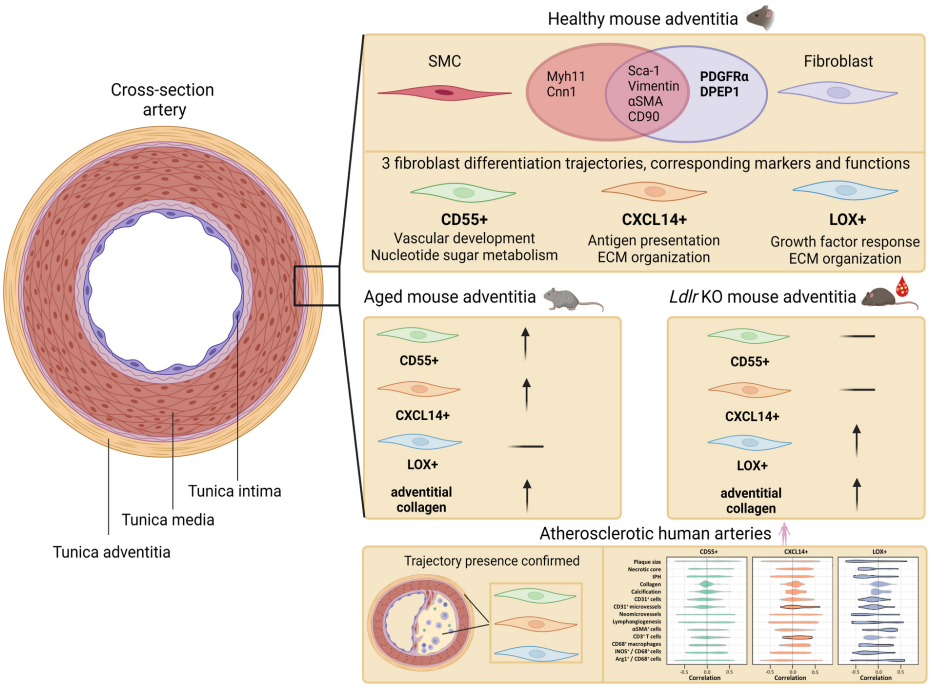
Paper of the Month August 2023:

‘Human and murine fibroblast single-cell transcriptomics reveals fibroblast clusters are differentially affected by ageing and serum cholesterol’

van Kuijk K, McCracken IR, Tillie RJHA, Asselberghs SEJ, Kheder DA, Muitjens S, Jin H, Taylor RS, Schreur RW, Kuppe C, Dobie R, Ramachandran P, Gijbels MJ, Temmerman L, Kirkwoord PM, Luyten J, Li Y, Noels H, Goossens P, Wilson-Kanamori JR, Schurgers LJ, Shen YH, Mees BME, Biessen EAL, Henderson NC, Kramann R, Baker AH, Sluimer JC

Cardiovasc Res. 2023 Jul 4;119(7):1509-1523. doi: 10.1093/cvr/cvad016.

Van Kuijk *et al.* identify in our August 2023 paper-of-the-month novel markers of fibroblast subpopulations of relevance to cardiovascular diseases (CVD). Cell-type markers and heterogeneity in murine and human arteries are established with a specific focus on the adventitial fibroblast response to hypercholesterolaemia and ageing. Various methods, ranging from single cell sequencing to immunohistochemistry and flow cytometry are being applied to identify novel and establish common fibroblast markers in different human and murine vasculatures. Hereby, the study reveals that platelet-derived growth factor receptor alpha (PDGFRA) and dipeptidase 1 (DPEP1) across human and murine aorta, carotid, and femoral arteries, whereas traditional markers such as the cluster of differentiation (CD)90 and vimentin label transgelin+ vascular smooth muscle cells. Pseudotime analysis indicates multiple fibroblast clusters differentiating along trajectories. Three trajectories, marked by CD55 (Cd55+), Cxcl chemokine 14 (Cxcl14+), and lysyl oxidase (Lox+), could be confirmed in an independent RNA-seq dataset. Gene ontology (GO) analysis further revealed divergent functional profiles of the three trajectories, related to vascular development, antigen presentation, and/or collagen fibril organization. Trajectory-specific genes included significantly more genes with known genome-wide associations (GWAS) to CVD than expected by chance, implying a key role in CVD. Indeed, differential regulation of fibroblast clusters by CVD risk factors was shown in the adventitia of aged C57BL/6J mice, and mildly hypercholesterolaemic LDLR KO mice on chow by flow cytometry. The expansion of collagen-related CXCL14+ and LOX+ fibroblasts in aged and hypercholesterolaemic aortic adventitia, respectively, coincided with increased adventitial collagen. Immunohistochemistry, bulk, and single-cell transcriptomics of human carotid and aorta specimens emphasized translational value as CD55+, CXCL14+ and LOX+ fibroblasts were observed in healthy and atherosclerotic specimens. Also, trajectory-specific gene sets appeared to be differentially correlated with human atherosclerotic plaque traits.


Cross-section artery
Tunica intima
Tunica media
Tunica adventitia
Healthy mouse adventitia
SMC
Myh11
Cnn1
Sca-1
Vimentin
αSMA
CD90
PDGFRα
DPEP1
Fibroblast
3 fibroblast differentiation trajectories, corresponding markers and functions
CD55+
Vascular development
Nucleotide sugar metabolism
CXCL14+
Antigen presentation
ECM organization
LOX+
Growth factor response
ECM organization
Aged mouse adventitia
CD55+
CXCL14+
LOX+
adventitial collagen
Ldlr KO mouse adventitia
CD55+
CXCL14+
LOX+
adventitial collagen
Atherosclerotic human arteries
Trajectory presence confirmed
CD55+
CXCL14+
LOX+
Correlation