

Stem cells in the adult heart

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, fredagen den 17 nov 2017, klockan 13:00

av **KRISTINA VUKUSIC**

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Avhandlingen baseras på följande delarbeten

- I. High density sphere culture of adult cardiac cells increases the levels of cardiac and progenitor markers and shows signs of vasculogenesis
Vukusic K, Jonsson M, Brantsing C, Dellgren G, Jeppsson A, Lindahl A. and Asp J.
Bio Med Research International 2013; 696837
- II. Left atrium of the human adult heart contains a population of side population cells
Sandstedt J, Jonsson M, **Kajic K**, Sandstedt M, Lindahl A, Dellgren G, Jeppsson A and Asp J. *Basic research in cardiology* 2012 Mar; 107(2):255
- III. Physical exercise affects slow cycling cells in the rat heart and reveals a new potential niche area in the atrioventricular junction
Vukusic K, Asp J, Henriksson HB, Brisby H, Lindahl A and Sandstedt J.
Journal of Molecular Histology 2015 Oct; 46(4-5):387-98
- IV. Atrioventricular junction of the human adult heart harbours stem cells, different stages of cardiomyocytes and shows signs of hypoxia, proliferation and migration
Vukusic K, Jansson M, Jonsson M, Sandstedt M, Oldfors A, Jeppsson A, Dellgren G, Lindahl A and Sandstedt J.
in Manuscript

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR BIOMEDICINE**



Stem cells in the adult heart

- 3D culture, isolation of Side Population cells and search for a stem cell niche

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Abstract

Cardiac tissue shows a poor regenerative capacity. From 2003 reports, mostly based on animal models, have showed existence of stem cells also in the heart. Using ^{14}C measurements, a slow but steady turnover of the cardiac cells was shown in humans, around 1%/year. As a source for this regeneration endogenous stem cells have been suggested.

The aim of this thesis was to identify, isolate and characterize cardiac stem cells and to find their niche. Therefore, in **Study I** a new “High Density Sphere” 3D culture system was adopted where cardiac- and progenitor biomarker levels increased over time. In **Study II** Side Population progenitors were isolated from the left human atria. In **Study III** the distribution of label retaining cells was investigated, throughout the adult rat heart and a region in the Atrio Ventricular junction (AVj) was proposed as a potential stem cell niche. To assess translatability human AVj was explored in **Study IV**. The concomitant appearance of all of the selected stem cell biomarkers in the AVj indicated that the normal human heart also harbors a potential stem cell niche which to our knowledge has not been described previously. The location of these findings in the humans coincides with the same region in rat hearts.

In conclusion we propose a new, 3D *in vitro* system for studies of cardiac cell phenotypes, identified Side Population cells and found an anatomic site, with features of a stem cell niche in rats and humans. The function of these potential niches is important to investigate in future. With these findings, we hope to contribute to better understanding of basic concepts of cardiac regeneration; an important step towards improved future therapies for patients.

Keywords: Heart, Cardiac stem cells, Stem cell niche, Atrio Ventricular junction, Side Population, 3D culture