Identification and characterization of progenitor populations in the human adult heart

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

I. **Sandstedt J**, Jonsson M, Lindahl A, Jeppsson A, Asp J. C-kit+ CD45- cells found in the adult human heart represent a population of endothelial progenitor cells. *Basic Res Cardiol*. 2010 Jul;105(4):545-56

II. **Sandstedt J**, Jonsson M, Dellgren G, Lindahl A, Jeppsson A, Asp J. Human C-kit+CD45- cardiac stem cells are heterogeneous and display both cardiac and endothelial commitment by single-cell qPCR analysis. *Biochem Biophys Res Commun*. 2014 Jan 3;443(1):234-8

III. **Sandstedt J**, Jonsson M, Kajic K, Sandstedt M, Lindahl A, Dellgren G, Jeppsson A, Asp J. Left atrium of the human adult heart contains a population of side population cells. *Basic Res Cardiol*. 2012 Mar;107(2):255

IV. **Sandstedt J**, Jonsson M, Dellgren G, Lindahl A, Jeppsson A, Asp J. SSEA-4+ CD34- cells in the human adult heart show molecular characteristics of a novel cardiomyocyte progenitor population. *Submitted.*

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ABSTRACT

Traditionally, the heart has been regarded as a non-regenerative organ. During the last 10 years, this notion has been challenged. By ^{14}C measurements, it was calculated that at the age of 50, about 45% of all cardiomyocytes had formed after birth. An endogenous population of progenitor cells in the heart has been suggested as the source of this regeneration. Until now, most studies have however been conducted in animal models which may not fully reflect the human situation.

The overall aim of this thesis was to add to our knowledge of the identity, distribution and function of endogenous progenitor cells in the human adult heart. In **paper I**, a small population of C-kit+ cells was identified, that could be sub-divided based on expression of the hematopoietic marker CD45. The C-kit+CD45+ population was determined to be of mast cell phenotype whereas the C-kit+CD45- population expressed endothelial associated markers. Differentiation assays showed further endothelial maturation but no evidence of cardiac differentiation. In **paper II**, heterogeneity within the C-kit+CD45- population was further investigated by single cell qPCR. The results indicated that while most of the C-kit+CD45- cells were committed to the endothelial lineage, a minor portion of them could represent cardiac progenitors. In **paper III**, Side Population (SP) cells were identified in the left atrium. The SP phenotype was linked to the MDR1 protein. On gene expression level, the SP cells expressed high levels of *MDR1* as well as stem cell associated genes *C-KIT* and *OCT-4*. Furthermore, the SP could be subdivided based on expression of the hematopoietic marker CD45. The CD45- SP cells had an endothelial profile while the CD45+ SP cells were neither committed to the endothelial, nor the cardiomyogenic lineage. In **paper IV**, expression of SSEA-1, 3 and 4 was investigated. All SSEAs were expressed at variable levels. The SSEA-1+ population was determined to be of hematopoietic origin. Of the SSEA-4+ cells, some co-expressed CD34. In right atrium, the SSEA-4+CD34- population displayed a high expression of cardiomyocyte genes. By immunohistochemistry, SSEA-4+ cells were identified both within and outside the myocardium.

In conclusions, in the present thesis, three different cell populations with characteristics were isolated from human cardiac biopsy material. One C-kit+CD45- population that consisted of both endothelial and cardiac committed progenitors. SP cells where the CD45- fraction showed evidence of endothelial commitment and SSEA-4+CD34- cells that showed signs of cardiac commitment.

Keywords: Cardiac progenitor cells, heart, C-kit, Side Population, Stage Specific Embryonic Antigens, FACS
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