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Lineage Tracing Suggests Possibility for Adulthood Activation of Neural Crest Genetic Signature and Common Origin for Different Cardiac Progenitor Cell Types in the Atrial Appendages

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Background:
We recently identified three distinct cardiac progenitor cell (CPC) populations from the left atrial appendages (LAAs) of adult murine hearts. These populations have distinct phenotype and characteristics. Type A CPCs are c-kit+/Sca-1+, Type B CPCs are c-kit+/CD45+ and more mature Type C CPCs are spontaneously derived from Type B in vitro. The purpose of this study was to further analyze the connection between different progenitor cell populations using gene profile data, histology analysis and lineage tracing.

Methods:
To analyze the transcriptomes of CPC populations, we performed whole-genome expression array experiments to the cell sorted Type A, Type B and Type C CPC populations. The LAA analyzed with immunostaining and tissue culture derived cells were analyzed using immunostaining and FACS. Neural crest lineage tracing was performed with Pax3-cre eYFP reporter mice.

Results
Transcriptome comparison demonstrated significant up-regulation of neural crest differentiation –pathway genes in Type A CPCs and also in Type C CPCs, which are derived from Type B CPCs. Type B CPCs expressed a gene profile, which matches that of non-hematopoietic, resident macrophage –like cells found in other tissues. Tissue analysis after Pax3 lineage tracing demonstrated traced cells (eYFP) in the subepicardial zone of the LAA, co-stained with F4/80 macrophage marker and c-kit. Closely attached were epicardially lined F4/80+ cells with no eYFP signal. In tissue culture, Pax3-cre-eYFP signal was strongest in the Type B CPC population and lower in the Type A CPC population. Fibroblasts in the culture were eYFP negative.

Conclusion
Our results suggest that rather than having distinct embryonic origins, the different types of CPCs in the LAA originate from the resident, non-hematopoietic macrophage progenitor population. The neural crest differentiation pathway can be activated in these cells during adulthood, possibly in cardiac stress situations, enabling differentiation to cardiac lineage.