecules was assessed by qPCR and flow cytometry. Telomere length was determined by a qPCR-based assay in iPSC-ECs after four (p4) and eleven population doublings [KN1] (p11) in fully supplemented growth medium.

Results: ACS-iPS-ECs showed a significantly stronger upregulation of E-selectin in response to inflammatory stimulation with TNF-a than healthy-iPS-ECs on mRNA level (ACS: 532.1-fold±48.7 vs. healthy: 322.3-fold±55.7, p=0.02). Similarly, ICAM1 protein upregulation was stronger in ACS-iPS-ECs than in healthy iPSC-ECs as assessed by flow cytometry (ACS: 1.4-fold±0.01 vs. healthy: 1.1-fold±0.0007; $p<0.001$) whereas VCAM1 upregulation was weaker in ACS-iPS-ECs compared to healthy controls (ACS: 1.8-fold±0.3 vs. healthy: 4.2-fold±0.9, $p<0.001$). Telomere shortening from p4 to p11 was significantly stronger in ACS-iPS-ECs compared to healthy controls (ACS: 35%±10 vs. healthy: 10%±5, $p<0.05$).

Conclusion: The more pronounced upregulation of specific adhesion molecules (E-Selectin, ICAM-1, but not VCAM-1) in response to inflammatory stimulation together with a stronger telomere attrition in ACS-iPS-EC hints at cells entering faster into a senescent state.