Role of smooth muscle-derived vascular progenitor cells in atherosclerosis

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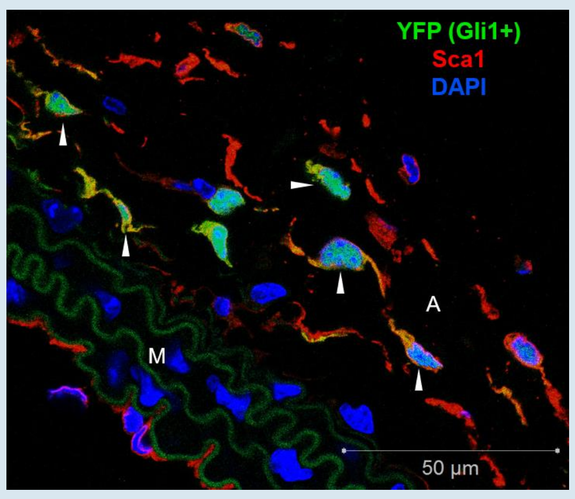
Background

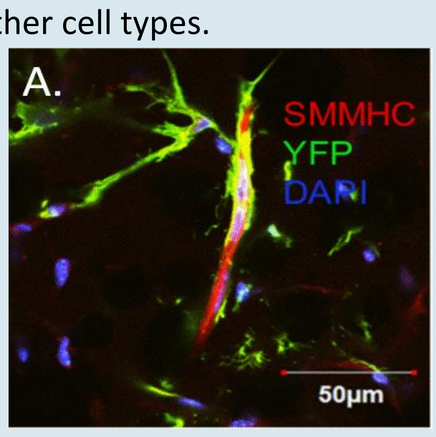
- Atherosclerosis is a major cause of morbidity and mortality worldwide, but current therapies fail to meet clinical needs.
- Expansion of adventitial microvessels, the vasa vasorum (VV), is believed to drive atherosclerosis progression by facilitating inflammatory cell infiltration.

Image adapted from https://www.earthslab.com/physiology/vasa-vasorum/



Lu, Sizhao, et al. "Smooth muscle–derived progenitor cell myofibroblast differentiation through KLF4 downregulation promotes arterial remodeling and fibrosis." *JCI insight* 5.23 (2020).

- Our group previously identified a unique population of resident stem cells (**AdvSca1-SM cells**) that derive from mature vascular smooth muscle cells (SMCs) and reside in the vessel adventitia.
- AdvSca1-SM cells are selectively enriched for Gli1 compared to other vascular cells.
- This allowed us to develop the Gli1-Cre/Rosa-YFP mouse model, which selectively and permanently labels AdvSca1-SM cells with YFP, even if they differentiate into other cell types.

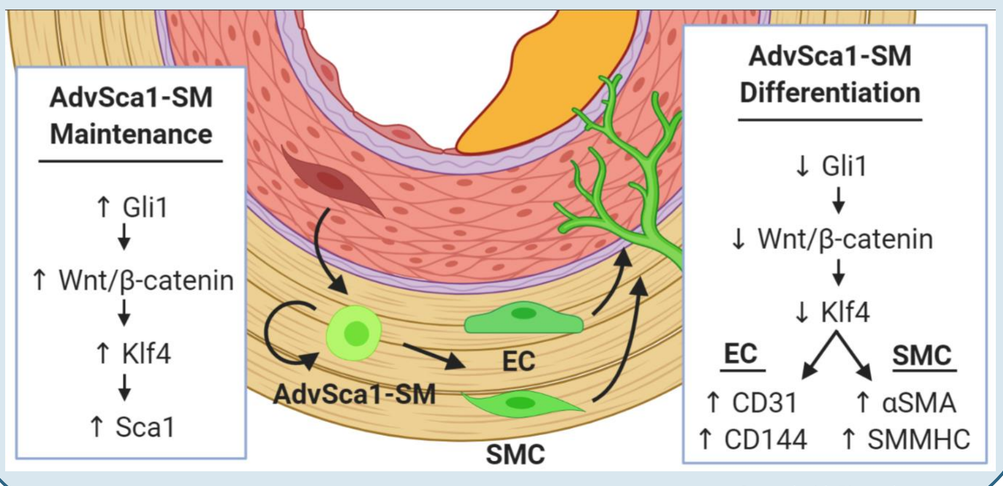


Majesky, Mark W., et al. "Differentiated smooth muscle cells generate a subpopulation of resident vascular progenitor cells in the adventitia regulated by Klf4." *Circulation research* 120.2 (2017): 296-311.

- *In vitro* studies demonstrated that AdvSca1-SM cells can differentiate into SMCs, endothelial cells (ECs), and myofibroblasts.
- *M*atrigel plug assays also showed that AdvSca1-SM cells contribute to in vivo vessel formation via differentiation to SMCs or ECs.

Hypothesis

In atherosclerosis, AdvSca1-SM cells will reprogram into smooth muscle or endothelial cells to contribute to vasa vasorum expansion and plaque progression.



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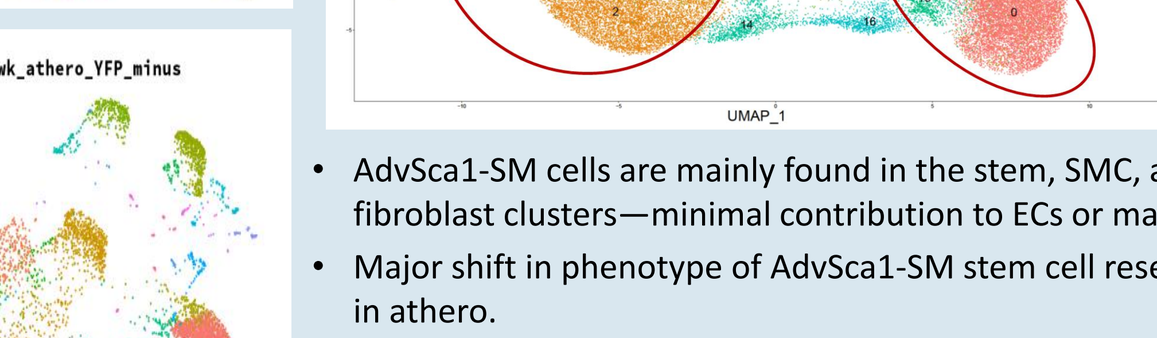
Methods



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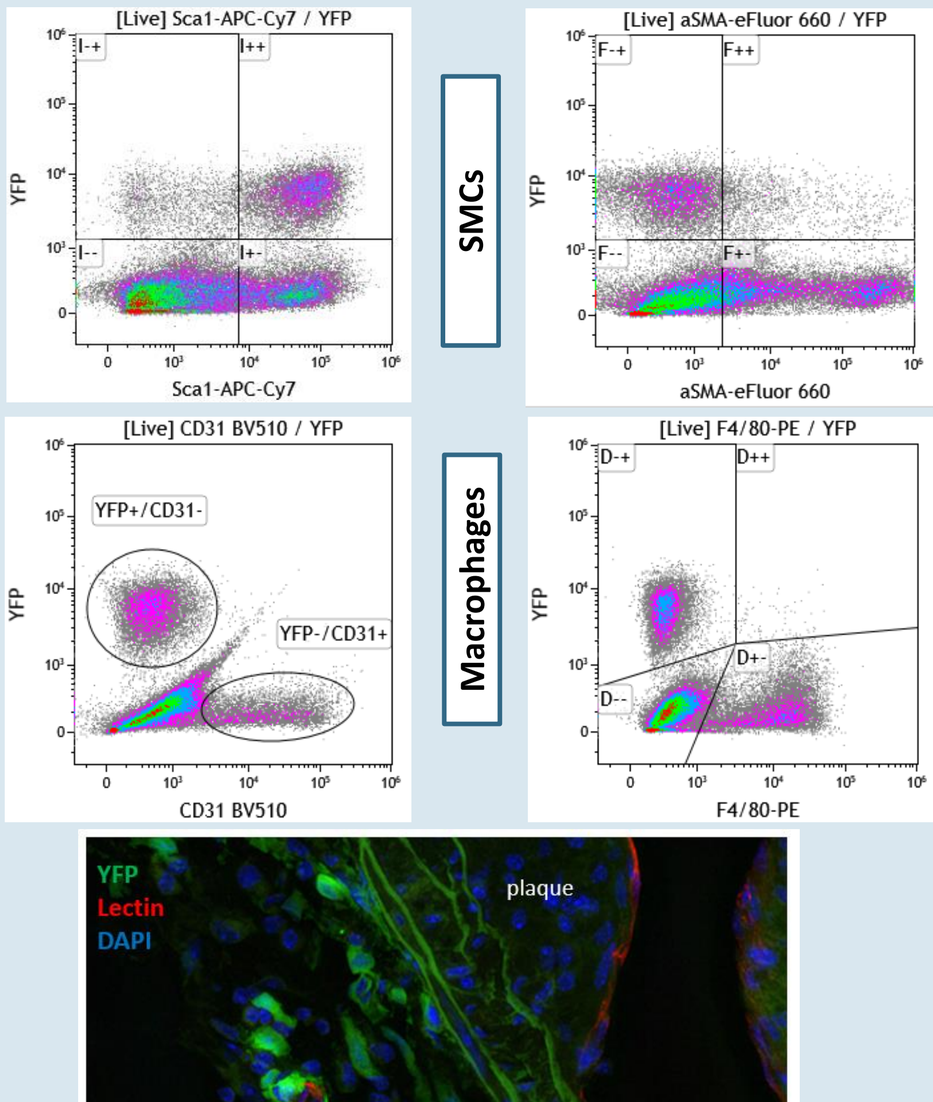
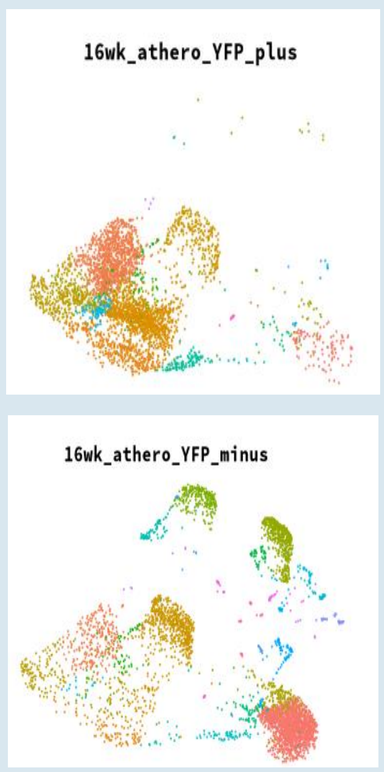
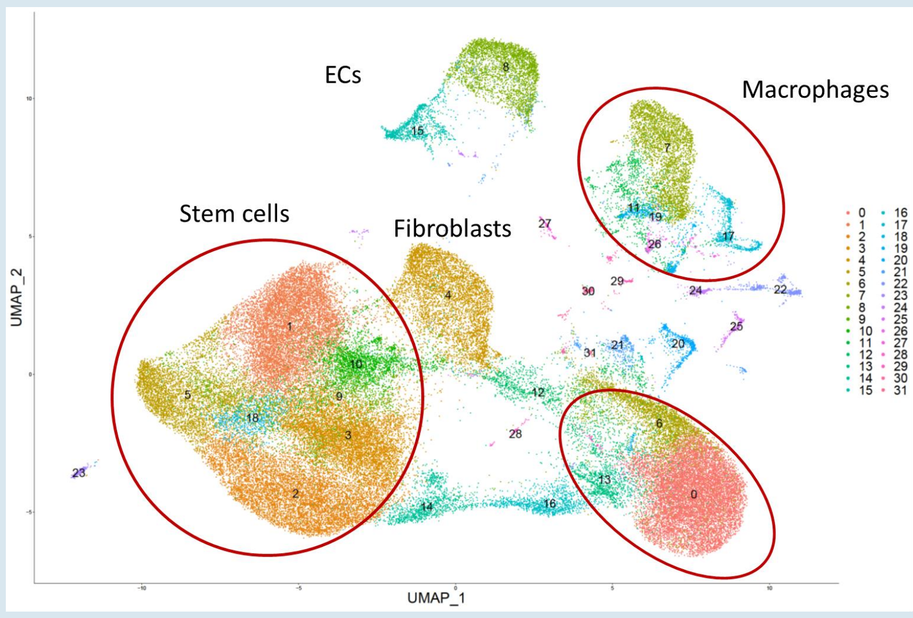
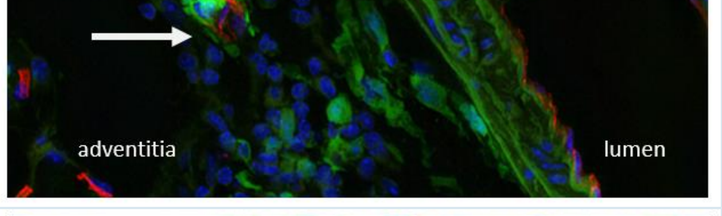
Results

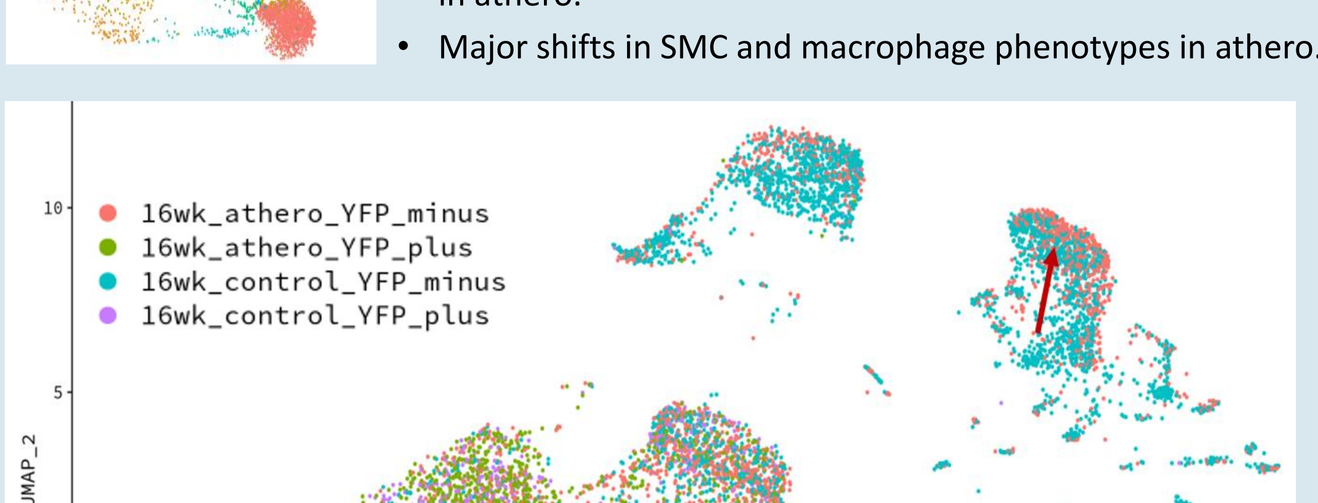






- AdvSca1-SM cells are mainly found in the stem, SMC, and fibroblast clusters—minimal contribution to ECs or macs.
- Major shift in phenotype of AdvSca1-SM stem cell reservoir in athero.
- Major shifts in SMC and macrophage phenotypes in athero.





Conclusions & Future Directions

- AdvSca1-SM cells are associated with adventitial microvessels after 16 weeks of atherogenic treatment.
- In both early and late stages of atherosclerosis, there is a large reservoir of AdvSca1-SM cells in a stem-like state. However, this population shows significant phenotypic shifts in atherogenic compared to control conditions.
- When AdvSca1-SM cells differentiate into other cell types in atherosclerosis, they primarily become mature SMCs, modulated SMCs, and myofibroblasts. AdvSca1-SM cells very rarely become endothelial cells or macrophages.
- Ongoing work with advanced lesions (24-30 weeks of treatment) will more fully define the functional role and spatial localization of AdvSca1-SM cells in atherosclerotic plaque progression.

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