Multipotent embryonic isl1+ progenitor cells lead to cardiac, smooth muscle, and endothelial cell diversification.

Cardiogenesis requires the generation of endothelial, cardiac, and smooth muscle cells, thought to arise from distinct embryonic precursors. We use genetic fate-mapping studies to document that isl1(+) precursors from the second heart field can generate each of these diverse cardiovascular cell types in vivo. Utilizing embryonic stem (ES) cells, we clonally amplified a cellular hierarchy of isl1(+) cardiovascular progenitors, which resemble the developmental precursors in the embryonic heart. The transcriptional signature of isl1(+)/Nkx2.5(+)/flk1(+) defines a multipotent cardiovascular progenitor, which can give rise to cells of all three lineages. These studies document a developmental paradigm for cardiogenesis, where muscle and endothelial lineage diversification arises from a single cell-level decision of a multipotent isl1(+) cardiovascular progenitor cell (MICP). The discovery of ES cell-derived MICPs suggests a strategy for cardiovascular tissue regeneration via their isolation, renewal, and directed differentiation into specific mature cardiac, pacemaker, smooth muscle, and endothelial cell types.