3. Doppelstunde ESF II 2018

1.3. Was ist eine Herzstammzelle?

1.5. Wie entsteht das Herz in Säugetieren?

1.6. Wie entstand das Herz im Laufe der Evolution?

1.4. Wo befinden sich Herzstammzellen im Herzen?

1.4.1. Wie kommen die Stammzellen in das Herz?

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1.5. → 1.6. → 1.4. → 1.3. → 1.7.

3. Doppelstunde ESF II 2018

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1.7. Kann man Stammzellen für die Therapie von Herzerkrankungen einsetzten?

1.4.1. Wie kommen die Stammzellen in das Herz?

Woher kommen die CVPCs im Laufe der Ontogenese?

Die ersten CVPCs findet man im Primitivstreifen (primtive streak) am Beginn der Gastrulation.

Diese Zellen exprimieren Brachyury (T), Eomesodermin (Eomes) und Mesp1.

Sie wandern durch den Primitivstreifen beiderseits in die distale ventrale Region des viszeralen (splanchnic) lateralen Mesoderms (Splanchnopleura) und von dort zur anterioren lateralen Position auf der Höhe des Nodes (Hensens node beim Huhn). → „Erstes Herzfeld“

Zellen in den zuerst bilateralen ersten Herzfeldern exprimieren Nkx2.5, Gata4, Tbx5, Tbx20 und Hand1 und bereits das muskelspezifische Intermediarfilamentprotein Desmin.

Die beiden Herzfelder fusionieren zuerst anterior und dann vollständig, wobei durch distal – proximales „Einrollen“ des Gewebes die primitive Herzröhre entsteht.

Das schlauchförmige Herz windet sich so, dass beide Enden des Schlauches auf der vorderen (anterioren) des Herzens zu liegen kommen = rostrale/craniale Seite des Embryos.

Gleichzeitig kommen Zellen aus den sekundären Herzfeld hinzu und beteiligen sich an der Ausbildung aller Teile des Herzens. Parallel wandern Zellen von einer transienten organähnliche Struktur , dem Proepikardium , ein und bilden das unter Anderem das Perikardium und die Koronargefäße aus.

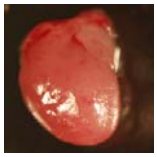
Schlussendlich wandern Neuralleistenzellen in den „outflow tract“ ein und diese führen zur Fertigstellung des Vierkammerherzens mit all seinen Septen, Klappen und venösen und arteriellen Zugängen.

1.3. Was ist eine Herzstammzelle?

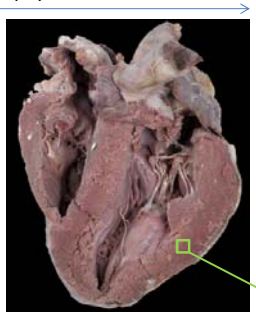
Hypertrophy

doi: 10.1073/nas.0609628104

E13.5

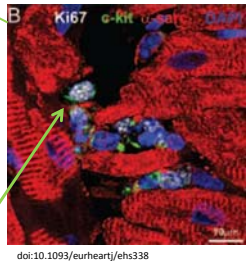


N2 Heart (mouse)



http://www.bioedonline.org

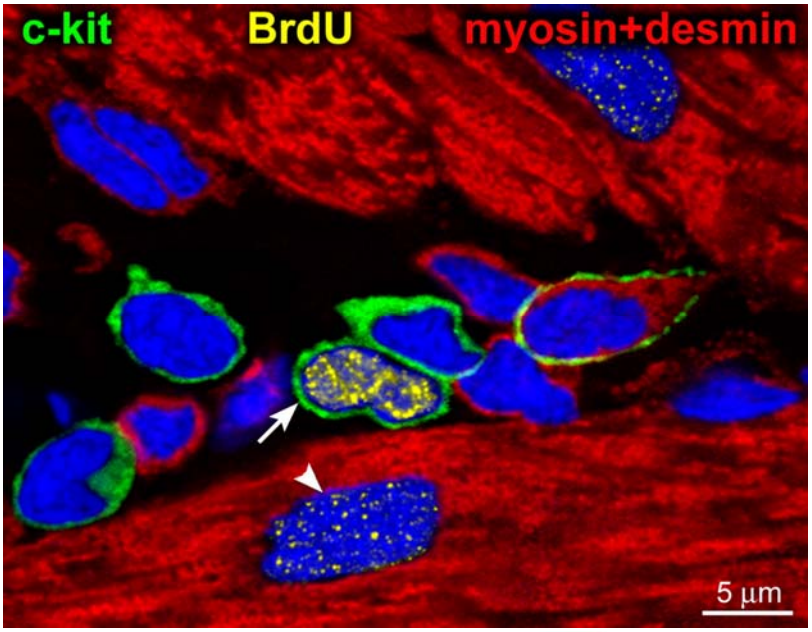
Adult Heart (sheep)



doi:10.1093/eurheartj/ehs338

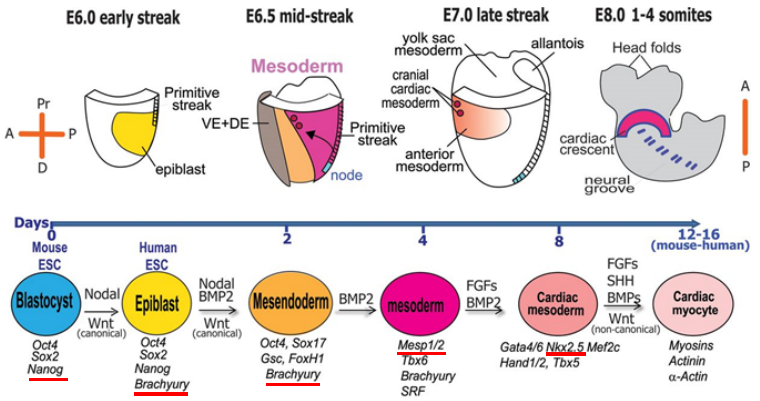
Cardiac stem cells in the „interstitial“ space

(human)



http://circres.ahajournals.org/content/110/11/1403

1.3.6. Zelluläre Stadien im Laufe der Kardiogenese und die sie unterscheidenden Molekularen Aspekte



DOI: http://dx.doi.org/10.1093/cvr/cvs270

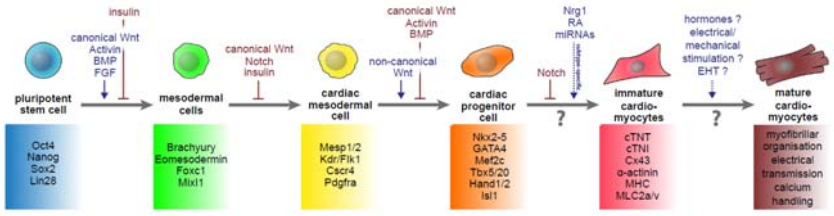
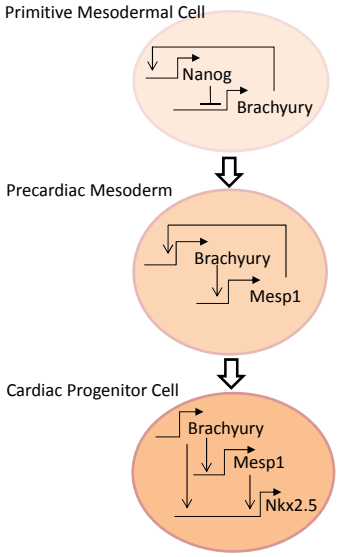
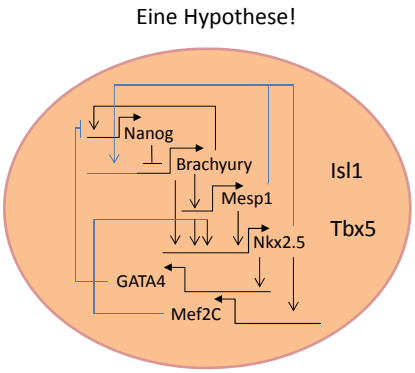


Figure 1: *In vivo* and *in vitro* cardiogenesis. Sequential steps in cardiac differentiation *in vitro* from pluripotent stem cells to functional cardiomyocytes. Positive (blue) and negative (red) acting signals influence cardiomyogenesis *in vitro* and display parallels to embryonic development. Early mesodermal cells are induced by canonical Wnt, activin, BMP and FGF signaling and inhibited by insulin. Diversification to cardiac mesodermal cells can be inhibited by canonical Wnts, notch and insulin signaling. Cardiac progenitor cell specification is promoted by non-canonical Wnts and negatively regulated by canonical Wnt, activin and BMP signaling. Notch signaling promotes cardiac progenitor cell differentiation and inhibits cardiomyocyte differentiation. Neurogenin 1 (Ngn1), retinoic acid (RA) and specific microRNAs (miRNAs) direct cardiomyocyte subtype-specific differentiation. Structural and functional maturation is not well understood. Maturation might be provoked by hormones, electrical and mechanical stimulation and organization in 3D engineered heart tissues (EHTs). Typical markers and characteristics for the different cell types are indicated.

http://dx.doi.org/10.4172/2155-9880.S11-008

Transkriptionelle Regulation in Vorläufer und Stammzellen während der Embryogenese und in adulten Herzstammzellen





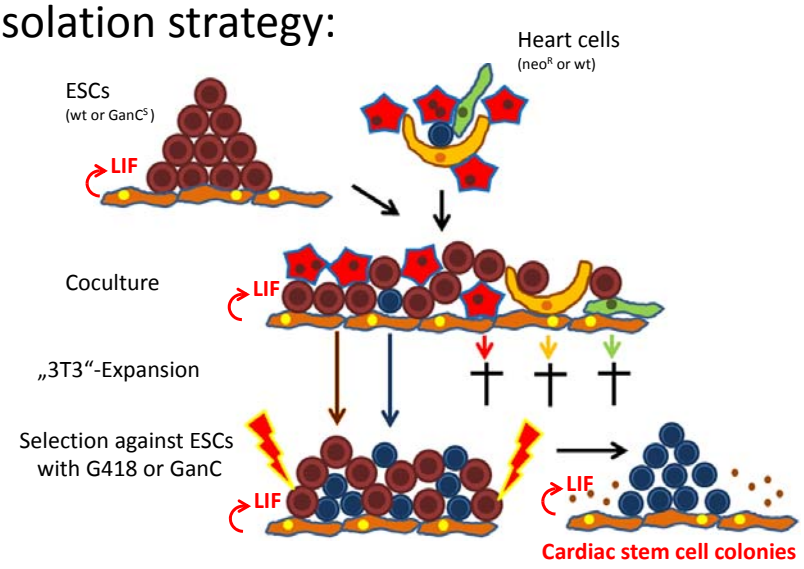
1.3.7. Wie kann man CSCs ohne FACS isolieren?

Mimicry of the cardiac stem cell niche

Requirements:	Known Facts:	In Vitro Niche Conditions:
Isolation procedure for extremely rare cells.	• Isolated somatic stem cells succumb to **anoikis**. • **ESCs** in colonies **support** each other to survive stress.	**Temporal presence** of **ESCs** at the beginning of the isolation procedure.

Culture conditions maintaining the phenotype* during isolation and continuous culture.
(*self-renewal and differentiation potential)
	• **Interstitial cardiac fibroblasts** are most likely part of the cardiac stem cell niche.
	• **Leukemia inhibitory factor**
	  • supports proliferation of ESCs and NSCs.
	  • is expressed in fetal and neonatal hearts.
		Continuous presence of
		• **Fibroblasts,** mimicing a cardiac stem cell niche.
		• **Leukemia inhibitory factor** supporting proliferation of cardiac stem cells.

Isolation strategy:



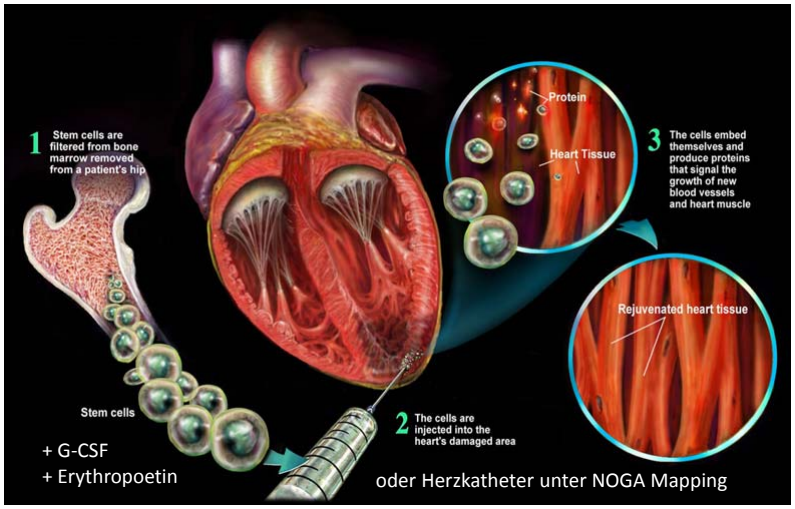
1.7. Kann man Stammzellen für die Therapie von Herzerkrankungen einsetzten?

Stem cell therapy of acute myocardial infarction (AMI)

Hypothetical resources:

- Embryonic stem cells ESCs → too risky because of tumor formation, ethical issues
- Induced pluripotent cells iPSC → too risky because of tumor formation
- Induced cardiomyocytes iCMCs → one pre-clinical study; too early for evaluation
- Cardiac stem cells CSCs → not available in sufficiently large quantities
- Induced cardiac stem cells iCSCs → -"-
- Adipose tissue-derived mesenchymal stem cells ADSCs → seems not to differentiate properly but may provide growth factors
- Bone marrow stem cells BMCSs / HSCs → safe, but are they suitable for cardiac therapy?

„How stem cell therapy works":



http://adultstemcells.web.unc.edu/files/2013/12/heart.jpg

Meta-analysis of stem cell therapy after AMI

International Journal of Cardiology 177 (2014) 764–770

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Effectiveness and safety of selected bone marrow stem cells on left ventricular function in patients with acute myocardial infarction: A meta-analysis of randomized controlled trials

Bei Liu [a,b], Chong-Yang Duan [c], Cheng-Feng Luo [d], Cai-Wen Ou [b], Kan Sun [e], Zhi-Ye Wu [a], He Huang [d], Chuan-Fang Cheng [d], Yun-Peng Li [a], Min-Sheng Chen [a,b,*]

Circulation Research

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INTEGRATIVE PHYSIOLOGY

Cardiac Stem Cell Treatment in Myocardial Infarction

A Systematic Review and Meta-Analysis of Preclinical Studies

Peter Paul Zwetsloot, Anna Maria Dorothea Végh, Sanne Johanna Jansen of Lorkeers, Gerardus P.J. van Hout, Gillian L. Currie, Emily S. Sena, Hendrik Gremmels, Jan Willem Buikema, Marie-Jose Goumans, Malcolm R. Macleod, Pieter A. Doevendans, Steven A.J. Chamuleau and Joost P.G. Sluijter

DOI: http://dx.doi.org/10.1161/CIRCRESAHA.115.307676

Published: April 15, 2016

Bone marrow cell therapy of myocardial infarction in humans

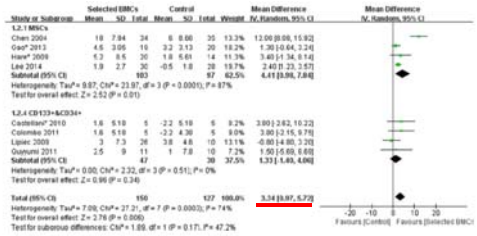


Fig. 6. Forest plot of mean difference (MD, with 95% confidence interval [CI]) in left ventricular ejection fraction (LVEF) comparing different cell types in the included trials. Subgroups were divided into (A) BMMSCs and (B) CD34 + combined with CD133 + .

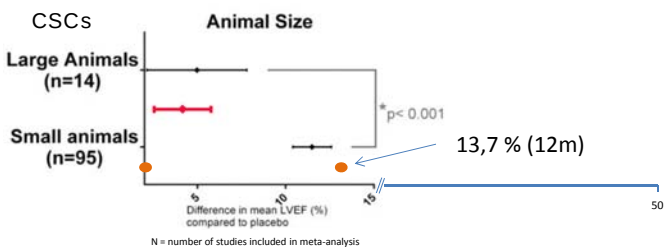
Cardiac stem cell therapy of myocardial infarction in animals

CSCs

BMCs

Human (n=10)

Human (n=2) → ?



N = number of studies included in meta-analysis

Literatur zur AMI-BMSCs und CSC Therapie

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Conclusion

- LVEF is normally between 55 and 70% and live-threatening if below 35 to 40%.
- Acute myocardial infarction (AMI) causes a LVEF well below 35%.

- Clinical studies with different bone marrow-derived cell populations resulted in ~ + 3.3% LVEF
- Animal experiments with different populations of cardiac stem cells
- resulted in ~ + 4.7% LVEF (+12% in small animals)

Take home message:

- Currently CSCs are not superior to BMCs in large animals (and humans).
- Both cell types cannot increase the quality of life after acute myocardial infarction.
- → Alternative strategies should be evaluated

Siehe auch: Guidelines for Stem Cell Research and Clinical Translation der ISSCR Guidlines

http://www.isscr.org/home/about-us/news-press-releases/2016/2016/05/12/isscr-releases-updated-guidelines-for-stem-cell-research-and-clinical-translation