Endogenous resident multipotent progenitors as cardiac tumor initiating cells

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Cardiac myxomas usually develop in the atria and consist of an acid-mucopolysaccharide-rich myxoid matrix with polygonal stromal cells scattered throughout. These human benign tumors are a valuable research model because of the rarity of cardiac tumors, their clinical presentation and uncertain origin. We assessed whether human adult cardiac stem/progenitor cells (CSCs) give rise to myxoma stromal cells. 23 myxomas were collected and processed/analyzed for the presence of multipotent CSCs. We detected myxoma cells positive for c-kit (c-kit^{pos}) but very rare Isl-1 positive cells. Most of the c-kit^{pos} cells were blood lineage-committed CD45^{pos}/CD31^{pos} cells. However, c-kit^{pos}/CD45^{neg}/CD31^{neg} cardiac myxoma cells expressed stemness and cardiac progenitor cell transcription factors. Approximately $\leq$10% of the c-kit^{pos}/CD45^{neg}/CD31^{neg} myxoma cells also expressed calretinin, a characteristic of myxoma stromal cells. *In vitro,* the c-kit^{pos}/CD45^{neg}/CD31^{neg} myxoma cells secrete chondroitin-6-sulfate and hyaluronic acid, which are the main components of gelatinous myxoma matrix *in vivo*. *In vitro*, c-kit^{pos}/CD45^{neg}/CD31^{neg} myxoma cells have stemness properties being clonogenic, self-renewing and sphere forming. They exhibited abortive cardiac differentiation potential with significant changes in their mRNA/microRNA transcriptome compared to c-kit^{pos}/CD45^{neg}/CD31^{neg} CSCs isolated from normal myocardial tissue. Importantly, myxoma-derived CSCs but not normal myocardium-derived CSCs seed human myxoma tumors in xenograft's experiments in NOD/SCID mice. In conclusion, myxoma-derived c-kit^{pos}/CD45^{neg}/CD31^{neg} fulfill the criteria expected of atrial myxoma-initiating stem cells. The transcriptome of these cells indicates that they belong to or are derived from the same lineage as the atrial multipotent c-kit^{pos}/CD45^{neg}/CD31^{neg} CSCs. Taken together these data suggest that human myxomas are the first-described CSC-related human cardiac disease.