Role of smooth muscle-derived vascular progenitor cells in atherosclerosis

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Abstract

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. 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/Rosa26-YFP mouse model, which selectively and permanently labels AdvSca1-SM cells with YFP, even if they differentiate into other cell types. In vitro studies demonstrated that AdvSca1-SM cells can differentiate into SMCs, endothelial cells (ECs), and myofibroblasts. Matrigel plug assays also showed that AdvSca1-SM cells contribute to vivo vessel formation via differentiation to SMCs or ECs. In addition, there remains a large reservoir of AdvSca1-SM cells in a stem-like state. AdvSca1-SM cells very rarely differentiate into endothelial cells. Despite previous evidence of SMCs gaining a macrophage-like phenotype in atherosclerosis, we identified only rare instances of AdvSca1-SM cells contributing to macrophage populations. Ongoing work with advanced lesions (24-30 weeks of treatment) will more fully define the functional role of AdvSca1-SM cells in atherosclerotic plaque progression.

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

Hypothesis

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

Methods

• Mice randomized to treatment group: - Control: Tamsulosin + standard chow - Atherosclerosis: Tamsulosin + PCSK9 (R: 3-16 weeks) + Western diet
• Mice harvested at 8, 16, or 24 weeks for histology, flow cytometry, or sRNA-Seq

Results

• AdvSca1-SM cells in atherosclerosis primarily differentiate into mature SMCs, modulated SMCs, and myofibroblasts.

Conclusions & Future Directions

• AdvSca1-SM cells in atherosclerosis primarily differentiate into mature SMCs, modulated SMCs, and myofibroblasts.
• AdvSca1-SM cells very rarely differentiate into endothelial cells.
• Despite previous evidence of SMCs gaining a macrophage-like phenotype in atherosclerosis, we identified only rare instances of AdvSca1-SM cells contributing to macrophage populations.
• Ongoing work with advanced lesions (24-30 weeks of treatment) will more fully define the functional role of AdvSca1-SM cells in atherosclerotic plaque progression.

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