Molecular Mechanisms of Cardiogenesis and PERHAPS of Cardiovascular Regeneration

VO SS2022 7. 4. 2022

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You find the lecture on my homepage /
Sie finden die Vorlesung und Lernunterlagen auf meiner Homepage unter dem URL

http://homepage.univie.ac.at/georg.weitzer/

MEDICAL UNIVERSITY OF VIENNA

Georg Weitzer
Zentrum für Medizinische Biochemie

2

Central Hypothesis - on which this lecture is based:

Understanding how molecular mechanisms contribute
to the development,
to the function,
to homeostasis,
to various diseases,
to ageing, and finally
to failure
of the heart, will help to understand the molecular mechanisms which contribute to the regeneration of the heart. – and perhaps migth be harrnessed for therapy.

Credit: The Olson LAB at UT Southwestern, Texas

Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair.
Xin M[1], **Olson EN**, Bassel-Duby R. Nat Rev Mol Cell Biol. 2013 Aug;14(8):529-41. doi: 10.1038/nrm3619. Epub 2013 Jul 10.

Inhalt / Content

- Entstehung, Anatomie und Funktionsweise des Herzens
  - Aufbau und Funktionsweise des Herzens
  - Entstehung des Herzens im Laufe der Embryogenese
  - Molekulare Regulation der Herzentstehung und Homöostase
- Die Stammzellen des Herzens
- Genetische (und epigenetische) Veränderungen, die zu Erkrankungen des Herzens führen und auf die Funktion der Stammzellen verweisen
- Stammzelltherapie des Herzens

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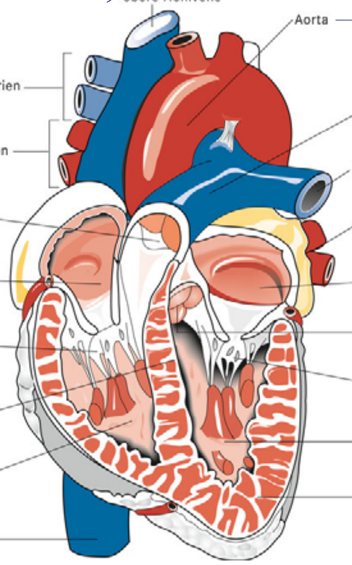
Aufbau des Herzens / Composition of the heart



https://www.duden.de/_media_/full/H/Herz-201020491596.jpg

Reizleitungssystem des Herzens / Cardiac pacemaker system

Sympathische und Parasympathische Nervensystem

Ventrale Ansicht / view

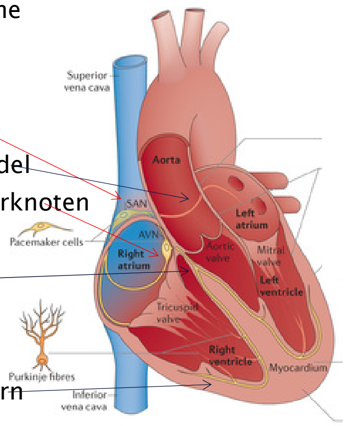
Sinusknoten

Bachmanns Bündel

Atrio-Ventrikulärknoten

Hiss-Bündel

Purkinje-Fasern



Nature Reviews | Molecular Cell Biology

Nat Rev Mol Cell Biol. 2013 Aug;14(8):529-41. doi: 10.1038/nrm3619. Epub 2013 Jul 10.
Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair.
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Die Versorgung des Herzens mit Blut / the supply of the heart with blood via the coronary artheries / Rechte und linke Herzkranz Arterie

Ventrale Ansicht (von vorne)

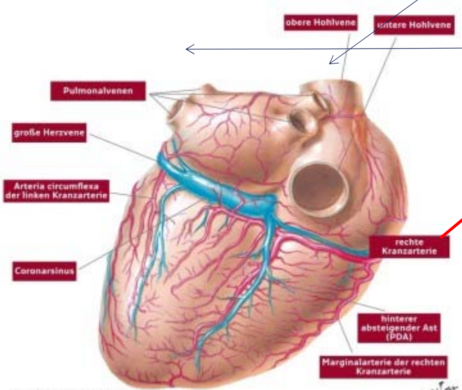
Das Herz von unten = dorsal (hinten)

Aorta

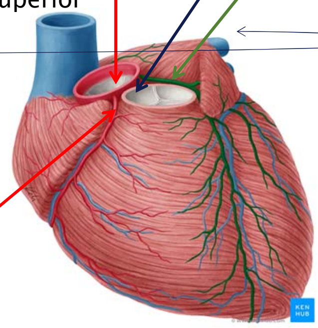
Vena cava superior

Pulmonararterie

linke Herzkranzarterie

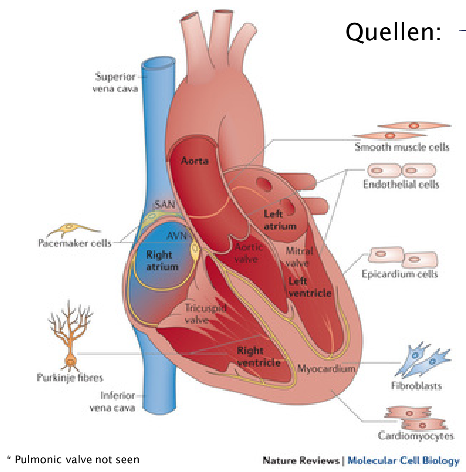


Quelle: **herzinfarkt**, Primar Dr. Georg Gaul
Verlag Holzhausen GmbH, www.verlagholzhausen.at



Aufbau des Säugetierherzens und die darin vorkommenden wichtigsten Zelltypen

Ventrale Ansicht



Nat Rev Mol Cell Biol. 2013 Aug;14(8):529-41. doi: 10.1038/nrm3619. Epub 2013 Jul 10. **Mending broken hearts: cardiac development as a basis for adult heart regeneration and repair.** Xin M[1], Olson EN, Bassel-Duby R.

Quellen:
- Erstes Herzfeld = Laterales Mesoderm
- Zweites Herzfeld = Rachen Mesoderm
- Craniale Neuralleistenzellen
- Proepicardiales Organ
- Mesangioblasten der Aorta
- Knochenmarksstammzellen (?)

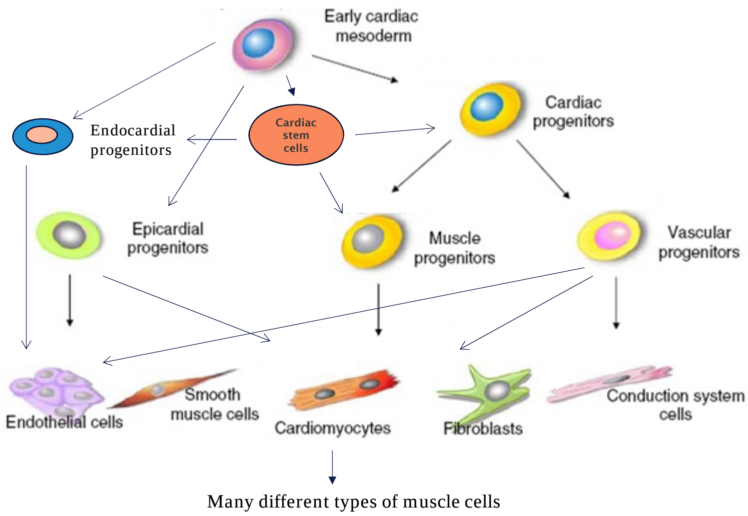
↓

- Epikardium
- Myokardium
- Endokardium
- Herzklappen (4*)

↓

Schrittmacherzellen
Atriale Kardiomyozyten
Ventrikuläre Kardiomyocyten
Kardiale Fibroblasten
Endothelzellen, glatte Muskelzellen
Telozyten, Perizyten
Mastzellen, Makrophagen, Treg cells .
Herzstammzellen

Die verschiedenen Zelltypen des Herzens / the different types of heart cells



2022: Abstammungshypothese, bereits überholt.

Modified from Alessandra Morettis Homepage: http://www.med1.mri.tum.de/ru/node/169

Die zelluläre Zusammensetzung des Herzens /
The cellular composition of the heart

- Das Herz besteht aus ca. 20 verschiedenen Zelltypen
- ~ 20% davon sind Kardiomyozyten; diese nehmen 70 - 80% des Raumes ein
- > 50% sind Fibroblasten, diese nehmen nur ~ 20% des Raumes ein
- ~30% andere Zelltypen
- Häufigkeit der Herzstammzellen: 1:30.000 -1:500.000

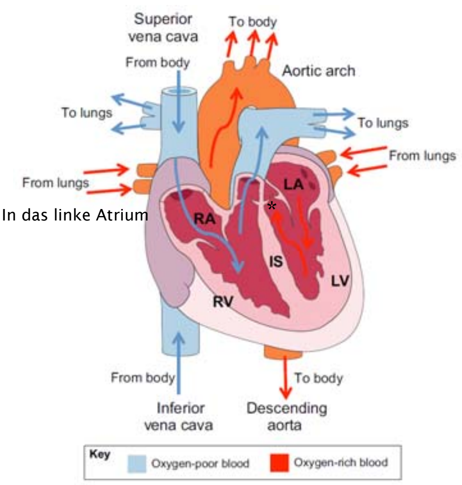
1. take home message:

There are at least 20 different types of cells in the heart, and only 20% are cardiomyocytes.

Entstehung, Anatomie und Funktionsweise des Herzens

- Aufbau des Herzens
- **Funktionsweise des Herzens / Mode of operation**
- Entstehung des Herzens
- Molekulare Regulation der Herzentstehung und Homöostase

Funktionsweise des Herzens / Mode of operation



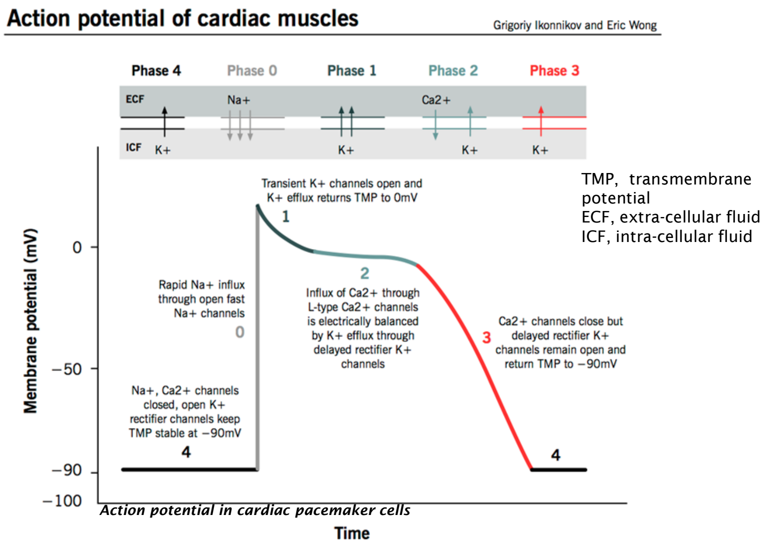
* Hinter Lungenarterie vorbeigehend

Abbildung aus :http://dev.biologists.org/content/143/8/1242

Fig. 1. The adult mammalian heart. The adult mammalian heart is made up of four chambers: the right and left ventricles (RV and LV) and right and left atria (RA and LA). The ventricles are separated by the interventricular septum (IS).
The vena cava and the aorta carry the flow of blood to and from the heart, respectively. Blood low in oxygen (blue arrows) from the different tissues is collected into the right atrium via the superior and inferior vena cava and flows to the lungs through the right ventricle. Oxygenated blood (red arrows) from the
lungs flows into the left atrium and is pumped into the aorta by the left ventricle.
This system allows oxygenated and non-oxygenated blood to be completely separate.

Link to Youtube lecture: https://www.khanacademy.org/science/health-and-medicine/circulatory-system/circulatory-system-introduction/v/flow-th

Die Herzmuskelzellenkontraktion in einer einzelnen Zelle betrachtet:

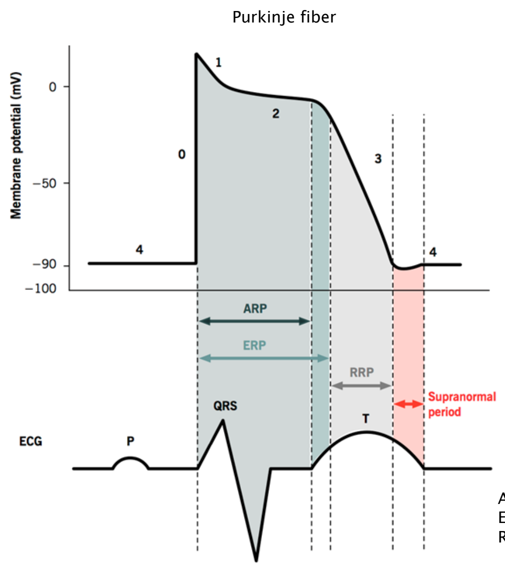


TMP, transmembrane potential
ECF, extra-cellular fluid
ICF, intra-cellular fluid

Ruhephase (4) – Depolarisation (0) - Frühe Repolarisation (1) – Ruhephase (2) - Repolarisation (3)

Zusammenhang zwischen Aktionspotentialen und EKG

Purkinje fiber



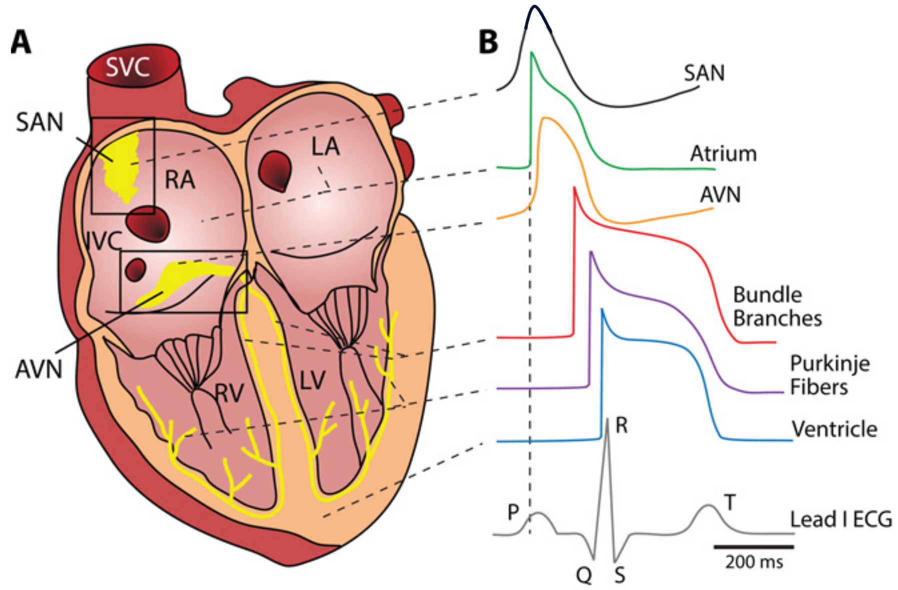
Gene für Ionenkanalproteine

(80 bis 100 Gene)

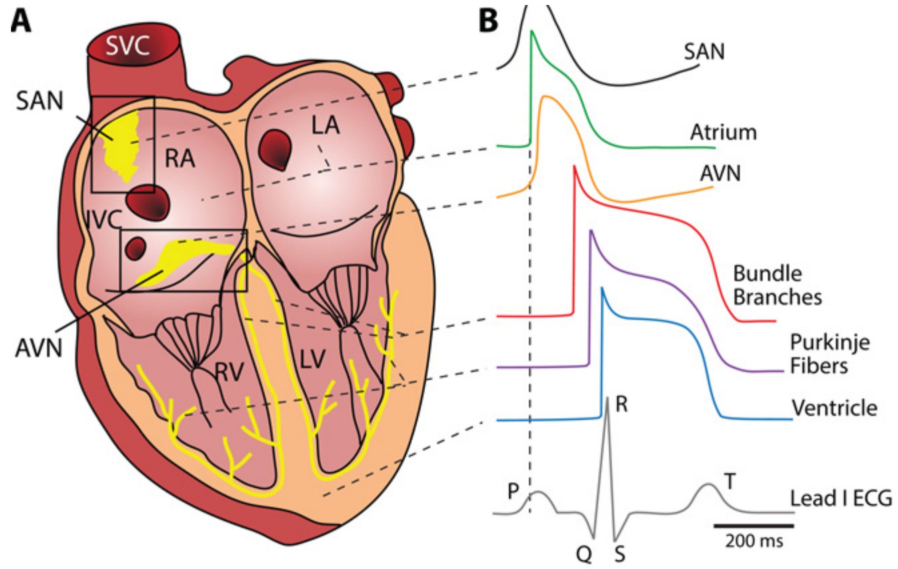
Cav1.3, Cav3.1, Cavα2δ2, Cx40, Navβ1, Kv1.3, Kv1.5, Kv1.6, Kv4.2, Kv4.3, SUR1, KCNE2, KCNE4, KCNE5, SK2, Kir3.1, Kir3.4, TWIK1, TASK1, HCN1, HCN4

Absolute refractory period (ARP)
Effective refractory period (ERP):
Relative refractory period (RRP):

http://www.pathophys.org/physiology-of-cardiac-conduction-and-contractility/

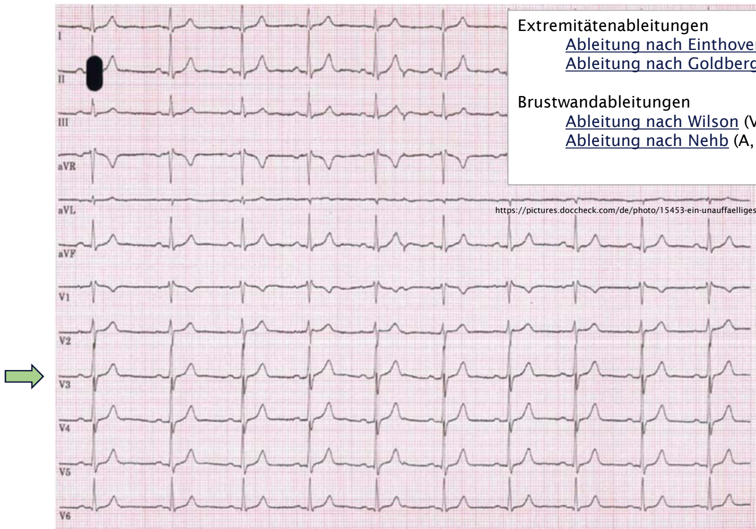


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516287/



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516287/

Wenn alle Zellen des Herzens zusammenwirken



Extremitätenableitungen
- Ableitung nach Einthoven (I, II, III)
- Ableitung nach Goldberger (aVR, aVL, aVF)

Brustwandableitungen
- Ableitung nach Wilson (V1-V6)
- Ableitung nach Nehb (A, I, D)

https://pictures.doccheck.com/de/photo/15453-ein-unauffaelliges-12-kanal-ekg

Zusammenhang zwischen Herzbewegungen und Elektrokardiogramm (link zu Youtube: https://www.youtube.com/watch?v=v3b-YhZmQu8)

2. take home message:

1. There are at least 80 different genes expressed in various cardiomyocytes wich are responsible for the individual action potentials of the different types of cardiomyocytes, and

2. The ECG is the sum of all individal action potentials of all contracting cells.

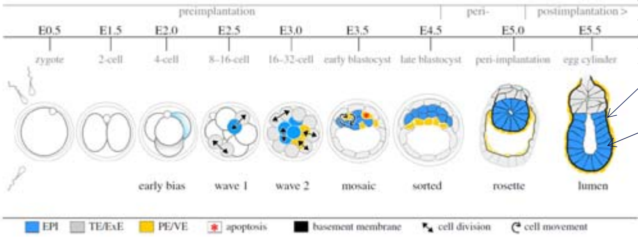
Entstehung, Anatomie und Funktionsweise des Herzens

- Aufbau des Herzens
- Funktionsweise des Herzens
- **Entstehung des Herzens im Laufe der Embryogenese / Development of the heart during embryogenesis**
- Molekulare Regulation der Herzentstehung und Homöostase

From where do all the different cell types in the heart come from?

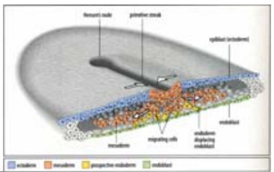
Wie entsteht das Herz während der Embryogenese?

Frühe Embryogenese bei der Maus

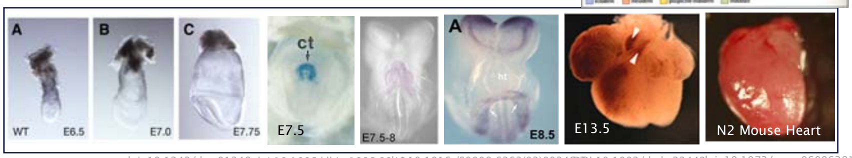


Gastrulation
Maus E6.5:
Node + primitve streak

Huhn/ Hase / Mensch E14



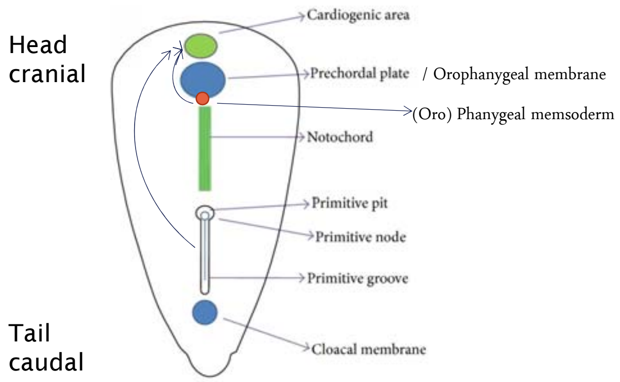
Kardiogenese bei der Maus



doi: 10.1242/dev.01248 doi:10.1006/dbio.1996.0046 doi: 10.1016 /S0008-6363(03)00246-3 DOI 10.1002/dvdy.22449 doi: 10.1073/pnas.060962810

Wo entstehen die ersten Herzzellen? / Where does the heart evolve?

Ventral view

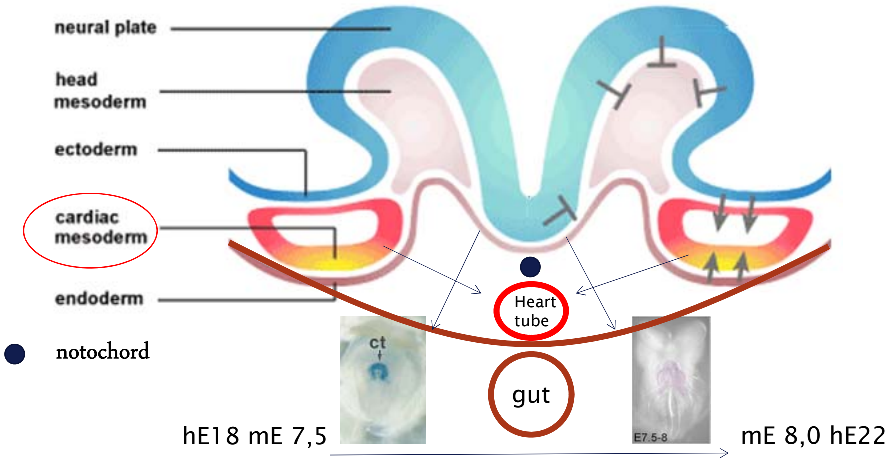


Schematic diagram: http://dx.doi.org/10.1155/2014/636375(1)

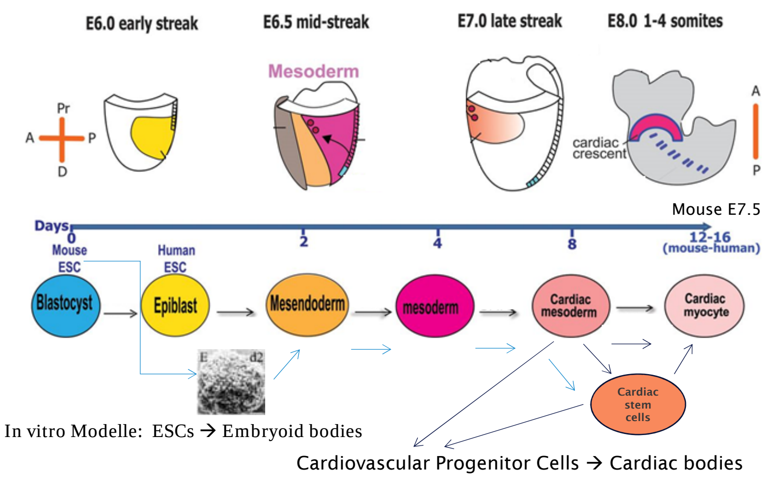
See video: https://www.youtube.com/watch?v=Ouge_rVI2aA

Wo entstehen die ersten Herzzellen? / Where does the heart evolve?

Cranial part of the embryo; transversal view



Stadien der Herzzellenentstehung auf zellulärer Ebene



https://www.researchgate.net/figure/224929158

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

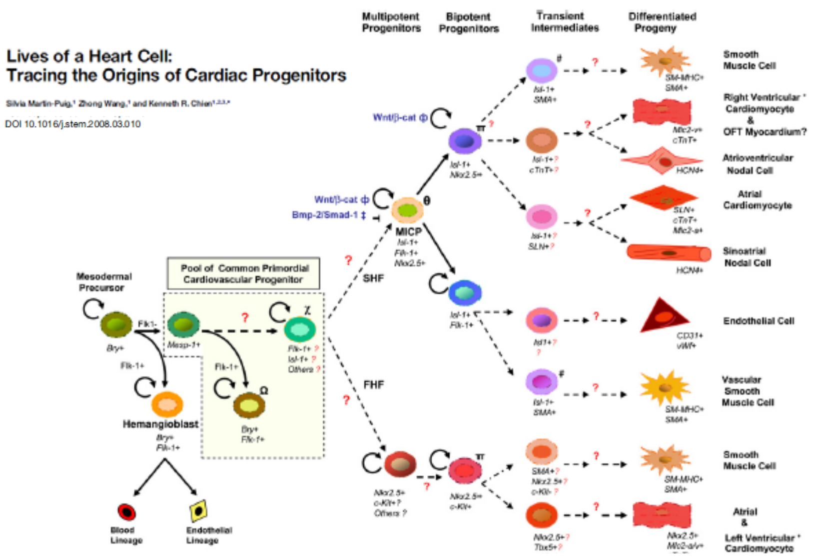
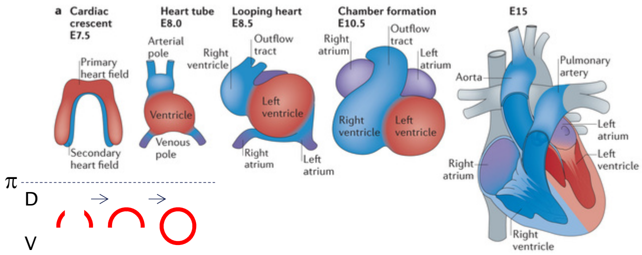


Figure 5. A Working Model of Heart Cell Lineage Diversification with a Proposed Cellular Hierarchy from Multipotent Mesodermal Progenitors

Entwicklung des Herzens während der Embryogenese bei der **Maus**



Nat Rev Mol Cell Biol. 2013 Aug;14(8):529-41. doi: 10.1038/nrm3619. Epub 2013 Jul 10.
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Nature Reviews | Molecular Cell Biology

Article

Single-cell transcriptomic characterization of a gastrulating human embryo

https://doi.org/10.1038/s41586-021-04158-y
Received: 28 July 2020

Richard C. V. Tyser[1,6], Elmir Mahammadov[2,3,4,6], Shota Nakanoh[5], Ludovic Vallier[5], Antonio Scialdone[2,3,4,7] & Shankar Srinivas[1,7]

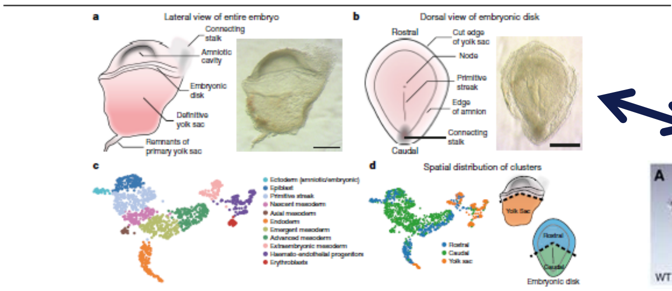
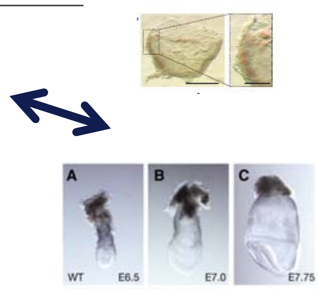


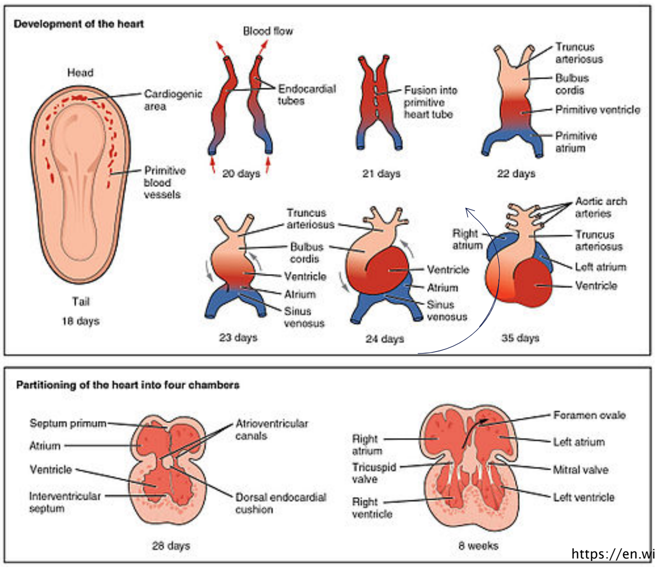
Fig. 1 | Morphological and transcriptional characterization of a CS7 human gastrula. a, Lateral view of the intact CS7 human embryo. Scale bar, 500 µm. **b**, Dorsal view of the dissected embryonic disk showing the primitive streak and node. Scale bar, 500 µm. **c**, Uniform manifold approximation and projection (UMAP) of all the cells computed from genes with highly variable expression. **d**, UMAP and schematics highlighting the anatomical region that cells were collected from (see also Extended Data Fig. 1b).



doi: 10.1242/dev.01248

Cardiac precursors can be identified 16 -19 days after conception.

Entwicklung des Herzens während der Embryogenese beim **Menschen**



For description of the cartoon see
https://courses.lumenlearning.com/suny-ap2/chapter/development-of-the-heart/

https://en.wikipedia.org/wiki/Heart_development

3. take home message:

Evolutionary and developmenal origin of heart cells

1. Splanchnic mesodern → first heart fieled → heart tube
2. Pharyngeal mesoderm → second heart field → poles of the heart tube
3. Neural plate border → cardiac neural crest cells → outflow tract + valves + + conduction system
4. Pronethros→ epicardia organ → epicardium + coronary vessels.

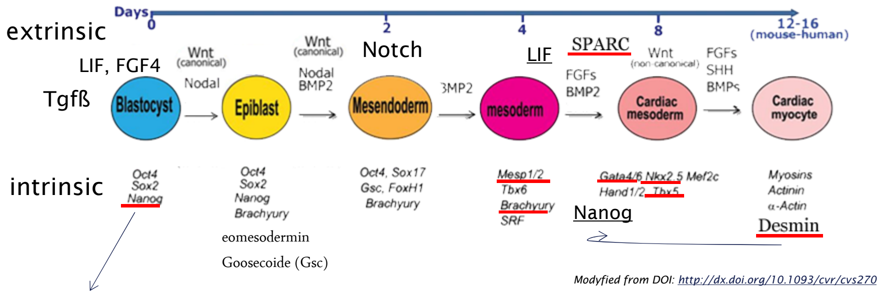
Entstehung, Anatomie und Funktionsweise des Herzens

- Aufbau des Herzens
- Funktionsweise des Herzens
- Entstehung des Herzens
- **Molekulare Regulation der Herzentstehung und Homöostase /**

  molecular regulation of cardiac development and homeostasts

Extrinsische und intrinsische Regulation der Kardiomyogenese?

(Mehr als 400 involvierte Gene bis jetzt gefunden)



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

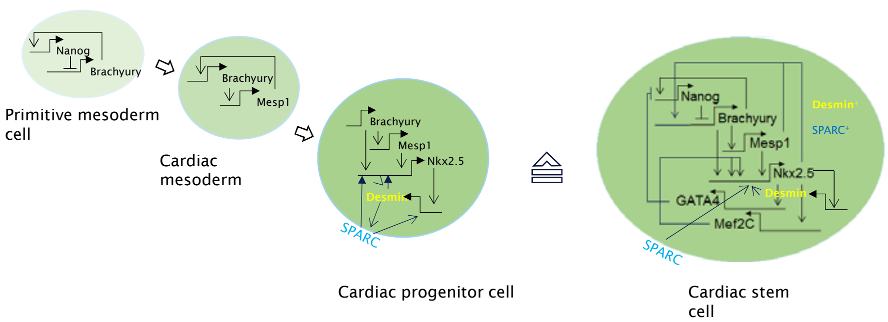
SON-network:

Each TF activates together with the 2 other TFs all 3 genes. → guarantees self renewal

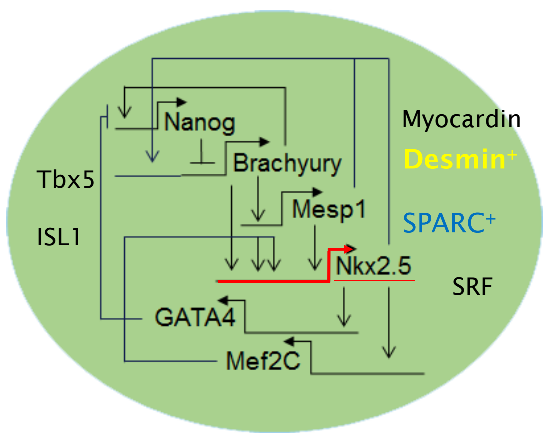
Intrinsic, cell autonomous regulation of cardiomyogenesis

Hirachische Abfolge während der Kardiomyogenese und Netzwerkbildung in adulten Stammzellen

(ein kleiner Ausschnitt des tatsächlichen Geschehens!)



Molekulare Regulation der Herzentstehung und Homöostase



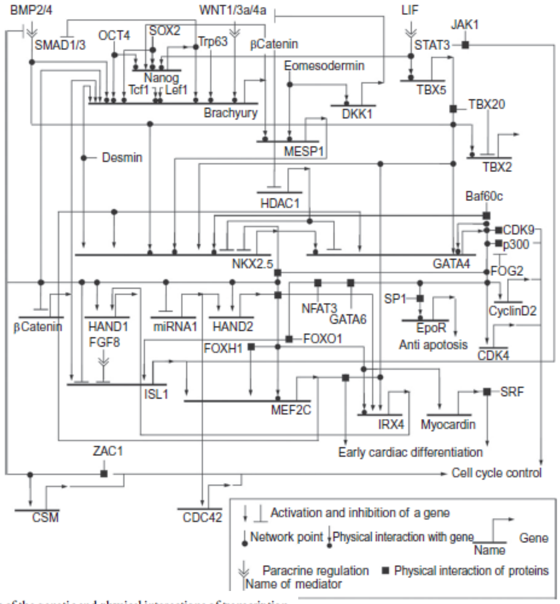


Figure 7.2 Model of a network of the genetic and physical interactions of transcription factors in cardiovascular progenitor cells. This model was inferred from data obtained

Taubenschmidt und Weitzer , 2012

4. take home message:

1. At least 400 genes are involved in the regulation of the heart cell development.
2. Nanog, Brachyury, Eomesodermin and Mesp1 are transiently important.
3. Nkx2.5, GATA4, Tbx5, and Mef2C seems to be at the core of the regulation of cardiac development and also during homeostastis in the adult and ageing heart.

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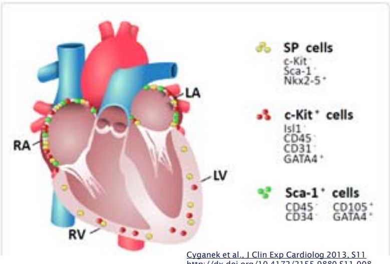
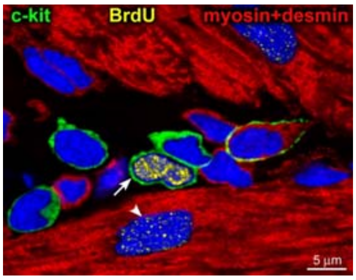
Vorkommen von Herzstammzellen im Herz

1998: Cardiac stem cells in the adult heart



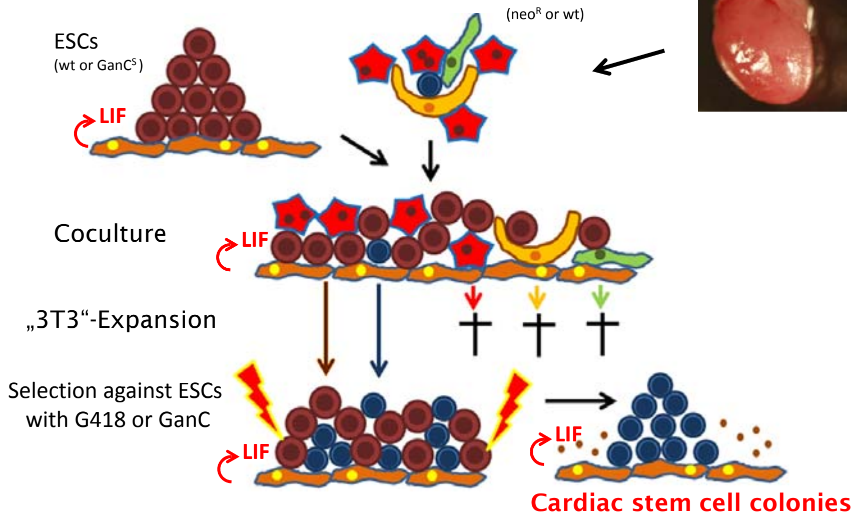
Cyganek et al., J Clin Exp Cardiolog 2013, S11
http://dx.doi.org/10.4172/2155-9880.S11-008

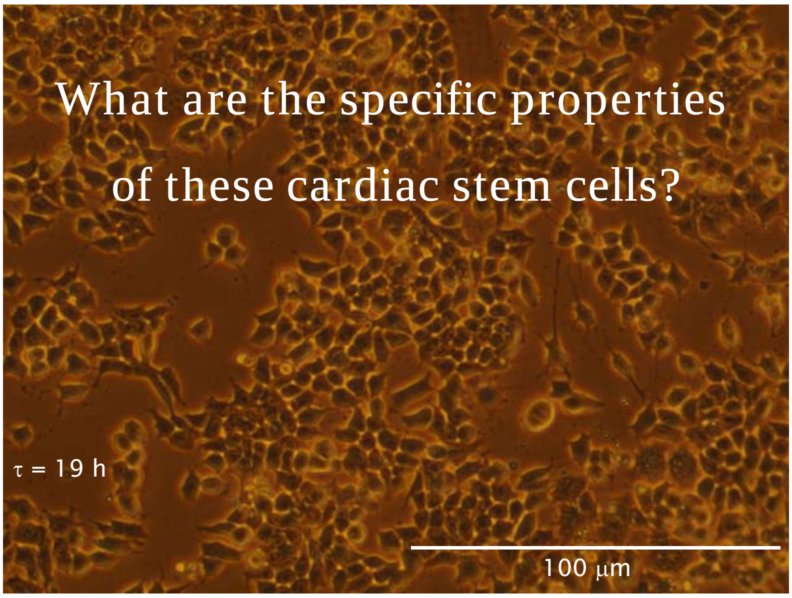


1998, Piero Anversa

- 1:30.000 – 1:500.000 heart cells is a cardiac stem cell.
- can be only isolated by FACS with surface markers also found in other stem cell populations.
- when forced, they differentiate to endothelial cells, smooth muscle cells and spontaneously contracting cardiomyocytes.
- FACS-isolated CSCs are not expandable. The niche conditions are not known.
- since not expandable ex vivo, they cannot be used for cell therapy so far. -with one exception:
- Cardiosperes: Aggregated populations of heart cells containing CSCs and their niche

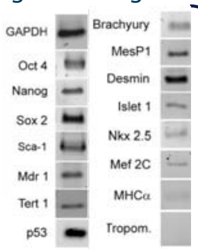
Isolation strategy:





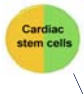
Gene expression profile and differentiation potential of cardiac stem cells

stemness genes | mesodermal genes



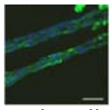
+ Klf4 Nodal LIF

+ Tbx5 GATA4 SPARC TGFß1+2

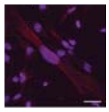


When aggregated these cells differentiate to:

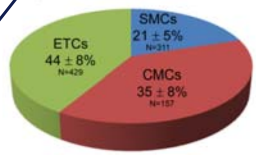
1) Endothelial cells (ETCs)



2) Smooth muscle cells (SMCs)



3) Cardiomyocytes (C



Höbaus et al., 2013

… but not to any cell type of the ectodermal or endodermal lineage.

5. take home message:

1. Cardiac stem cells do exist.
2. It is still not clear whether they are homogenous or a population of stem cells of different origin and with different properties.

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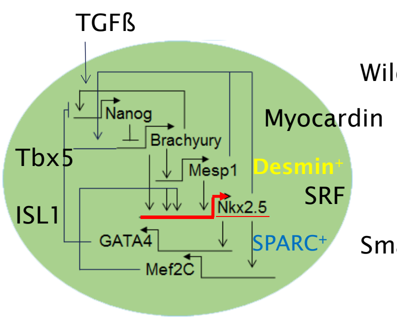
  - Entstehung des Herzens im Laufe der Embryogenese
  - Molekulare Regulation der Herzentstehung und Homöostase
- Die Stammzellen des Herzens
- Genetische Veränderungen, die zu Erkrankungen des Herzens führen und auf die Funktion der Stammzellen verweisen / Genetic defects leading to heart diseases and hinting at the function of cardiac stem cells
- Stammzelltherapie des Herzens

Genetische Veränderungen die zu Erkrankungen des Herzens führen

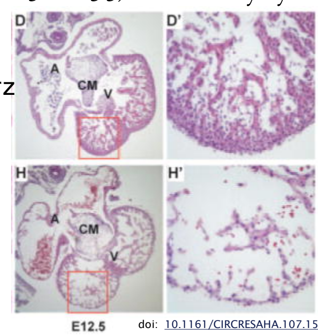
Embryonal tödlich:

- Nanog and Brachyury (T) KO: no heart at all
- Mesp1 KO: lethal before E9.5, malformation of the heart
- Smad4 heart-specific KO: lethal between E11.5 – E13.5, less cardiomyocytes



Wildtyp Mäuseherz

Smad4 KO Herz



doi: 10.1161/CIRCRESAHA.107.155630

Genetische Veränderungen die zu Erkrankungen des Herzens führen (siehe OMIM Datenbank des NIH)

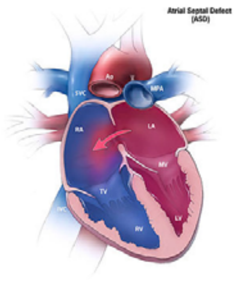
Fötal bis Juvenil, lebensverkürzend: Tbx5, Nkx2.5, GATA4

- **Tetralogy of Fallot** (TOF) can be caused by heterozygous mutation in the NKX2 . 5 gene on chromosome 5q35, the GATA4 gene on chromosome 8p23. or the JAG1 gene on chromosome 20p12 (Jagged-1 is a ligand of the Notch receptor), TOF is also a well-recognized feature of many syndromes, including the 22q11 microdeletion syndrome and trisomy 21, and has been found to be caused by mutations in several genes, including ZFPM2 ,(Friend of GATA "(FOG) is a zinc finger protein that interacts with GATA2 and modulates its transcriptional activity),TBX1 (also DiGeorge syndrome), and GATA6.

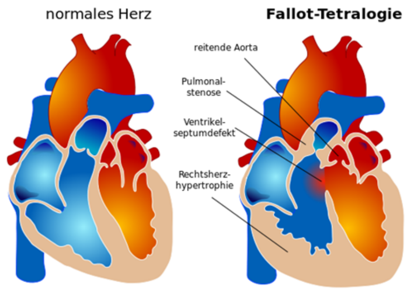
- **Holt-Oram syndrome** (HOS) is caused by heterozygous mutation in the TBX5 gene on chromosome 12q24. Holt-Oram syndrome is an autosomal dominant disorder characterized by abnormalities of the upper limbs and shoulder girdle, associated with a congenital heart lesion. The typical combination is considered to be a triphalangeal thumb with a secundum **atrial septal defect** (ASD), but there is a great range in the severity of both the heart and skeletal lesions.

https://www.google.com/search?q=triphalangeal+thumb+and+holt+oram&client=firefox-b&tbm=isch&tbo=u&source=univ&sa=X&ved=0ahUKEwj-w-2hl8vbAhWBBZoKHTm-AA0QsAQILQ&biw=1716&bih=941#imgrc=YfAANgkUnzH24M:

Holt-Oram Syndrom



Tetralogy of Fallot



Mutations in the Nkx2.5, Tbx 5, and GATA4 genes contribute also to congenital heart diseases manifested during adulthood.

Von Tetralogy_of_Fallot.svg: Mariana Ruiz LadyofHatsderivative work:Bikedoc - File:Bluebaby syndrom.svg, CC0, https://commons.wikimedia.org/w/index.php?curid=19210105

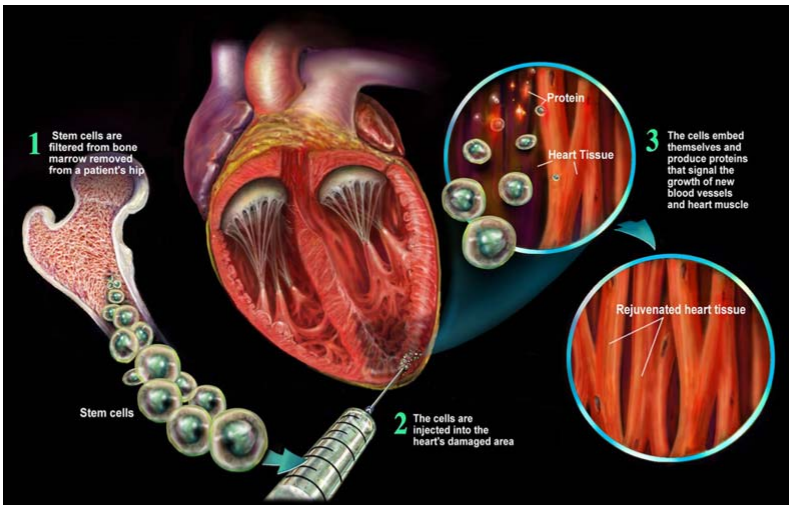
6. take home message:

1. Core transcription factors such as Nkx2.5, GATA4 and Tbx5 are expressed in progenitor and stem cells, are essential for heart development, and the maintenance of the function of the adult heart.

Inhalt / Content

- Entstehung, Anatomie und Funktionsweise des Herzens
  - Aufbau und Funktionsweise des Herzens
  - Entstehung des Herzens im Laufe der Embryogenese
  - Molekulare Regulation der Herzentstehung und Homöostase
- Die Stammzellen des Herzens
- Genetische (und epigenetische) Veränderungen, die zu Erkrankungen des Herzens führen und auf die Funktion der Stammzellen verweisen
- Stammzelltherapie des Herzens Stem Cell Therapy of the heart

„How stem cell therapy works“ (2016):



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

Mending broken hearts

Stem cell therapy of acute myocardial infarction (AMI)

- Embryonic stem cells (allogenic) → too risky because of tumor formation, ethical issues
- Induced pluripotent cells → too risky because of tumor formation
- Induced cardiomyocytes → one pre-clinical study; too early for evaluation
- Cardiac stem cells (allogenic) → not available in sufficiently large quantities
- Adipose tissue-derived
- mesenchymal stem cells → seems not to differentiate properly but provide growth factors
- Bone marrow stem cells → safe, but not suitable for cardiac regeneration

Meta-analysis of stem cell therapy after AMI

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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

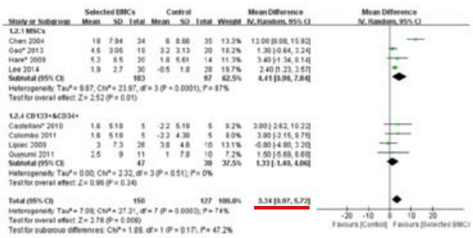


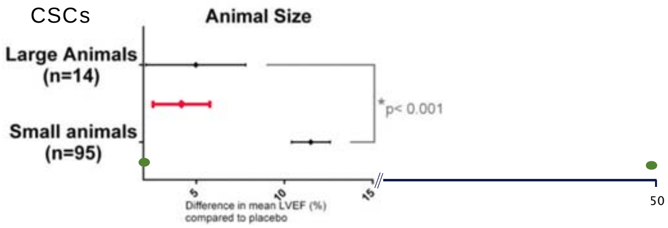
Fig. 6. Forest plot of mean difference (MD, with 95% confidence interval [CI]) in left ventricular ejection fraction (LVEF) comparing different cell types in the included trials. Subgroups were divided into (A) BMMSCs and (B) CD34+ combined with CD133+.

Cardiac stem cell therapy of myocardial infarction in animals

CSCs BMCs CSCs

Human (n=10)

Human (n=2) → ?



N = number of studies included in meta-analysis

Conclusion I

- 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)

Georg Weitzer
Department für Medizinische Biochemie

Conclusion II

Ad Regenerationsvermögen des Herzens:

(oder Warum ich keine Herzstammzelltherapie Vorlesungen mehr abhalte. (2016)

Herzen haben Herzstammzellen.

Herzzellen können sich auch weiter teilen (ca. 0,5-1% pro Jahr).

Herzzellen sind nicht in der Lage durch Teilung Defekte zu reparieren.

Therapeutisch eingebrachte Stammzellen zeigten bis heute keinen, die Qualität des Lebens verbessernden Effekt.

„Herz-Stammzellentherapie“ ist seit 22 Jahren erfolglos.

Derzeitige Hypothese:„Stammzelltherapien“ könnten positive parakrine Effekte auslösen.

Version 3/2022

Review

Heart regeneration: 20 years of progress and renewed optimism

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*Correspondence: richard_lee@harvard.edu
https://doi.org/10.1016/j.devcel.2022.01.012

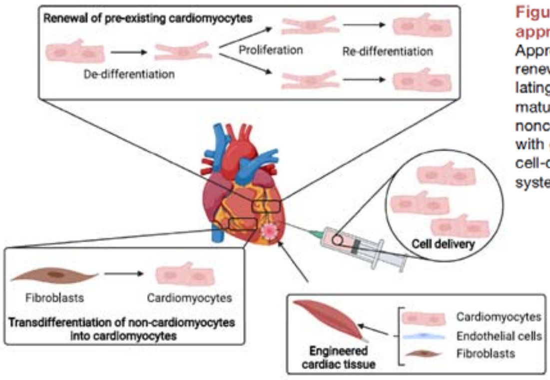

Figure 1. Overview of heart-regeneration approaches
Approaches to regenerate myocardium include renewal of pre-existing cardiomyocytes by stimulating de-differentiation and proliferation of existing, mature cardiomyocytes, transdifferentiation of noncardiomyocytes into cardiomyocytes such as with gene-therapy methods, and delivery of stem-cell-derived cardiomyocytes either as an injectable system or as a tissue-engineered patch.

Content of the review

Lesson 1:
Mammalian adult cardiomyocytes can re-enter the cell cycle — 0.5-1%

Lesson 2:
Multiple models reveal mechanisms for successful heart regeneration — Only small animals

Lesson 3:
Adult stem cells do not participate in cardiomyocyte regeneration — Most likely but no final proof

Lesson 4:
Multiple approaches can lead to new cardiomyocytes for failing hearts — trivial

Lesson 5:
Important barriers to human therapy are being addressed by fundamental research — trivial

7. take home message

1. Currently CSCs are not superior to BMCs in large animals (and humans).

2. No cell type can increase the quality of life after acute myocardial infarction.

3. Hence alternative strategies should be evaluated.

The question we ask in our research group at the Max Perutz Labs:

Why have cardiac stem cell be maintained during evolution in mammals if they do not contribute to heart repair?

First evident mammal: Juramaia sinensis
Late Jurassic, 160.89 – 160.25Ma

What are the roles of cardiac stem cells in homeostatic adult and ageing heart?

What is the purpose of CSCs in the adult heart if not the replenishment of the myocardium by proliferation and differentiation?

What is the transcriptional control of the balance between self-renewal and cardiomyogenesis?

Scientific Interest:

The homeostasis of cardiac stem cells and the molecular mechanisms which contribute to the regulation of cardiomyogenesis and homeostasis in the adult heart.

General Aim of Research:

is to understand the role of cardiac stem cells in the healthy, aging and diseased heart

- and as a surplus -

to possibly contribute to new therapies of acute and chronic heart diseases.

Specific Aim of Research:

is to understand the transcriptional regulation of the balance between self-renewal and differentiation of cardiac stem cells by two *non-transcription factor* proteins, desmin and SPARC – during homeostasis, in adulthood, and in ageing.

The End

You find all slides and the cited review

on my homepage at

https://homepage.univie.ac.at/georg.weitzer/