May 2024 EVBO Paper-of-the-month

Mocci G, Sukhavasi K, Örd T, Bankier S, Singha P, Arasu UT, Agbabiaje OO, Mäkinen P, Ma L, Hodonsky CJ, Aherrahrou R, Muhl L, Liu J, Gustafsson S, Byandelger B, Wang Y, Koplev S, Lendahl U, Owens GK, Leeper NJ, Pasterkamp G, Vanlandewijck M, Michoel T, Ruusalepp A, Hao K, Ylä-Herttuala S, Väli M, Järve H, Mokry M, Civelek M, Miller CJ, Kovacic JC, Kaikkonen MU, Betsholtz C, Björkegren JLM. **Single-Cell Gene-Regulatory Networks of Advanced Symptomatic Atherosclerosis**. *Circ Res*. 2024 May 24;134(11):1405-1423. doi:10.1161/CIRCRESAHA.123.323184.

In our May 2024 EVBO Paper-of-the-month, Mocci *et al* generate an RNA sequence dataset of atherosclerosis obtained from atherosclerotic progression in *Ldlr*$^{-/-}$ *Apob*$^{100/100}$ mice as well as symptomatic and asymptomatic patients with carotid artery disease. The authors were able to reidentify and markedly expand the gene content of three inflammatory- and osteogenic-related smooth muscle cell (SMC) subtypes, and three M1-type proinflammatory and Trem2-high lipid-associated-like macrophage subtypes critical for the development of advanced and symptomatic atherosclerotic lesions. Mocci and colleagues further provide pathophysiological and clinical context to these six subcellular clusters by integrative analysis with a CAD framework of 135 human gene-regulatory networks (GRNs), identifying three arterial wall GRNs; the MP-specific GRN33 and GRN122, and the SMC-specific GRN39, of which GRN39 was reconfirmed in five independent human datasets and experimentally in human vascular smooth muscle cells. The authors show that GRN39 is critical for the transformation of contractile SMCs into an osteogenic phenotype promoting advanced-stage and symptomatic atherosclerotic plaques.