

Atrial Appendages Harbor a Vast and Diverse Population of Cardiac Progenitor Cells

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Background: The regenerative capability of the adult heart has gained evidence, but the mechanism remains unknown. Cardiac progenitor cells (CPCs) are a heterogenic population and are thought to be concentrated in certain areas (e.g. ventricular apex). We hypothesized that the atrial appendages, being from an earlier stage of embryological development than the rest of the heart, contain a large amount of CPCs.

Methods: Immunostaining was performed on the frozen left atrial appendage (LAA) sections. LAAs from adult mice were harvested and digestion of explants was performed with three different concentrations of enzymes. Differentiation was induced through Dexamethasone or 5-Azacytidine. Cells were analyzed with FACS and immunostaining.

Results: The LAA contained a high number of c-Kit⁺ cells, from which >60% were Nkx2.5⁺. In culture, tissue from both appendages had an equal growth potential, but the ventricular apex showed only minimal cell growth (40x lower than the appendages, *figure*). Two distinct progenitor cell populations grew depending on the strength of enzymatic digestion: Type A, which was c-Kit⁺ and CD45⁻ and Type B, which was c-Kit⁺ and CD45⁺. Nkx2.5 and GATA-4 were positive in both cell populations. Sca-1 expression was abundant in Type A cell populations (~90%), in contrast to Type B populations. Both CPC types were found from the apex-derived cells as well. Differentiation was induced to the Type A population using Dexamethasone, with organized expression of sarcomeric proteins and atrial natriuretic factor. Type B population was induced to differentiation with 5 –Azacytidine. Possibility of a mast cell contamination was ruled out by RT-PCR.

Conclusion: The atrial appendages contained multiple types and a higher concentration of CPCs than the left ventricle. Different enzymatic digestion method caused major differences in the resulting CPC population. The progenitor cells differentiated into cardiomyocytes with different mechanisms depending on their cell type.