January 2024 EVBO Paper-of-the-month

Faleeva M, Ahmad S, Theofilatos K, Lynham S, Watson G, Whitehead M, Marhuenda E, Iskratsch T, Cox S, Shanahan CM. Sox9 Accelerates Vascular Aging by Regulating Extracellular Matrix Composition and Stiffness. *Circ Res*. 2024; 134(3):307-324. doi: 10.1161/CIRCRESAHA.123.323365.

In our January 2024 EVBO Paper-of-the-month, Faleeva *et al* discover that Sox9 (SRY-box transcription factor 9) is a strong regulator of chondrocytic differentiation, regulating gene expression involved in extracellular matrix (ECM) remodelling during vascular ageing. It had been known before that vascular smooth muscle cells (VSMCs) differentiate into an osteo/chondrogenic phenotype during vascular calcification and aging. The authors discovered that Sox9 drives the senescent ECM phenotype, impacting stiffness, organization, and protein composition. The senescent ECM promotes VSMC DNA damage and exit from the cell cycle, while young ECM promotes senescent VSMCs to reenter the cell cycle. During this process, Sox9 triggers cellular senescence *via* an increase of LH3 (procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3) deposition in the ECM through extracellular vesicles increasing ECM stiffness. These novel findings highlight an underappreciated role of the ECM in regulating VSMC aging and identify key factors including LH3 as drivers of VSMC stiffening with age.