SPECTRUM OF SMOOTH MUSCLE CELL AND FIBROBLAST SUBTYPES IN ATHEROSCLEROSIS

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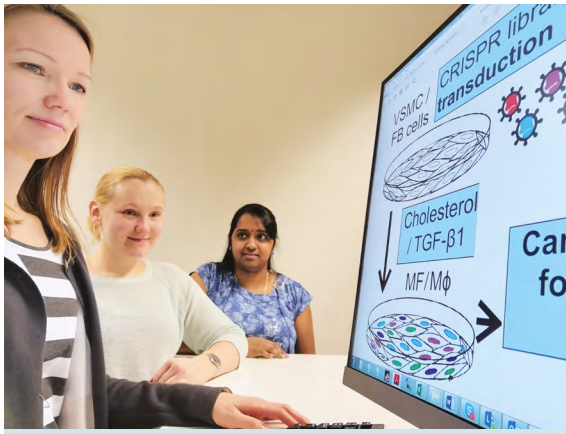
Atherosclerotic coronary artery disease is the leading cause of death in the Western world. In spite of interventional and statin therapy, the risk for recurrent myocardial infarction remains high and novel therapies are urgently needed. To achieve this, better understanding of the biological mechanisms that promote the progression of the disease is needed. Especially, we are far from understanding how different cell types contribute to disease development. Among these, the role of vascular smooth muscle cells (VSMCs) and fibroblasts (FBs) remains largely understudied.

Recent evidence suggests that VSMCs display extraordinary plasticity and can acquire macrophage-like features during disease progression. Indeed, it has been estimated that over half of the foam cells in human advanced lesions originate from VSMCs. This is alarming, since increased number of foam cells is associated with plaque instability and rupture. Similarly, VSMCs and FBs can transdifferentiate to myofibroblasts that leads to increased local expression of inflammatory cytokines and growth factors promoting the disease. It has been suggested that transdifferentiation to myofibroblasts may contribute to plaque remodeling and facilitate plaque rupture through the continuous production of contractile force. Further study of this this mechanism has been hampered by the fact that myofibroblasts and VSMCs share several major markers. Therefore, new ways to reliably identify myofibroblasts and VSMCs are needed to understand contribution of these cell types to atherosclerosis.

In this study we aim to bring the characterization of the phenotypic spectrum of VSMCs and FBs to date by analyzing alterations in cell subtypes using single cell RNA-sequencing. Characterizing the unique gene expression patterns of these cell types in mouse model of atherosclerosis allows us to gain better understanding of the pathological transformation of cells and to identify reliable markers for cell subtypes and disease states. Detailed mechanistic analysis of the pathogenic phenotype transitions of VSMCs and FBs is further used to identify transcription factors and signaling pathways that could provide targets for future drug development. Unveiling the key regulatory factors and networks driving the pathological transformation of cells could pave the way towards better understanding of the disease process which is imperative for the future development of preventive and therapeutic measures.



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