Heart Development

- Origins of congenital heart defects
- Properties of cardiac progenitor cells

Robert G. Kelly
Animal models of heart development
The gene *tinman* is required for specification of the heart and visceral muscles in *Drosophila*

Rolf Bodmer
Tinman/Nkx2.5 expression in different species

In situ hybridisation

Harvey 1996
Dev Biol 178:203-16
Myogenic and morphogenetic defects in the heart tubes of murine embryos lacking the homeo box gene Nkx2-5.

Lyons, L M Parsons, L Hartley, et al.

*Genes Dev.* 1995 9: 1654-1666
Congenital Heart Disease Caused by Mutations in the Transcription Factor NKX2-5
Jean-Jacques Schott, et al.
Heart Development

- From the cardiac crescent to the embryonic heart
- Second heart field cardiac progenitor cells
- Cardiac septation and chamber morphogenesis
- Conduction system and epicardial development
Specifying cardiac fate in the early embryo

Inductive signals
- Baf60c-Gata4
- Tbx5
- Mef2c, Nkx2.5, Hand, Isl1

Muscle gene activation
- Beating heart muscle

Harvey 2002
Nat Rev Genet 3:544-56

Takeuchi and Bruneau 2009
Nature 459:708-11

Kirby 2007
Cardiac Development

Ieda et al 2010
Cell 142:375-86
From the cardiac crescent to the embryonic heart
The right ventricle and outflow tract are added progressively to the elongating heart tube.

Dil labeling, 24hr embryo culture
Transcriptional programs in the first and second heart field

Olson 2006
Science 313:1922-27
Clonal analysis in the embryonic heart: evidence for the existence of two myocardial lineages

\[ \alpha_c \text{actin } nlaacZ \]

Meilhac et al., 2004
Dev Cell 6:685-98
Cardiac progenitor cell lineages

Second heart field

First heart field

Gene expression in the second heart field

*Isl1*  

*Isl1-Cre*  

*Rosa26-Stop-lacZ*  

Wildtype  

*Isl1*−/−  

Cai *et al.* 2003  
*Dev Cell* 5:877-89

*Fgf10*  

E8.5  

*Fgf10 lacZ*  

*Pitx2c*
$Tbx1$: DiGeorge Syndrome candidate gene expressed in the second heart field

Chen et al. 2009
Circ Res 105:842-51
The second heart field and conotruncal congenital heart defects

Di Felice and Zummo 2009
Trends Cardiovasc Med 19:130-5
The second heart field and cardiac neural crest cells

Hutson and Kirby, 2007
Sem Cell Dev Biol

Wnt1-Cre R26R

Jiang et al. 2000
Development 127:1607-16

Fgf10 lacZ

Jiang et al. 2000
Development 127:1607-16

Hutson and Kirby, 2007
Sem Cell Dev Biol

Neural crest

Mesoderm
Ablation of the cardiac neural crest impairs second heart field development

Yelbuz et al, 2002
Circulation 106:504-10
Signaling pathways controlling second heart field development
Regulation of second heart field differentiation by microRNAs

Wang et al 2010
Dev Cell 19:903-12
Fgf8 is required for second heart field and outflow tract development

Ilagan et al. 2006
Development 133:2435-45

Reifers et al. 2001
Development 126:225-35
Latent TGF-β binding protein 3 identifies a second heart field in zebrafish

Yong Zhou¹,², Timothy J. Cashman¹,², Kathleen R. Nevis¹,², Pablo Obregon¹,², Sara A. Carney³, Yan Liu²,⁴, Aihua Gu¹,²,⁵, Christian Mosimann²,⁶, Samuel Sondalle¹,²,⁷, Richard E. Peterson³, Warren Heideman³, Caroline E. Burns¹,²,⁷ & C. Geoffrey Burns¹,²

Zhou et al 2011
Nature 474:645-8
Second heart field contribution at the venous pole of the heart

Briggs et al. 2012
Differentiation 84:117-30

ISL1
NKX2.5
Second heart field contribution to atrial and AV septation

Hoffman et al 2009
Development 136:1761-70
The second heart field is part of a cardiocraniofacial developmental field.

 Isl1-Cre
 R26R
 β-gal
 MF20

Nathan et al. 2008
Development 135:647-657
A common lineage relationship between head muscles and SHF-derived myocardium

\[ \alpha_c \text{actin nlacZ} \]

\[ \alpha_c \text{actin nlacZ} \]

\[ Tbx1^{+/-} \]

\[ Tbx1^{-/-} \]

Kelly et al. 2004
Hum Mol Genet
13:2829-40

Lescroart et al 2010
Development 137:3269-79
Heart Development

- From the cardiac crescent to the embryonic heart
- Second heart field cardiac progenitor cells
- Cardiac septation and chamber morphogenesis
- Conduction system and epicardial development
Cardiac chamber formation: the ballooning model

Moorman and Christoffels. 2003
Physiol Rev 84:1223-67
Differential gene expression during chamber formation

ANF/Nppa

700bp promoter

nlacZ

Habets et al. 2002
Genes Dev 16:1234-46
A T-box gene network regulates chamber formation

ANF/Nppa promoter lacZ activity

Habets et al. 2002
Genes Dev 16:1234-46
A T-box gene network regulates chamber formation

Hoogaars et al. 2007
Cell Mol Life Sci 64:646-660

Wildtype

Tbx2⁻/⁻

ANF/Nppa

Harrelson et al. 2004
Development 131, 5041-5052
A T-box gene network regulates chamber formation

Wildtype | Tbx20^-/
---|---

ANF

Tbx2

Singh et al. 2009
Circ Res 105:442-52
Conduction system development

Tbx3

Cx40

SA node

AV node

Bundle branches

Purkinje fibres

Central conduction system: AV node

Purkinje fibre network

Cx40 GFP
Clonal analysis of the origin of the ventricular conduction system

- Biphasic development of the conduction system – specification from a common progenitor followed by outgrowth

Congenital Heart Disease Caused by Mutations in the Transcription Factor NKX2-5
Jean-Jacques Schott, et al.
Purkinje fibre hypoplasia in \( Nkx2.5 \) haploinsufficient hearts

\[ Cx40^{eGFP} \quad \quad Cx40^{eGFP};Nkx2.5^{+/-} \]

Meysen et al. 2007
Dev Biol 303:740-51
The epicardium regulates ventricular growth

Wessels and Sedmera, 2003
Physiol. Genomics 15: 165-176
Fate of the epicardium and origin of the coronary vasculature

Chien et al. 2008 Science 322:1494-7

Smooth muscle cells
Cardiac fibroblasts
Epicardial-derived cells

Endocardium is a major source of coronary endothelial cells

E11.5
E12.5-13.5
E14.5-16.5

Wu et al. 2012
Cell 151:1083-96

Myocardium
Coronary endothelial cells

O2 level
Vegf-a level
angiogenesis and artery formation
Coronary artery
Heart Development

- The second heart field is a population of cardiac progenitor cells in pharyngeal mesoderm.
- Perturbation of second heart field development results in congenital heart anomalies.
- Chamber formation and conduction system development are regulated by a network of T-box transcription factors.
- The epicardium is required for myocardial growth and coronary smooth muscle development.
Heart Development – bibliography and meetings

• “Cardiac Development”, 2008, ML Kirby, Oxford
• Miquerol L, Kelly RG. Organogenesis of the vertebrate heart. WIRES Dev Biol 2013. 10.1002/wdev.68
• Cardiovascular Research – Spotlight issue on Cardiac Development, July 2011

ESC WG on Development, Anatomy and Pathology Annual meeting – Berlin, 26-29 September 2013
Weinstein Cardiovascular Development Meeting Meeting, USA