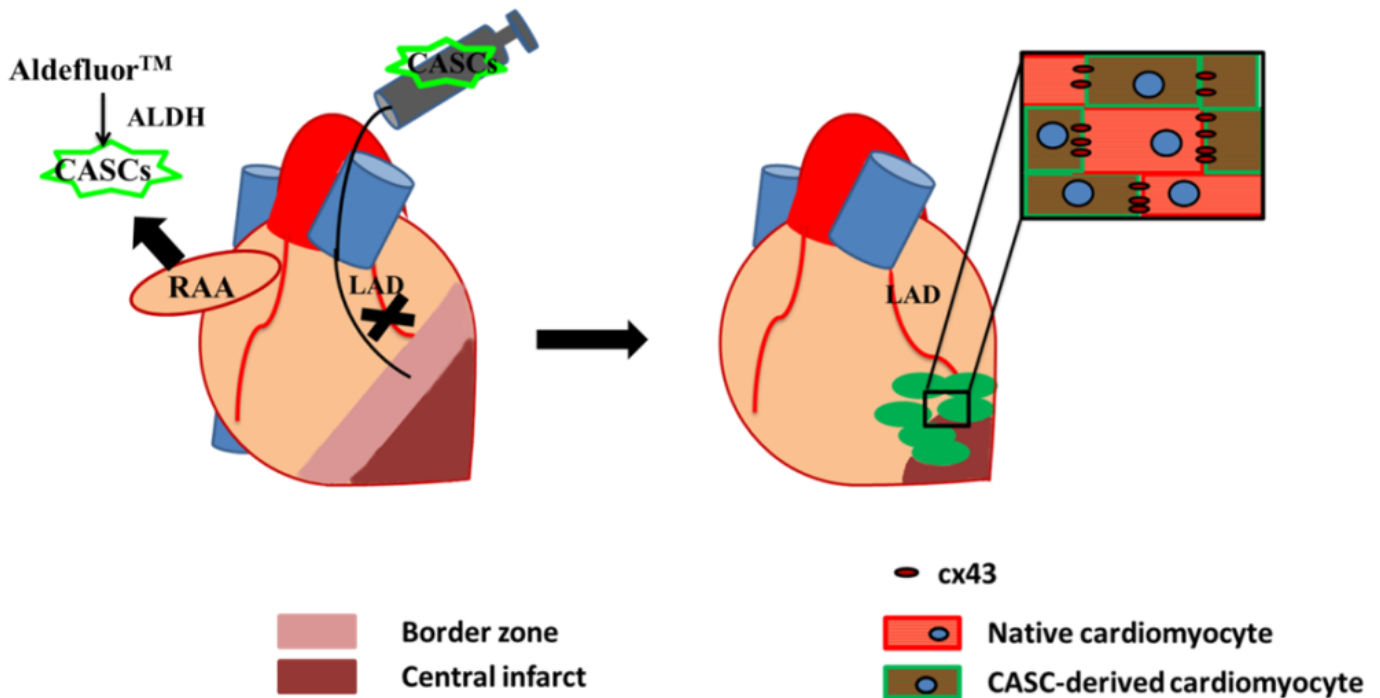


Cardiac atrial appendage stem cells: bright cells for a bright future for patients with ischemic heart disease

Ischemic heart disease is still one of the major causes of global morbidity and mortality. Although significant improvements in medical and surgical treatments have been accomplished over the last few decades, these are still not able to repair the heart and are thus somehow no more than palliative care. Stem cells are very promising to replace the lost cardiac muscle with functional healthy tissue, since they are able to differentiate into specialized cells. Animal experiments showed beneficial effects for stem cells from various sources, such as bone marrow, peripheral blood, skeletal muscle and adipose tissue. Unfortunately, first clinical studies on humans revealed only minor improvements in heart function, which could be explained by the limited differentiation towards cardiomyocytes by these stem cells. The discovery of stem cell in the adult heart itself brought new hope, as these cardiac stem cells were thought to be predestined to form heart muscle cells. Different cardiac stem cell types were investigated for cardiac repair, however, also their cardiomyogenic differentiation is now being questioned.

Our research group identified yet another stem cell type in the adult human heart, called the cardiac atrial appendage stem cell (CASC). These CASCs are isolated based on a high aldehyde dehydrogenase (ALDH) enzyme activity. Only ALDH^{bright} cells convert the substrate AldefluorTM into a green fluorescent product. These brightly green CASCs can then be sorted by flow cytometry and grown in culture until used for transplantation. In contrast to the other stem cell types described above, CASCs do show a strong differentiation potential towards heart muscle cells. Therefore, the safety and therapeutic efficacy of CASC transplantation was recently explored in a minipig myocardial infarction model. CASCs were isolated from right atrial appendages of female Göttingen minipigs, labeled with green fluorescent protein and expanded up to clinically relevant cell numbers. Myocardial infarction was induced in the minipigs by a 2h ligation of the left anterior descending coronary artery. Afterwards, CASCs animals were treated with their own CASCs, while the control group received sham treatment. CASC were administrated via trans-endocardial catheter-based injections in combination with three-dimensional electromechanical mapping of the heart. Targeted injections of CASCs into the infarct border zones leads to a better integration of the cells in the heart muscle with a better clinical outcome.



CASCs preserve cardiac function after myocardial infarction via myocardial regeneration.

After 2 months, heart function was better preserved in CASCs animals compared to the control group. Infarct size was also smaller in the CASC pigs compared to the controls, suggesting regeneration of the lost heart muscle. When examining the heart muscle of the CASC transplanted pigs, on average 19% of the transplanted cells were still detectable in the infarct regions. Furthermore, 98% of these engrafted cells differentiated towards cardiomyocytes. Specialized connections, called gap junctions, could be detected between CASC-derived cardiomyocytes and native heart muscle cells, indicating functional integration of CASC cardiomyocytes into the existing cardiac muscle. Bad communication between transplanted cells and native heart muscle can lead to heart rhythm problems. However, no cardiac arrhythmias could be detected in CASC-transplanted animals, which is an important first safety confirmation.

In conclusion, autologous CASC transplantation improves cardiac function based on myocardial repair in a minipig MI model. Further studies should address the safety and long-term therapeutic effect of CASC transplantation after MI.

CASC were isolated from the right atrial appendage of minipigs based on a high ALDH activity. The cells were labeled with green fluorescent protein and expanded. Myocardial infarction was induced by a 2h ligation of the left anterior descending coronary artery, after which CASCs were transplanted trans-endocardially into the infarct border zones. It was shown that CASCs preserve

myocardial function based on a high cell retention and extensive cardiomyogenic differentiation. Functional integration into the host myocardium was demonstrated by cx43 expression between CASC-derived cardiomyocytes and native cardiomyocytes.

Publication

[Cardiac atrial appendage stem cells engraft and differentiate into cardiomyocytes in vivo: A new tool for cardiac repair after MI.](#)

Fanton Y, Robic B, Rummens JL, Daniëls A, Windmolders S, Willems L, Jamaer L, Dubois J, Bijmens E, Heuts N, Notelaers K, Paesen R, Ameloot M, Mees U, Bito V, Declercq J, Hensen K, Koninckx R, Hendrikx M

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