INTRODUCTION TO HUMAN HEART DEVELOPMENT

Debbie Yelon
Developmental Genetics Program
Department of Cell Biology
Skirball Institute, NYU School of Medicine
HUMAN HEART DEVELOPMENT

- **21 days**: Bulbus cordis, Aortic arch I, Truncus arteriosus, Ventricle, Atrium
- **25 days**: Left atrium, Truncus arteriosus, Right atrium, Conus arteriosus
- **28 days**: I, II, III, IV
- **30 days**: III, IV, VI, Right atrium, Left atrium, Conus arteriosus, Right ventricle, Left ventricle
- **35 days**: Left atrium
POSTNATAL CIRCULATION

PULMONARY CIRCULATION
RIGHT CHAMBERS

SYSTEMIC CIRCULATION
LEFT CHAMBERS
HUMAN HEART DEVELOPMENT

- HEART TUBE FORMATION
- CARDIAC LOOPING
- CHAMBER SEPTATION
- VALVE AND OUTFLOW FORMATION
CONGENITAL HEART DISEASE

- RELATIVELY COMMON
- GENERALLY INITIATED BY EARLY DEVELOPMENTAL ERRORS
- CAN BE CAUSED BY EXPOSURE TO TERATOGENS
- CAN ORIGINATE WITH GENETIC DEFECTS
LONGITUDINAL FOLDING
POSITIONS CARDIAC CELLS
LATERAL FOLDING FACILITATES TUBE FORMATION
TUBE FORMATION BEGINS ROSTRALLY
PRIMITIVE HEART TUBE

- TRUNCUS ARTERIOSUS
- BULBUS CORDIS
- PRIMITIVE VENTRICLE
- PRIMITIVE ATRIUM
- SINUS VENOSUS
CARDIAC LOOPING

Aortic roots

Bulbus cordis

Ventricle

Atrium

Sinus venosus

Pericardium

Pericardial cavity

Bulboventricular sulcus

Sinus venosus

Left atrium
CARDIAC LOOPING
DEXTROCARDIA AND SITUS INVERSUS
GENETIC BASIS FOR HETEROTAXY

- NODAL FAMILY OF GROWTH FACTORS REQUIRED FOR ESTABLISHMENT OF LEFT-RIGHT AXIS

- CFC1 GENE ENCODES A COMPONENT OF THE RECEPTOR FOR NODAL FACTORS

- MUTATIONS IN CFC1 CAUSE HETEROTAXY
FROM FETAL TO POSTNATAL CIRCULATION
PARTITIONING THE HEART

- ATRIAL SEPTATION
- VENTRICULAR SEPTATION
- ATRIOVENTRICULAR VALVE FORMATION
- DIVISION OF THE OUTFLOW TRACT
ATRIAL SEPTATION I: SEPTUM PRIMUM PRIMUM

RA, right atrium
RV, right ventricle
LA, left atrium
LV, left ventricle

Dorsal endocardial cushions

Septum primum
Foramen primum

Perforations representing developing foramen secundum in septum primum

Fused endocardial cushions

Red arrows—well oxygenated blood
Blue arrows—poorly oxygenated blood
ATRIAL SEPTATION II: FORAMEN SECUNDUM

RA LA

Developing septum secundum

Foramen secundum

Foramen primum

Septum primum

Foramen primum closed
ATRIAL SEPTATION III: SEPTUM SECUNDUM

- Septum secundum (upper limb)
- Foramen secundum
- Valve of foramen ovale (derived from septum primum)
- Septum (lower limb secundum)
- Foramen ovale
- RA (Right Atrium)
- LA (Left Atrium)
ATRIAL SEPTATION IV: COMPLETION
ATRIAL SEPTAL DEFECTS

NORMAL

OSTIUM SECUNDUM (HIGH) ASD
GENETIC CAUSES OF ASD

HETEROZYGOSITY OF MUTATIONS IN GENES LIKE:

– *Nkx2-5*, encoding a homeodomain transcription factor
– *TBX5*, encoding a T-box transcription factor (Holt-Oram Syndrome)
BEGINNING OF VENTRICULAR SEPTATION

- Plane of section D
- Fused endocardial cushions
- Arrow passing through right atrioventricular canal
- Septum primum
- Sinoatrial valve guarding orifice of sinus venosus
- Foramen primum
- Left atrioventricular canal
- Fused endocardial cushions
- Developing interventricular septum
PROGRESSION OF VENTRICULAR SEPTATION
COMPLETION OF VENTRICULAR SEPTATION

MUSCULAR SEPTUM

MEMBRANOUS SEPTUM

CONOTRUNCAL SEPTUM
VALVE FORMATION

- Cusps of mitral valve
- Membranous part of interventricular septum
- Developing mitral valve
- Cusps of tricuspid valve
- Chordae tendineae
- Papillary muscle
OUTFLOW SEPTATION

Aorta

Pulmonary trunk

Aorta
OUTFLOW SEPTATION
DEFECTS IN OUTFLOW SEPTATION

NORMAL

NO SEPTUM:
PERSISTENT TRUNCUS ARTERIOSUS

STRAIGHT SEPTUM:
TRANSPOSITION OF GREAT VESSELS

ASYMMETRIC SEPTUM:
PULMONARY STENOSIS;
TETRALOGY OF FALLOT
NEURAL CREST AND OUTFLOW TRACT SEPTATION

A
- Nodose placode
- Cardiac neural crest

Cardiac outflow tract

Cardiac neural crest removed

B
- Persistent truncus arteriosus containing some nodose placode cells
GENETIC BASIS FOR OUTFLOW DEFECTS

• *TBX1* ENCODES A TRANSCRIPTION FACTOR EXPRESSED NEAR MIGRATING NEURAL CREST CELLS

• *TBX1* MUTATION IN MICE CAUSES DEFECTS RESEMBLING DIGEORGE SYNDROME

• DELETION OF *TBX1* FOUND IN MANY DIGEORGE SYNDROME PATIENTS
HUMAN HEART DEVELOPMENT

- HEART TUBE FORMATION
- CARDIAC LOOPING
- CHAMBER SEPTATION
- VALVE AND OUTFLOW FORMATION
SINUS VENOSUS AND RIGHT ATRIUM

Common cardinal vein
Left sinus horn
Left umbilical vein
Right vitelline vein
24 days

Bulbus cordis
Left sinus horn
Right ventricle
Left ventricle
35 days

Right sinus horn
Inferior vena cava
Left atrium
Oblique vein of left atrium
Coronary sinus

24 days
35 days

24 days
35 days
PULMONARY VEINS AND LA

- Pulmonary veins
- Primordial pulmonary vein
- Primordial left atrium
- Part of left atrium formed from absorbed pulmonary vein tissue
- Right and left pulmonary veins
- Primordial left atrium
- Entrance of four pulmonary veins
- Smooth-walled part of left atrium
ATRIAL SEPTAL DEFECTS

• OSTIUM PRIMUM (LOW) ASD

• OSTIUM SECUNDUM (HIGH) ASD

• SINUS VENOSUS ASD
End