

Heart Development



II. Later stages of development

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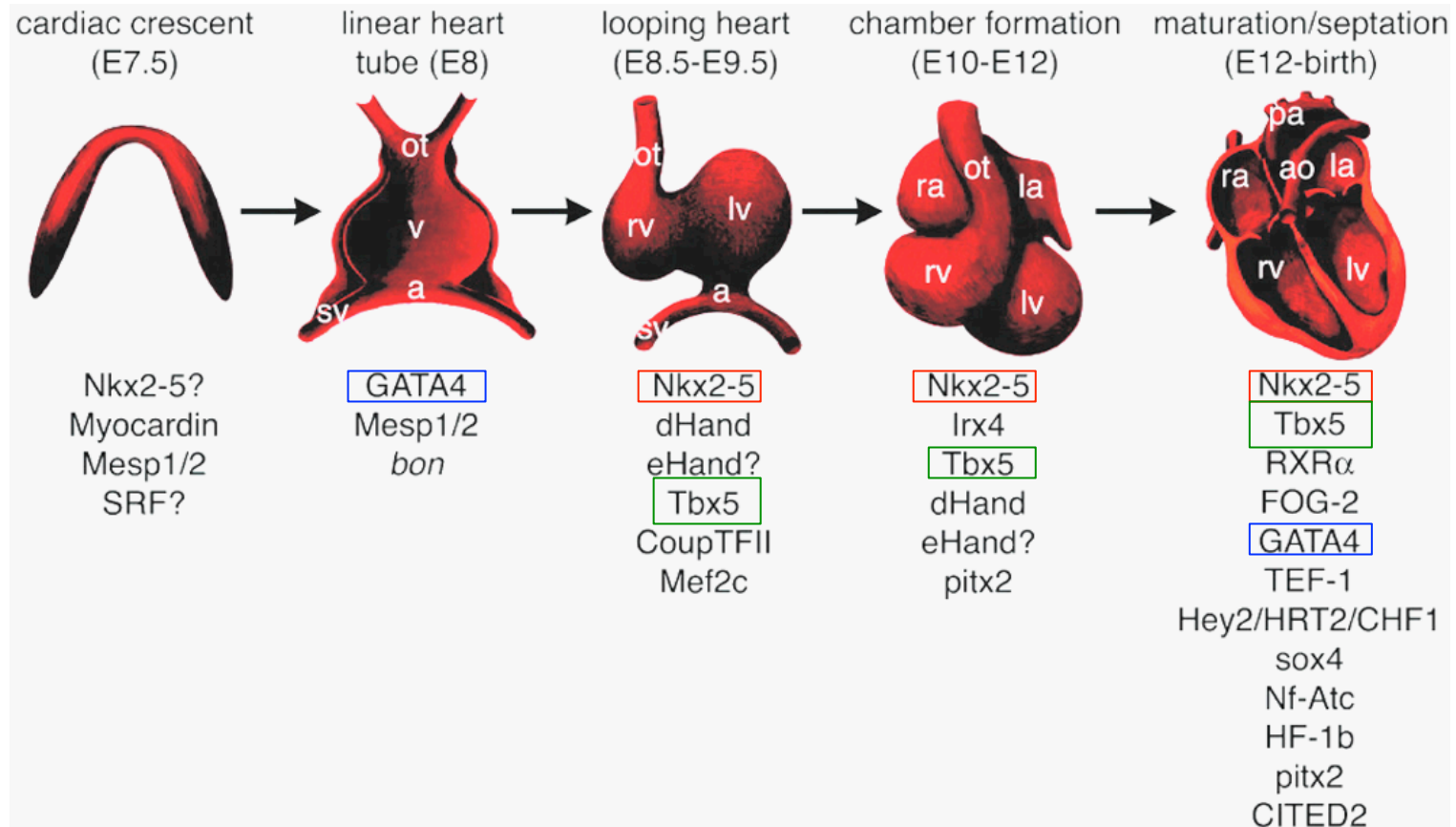
1. The ballooning model
2. Development of cardiac conduction tissue
3. Valve formation

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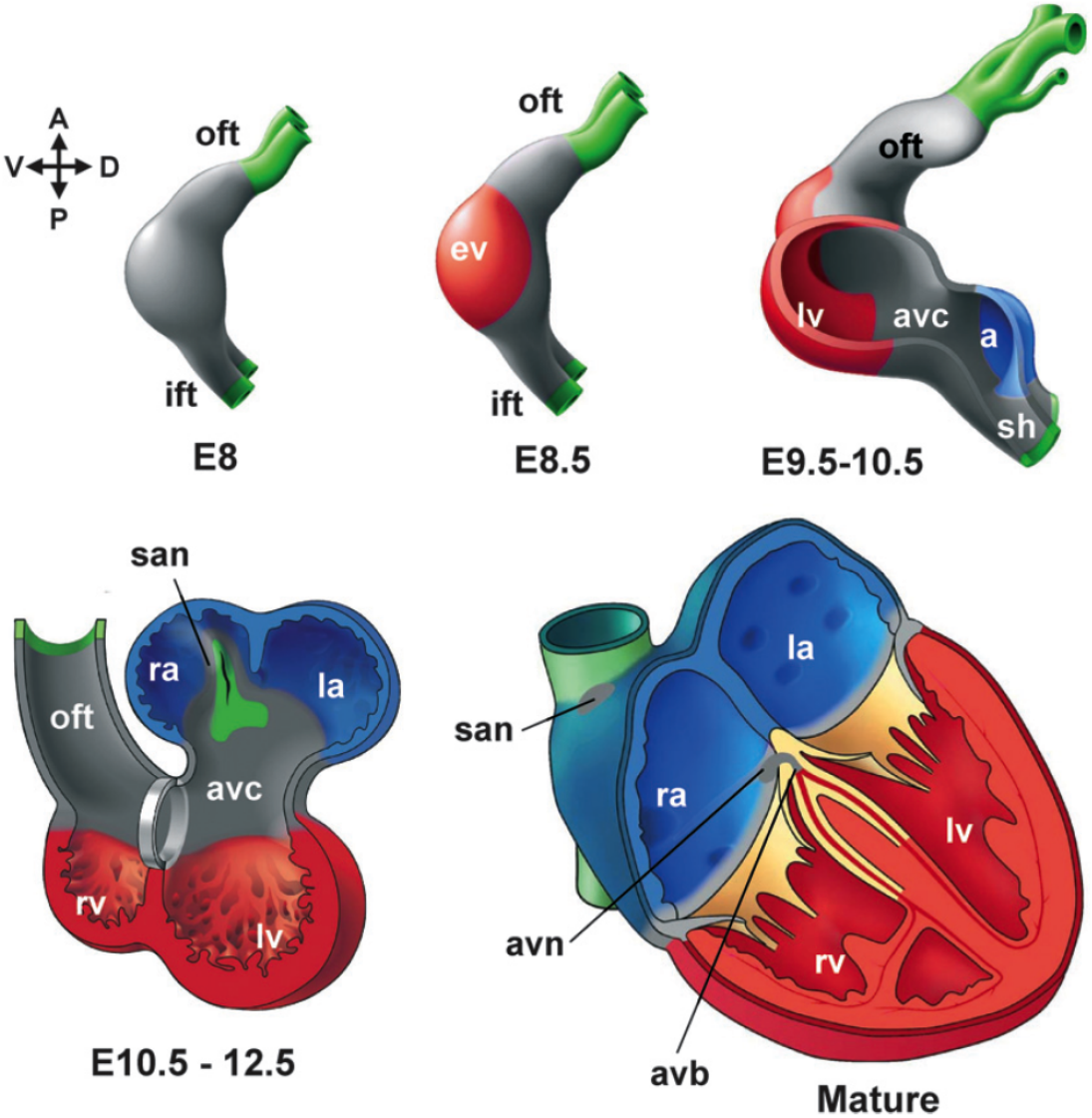
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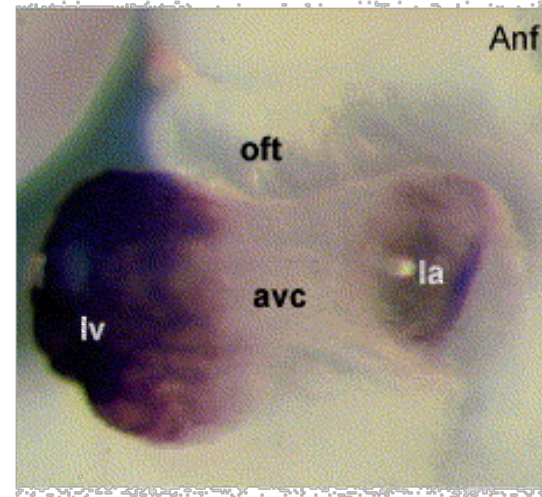
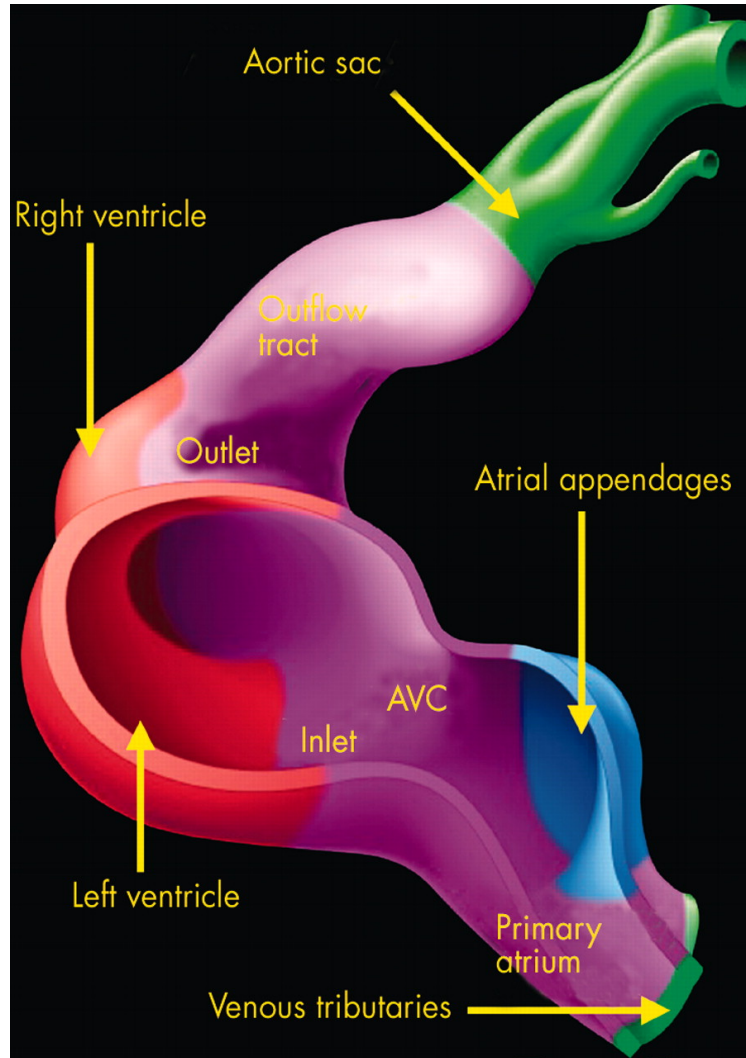
Cardiac Transcription Factors



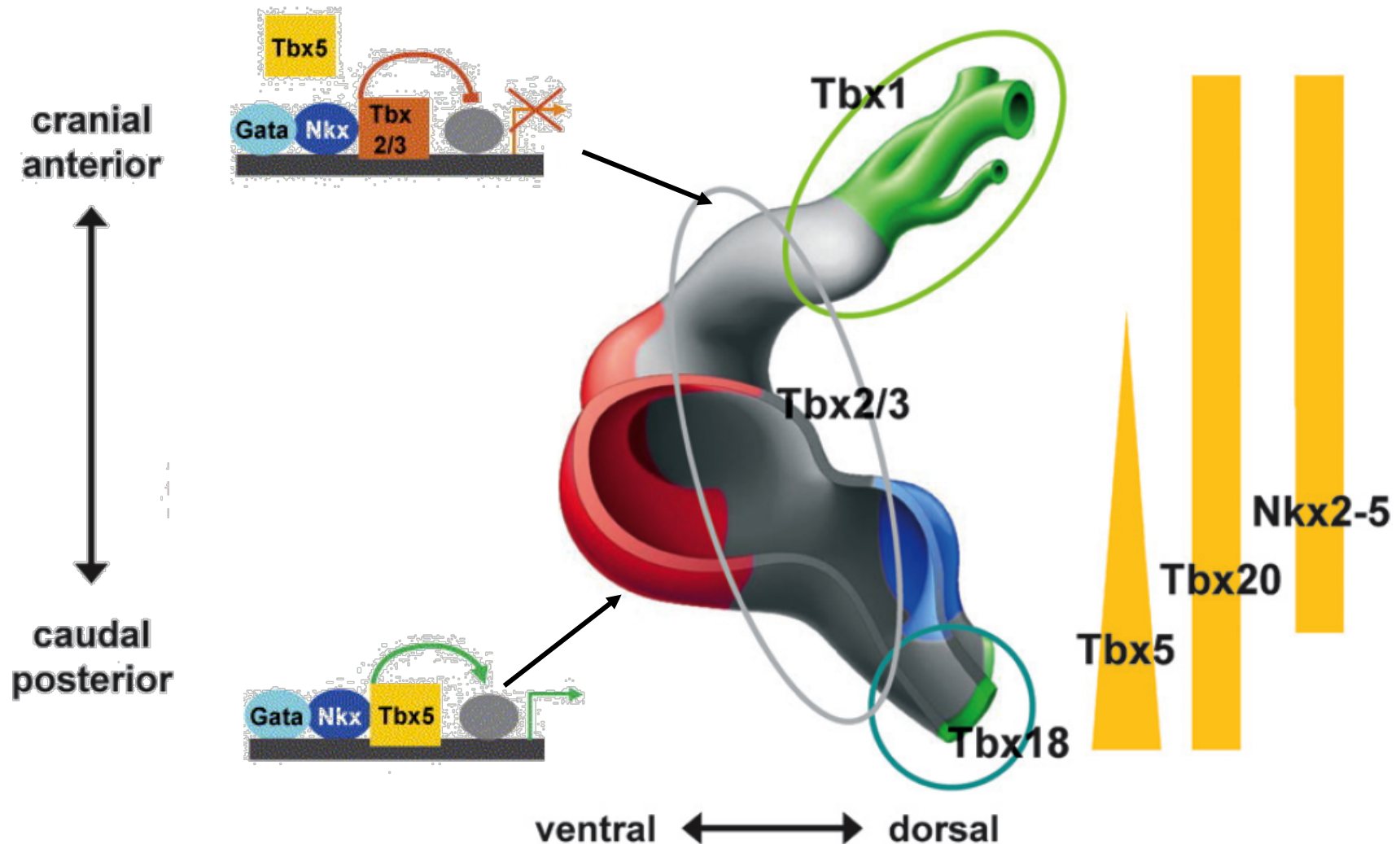
Cardiac chamber development



The *ballooning* model



The chamber-specific program is activated or repressed by the regionalized expression of Tbx genes



Summary

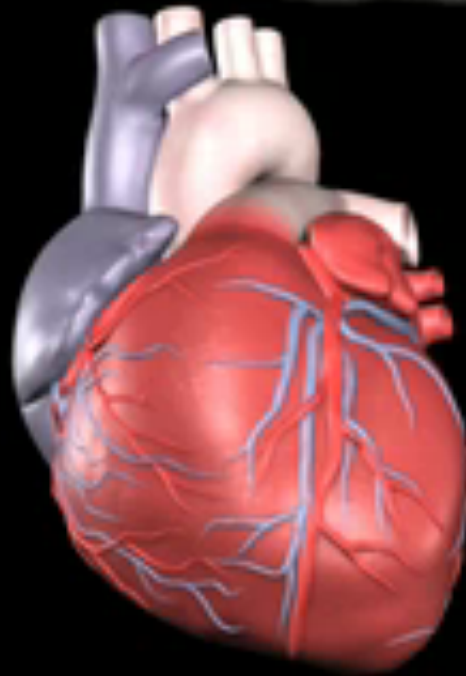
- Today we know a large fraction of the transcription factors that are expressed in the developing heart. These factors include Nkx2.5 and GATA4, which are both involved in the recruitment of cells to the cardiac lineage. Mef2, which is involved in controlling cardiac differentiation, and the helix-loop helix factors dHand and eHand, which are involved in chamber specification.
- Often the same transcription factor is utilized multiple times during cardiac development. Nkx2.5 for example is important for cardiac recruitment, but also is required for cardiac septation and cardiac conduction tissue development.
- The linear heart tube and the heart chambers differ in their gene expression programs. This becomes apparent in the expression of the ANF gene, which is expressed in chamber myocardium but is absent from the tubular heart myocardium.
- The development of cardiac chambers is best described by the ballooning model which explains how cardiac chambers are growing out from the primary myocardium. The shift in gene expression is governed by the expression of chamber specific transcription factors that belong to the T-box gene family. Cardiac chambers express Tbx5 and Tbx20, while Tbx2 and Tbx3 are expressed in the tubular heart myocardium.

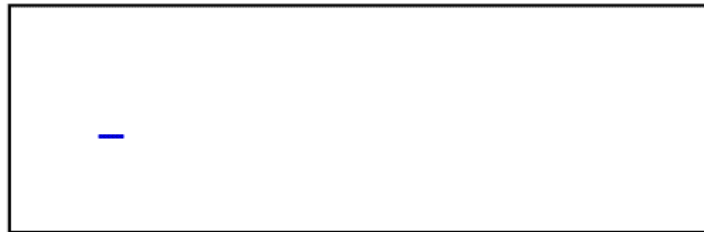
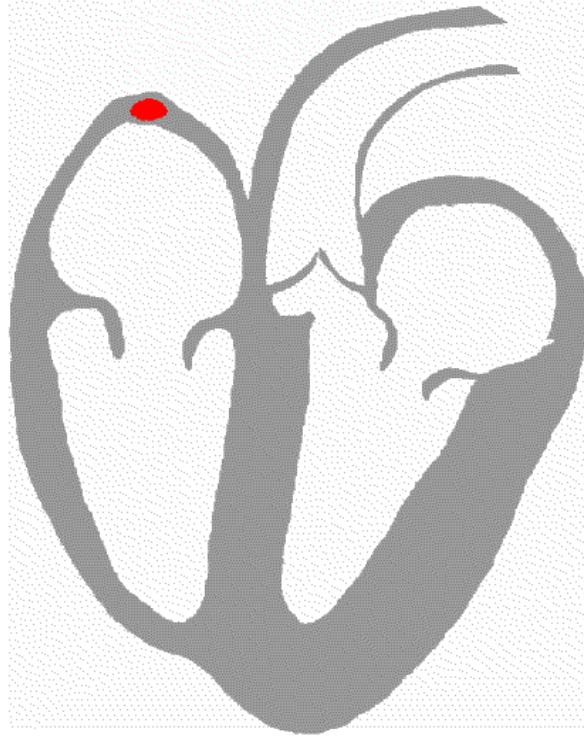
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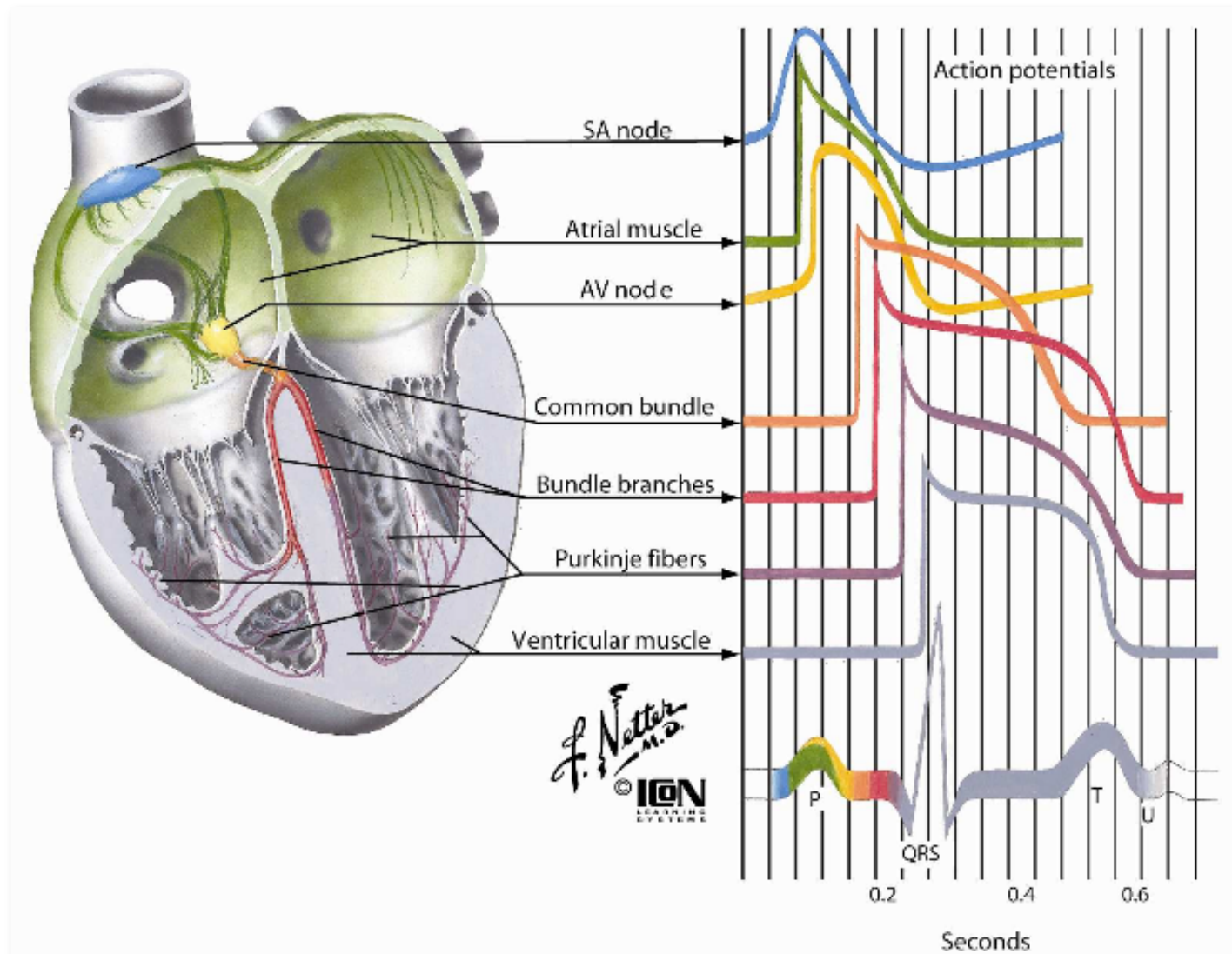
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Normal Heartbeat

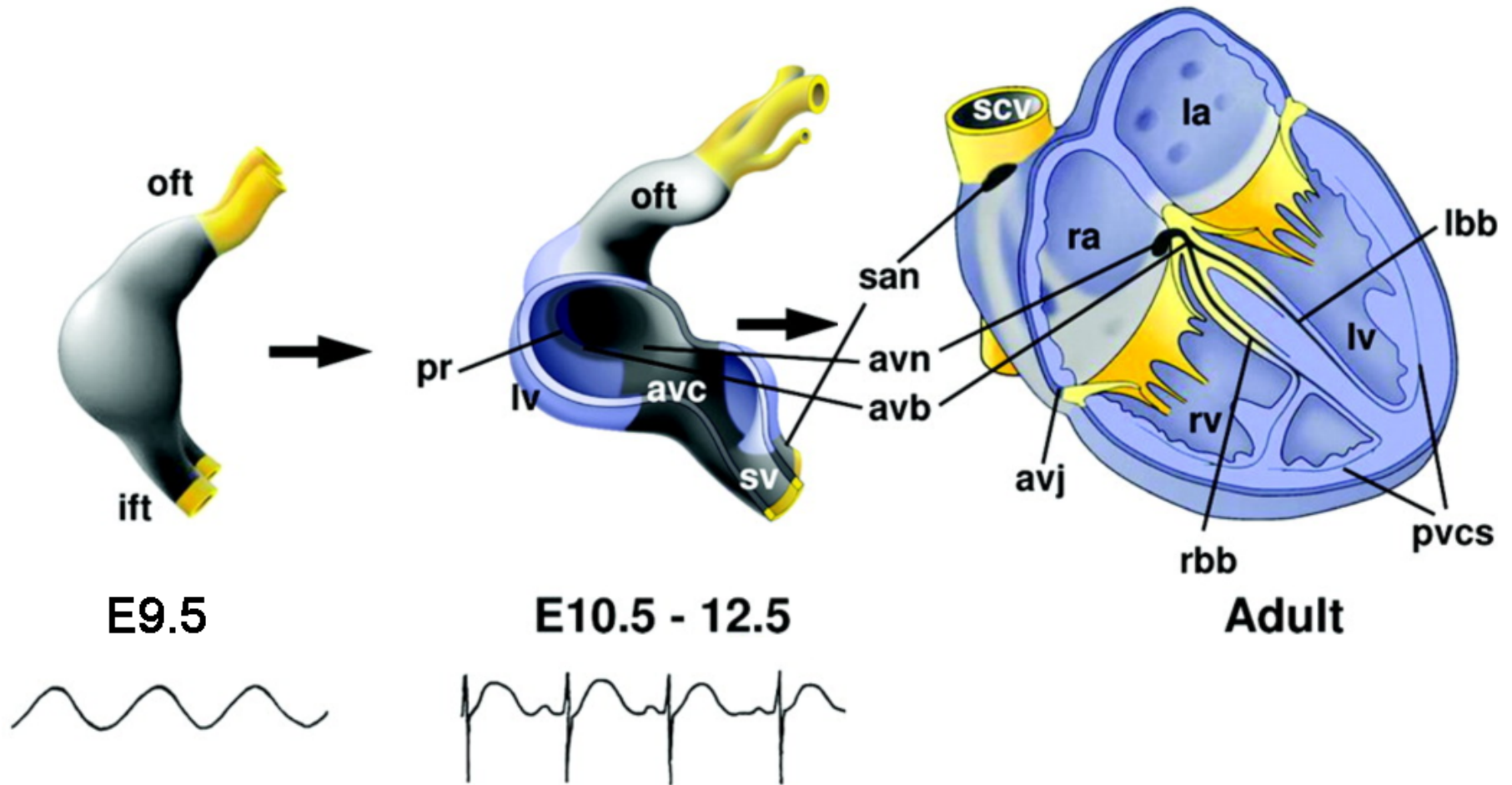




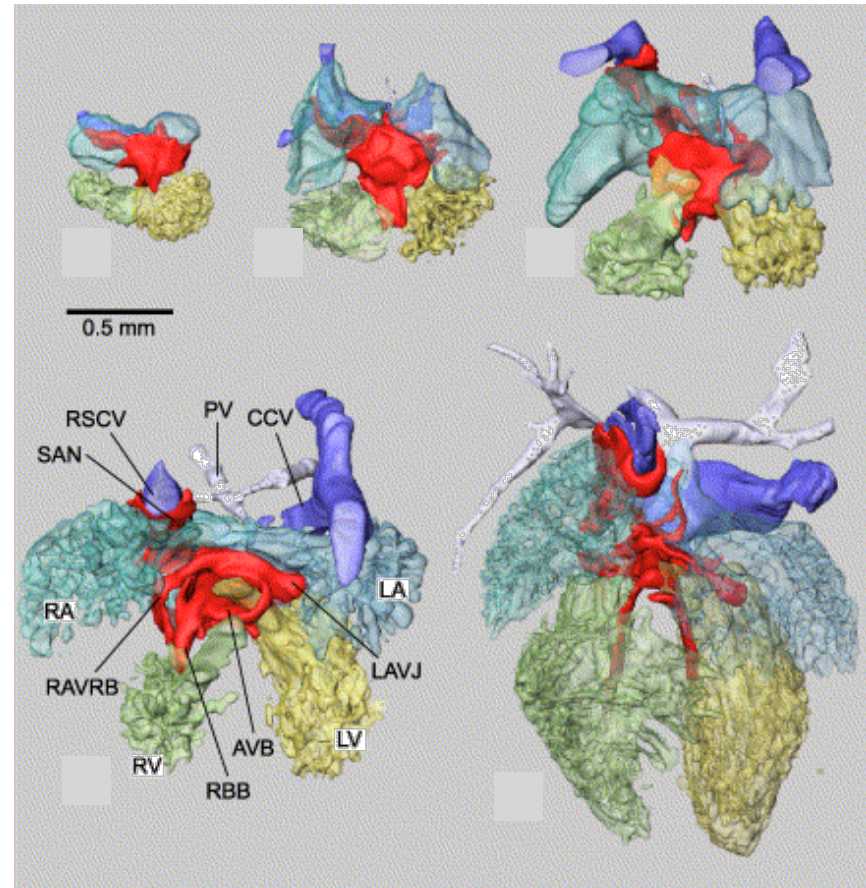
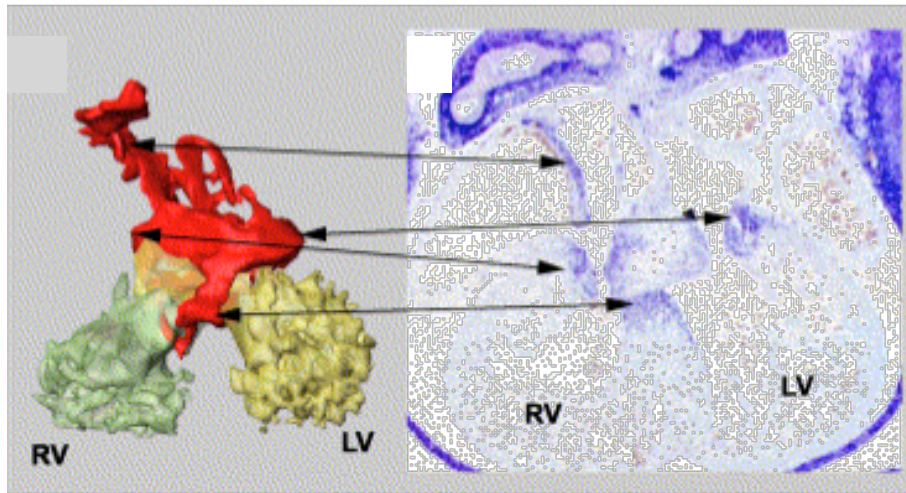
The cardiac conduction system



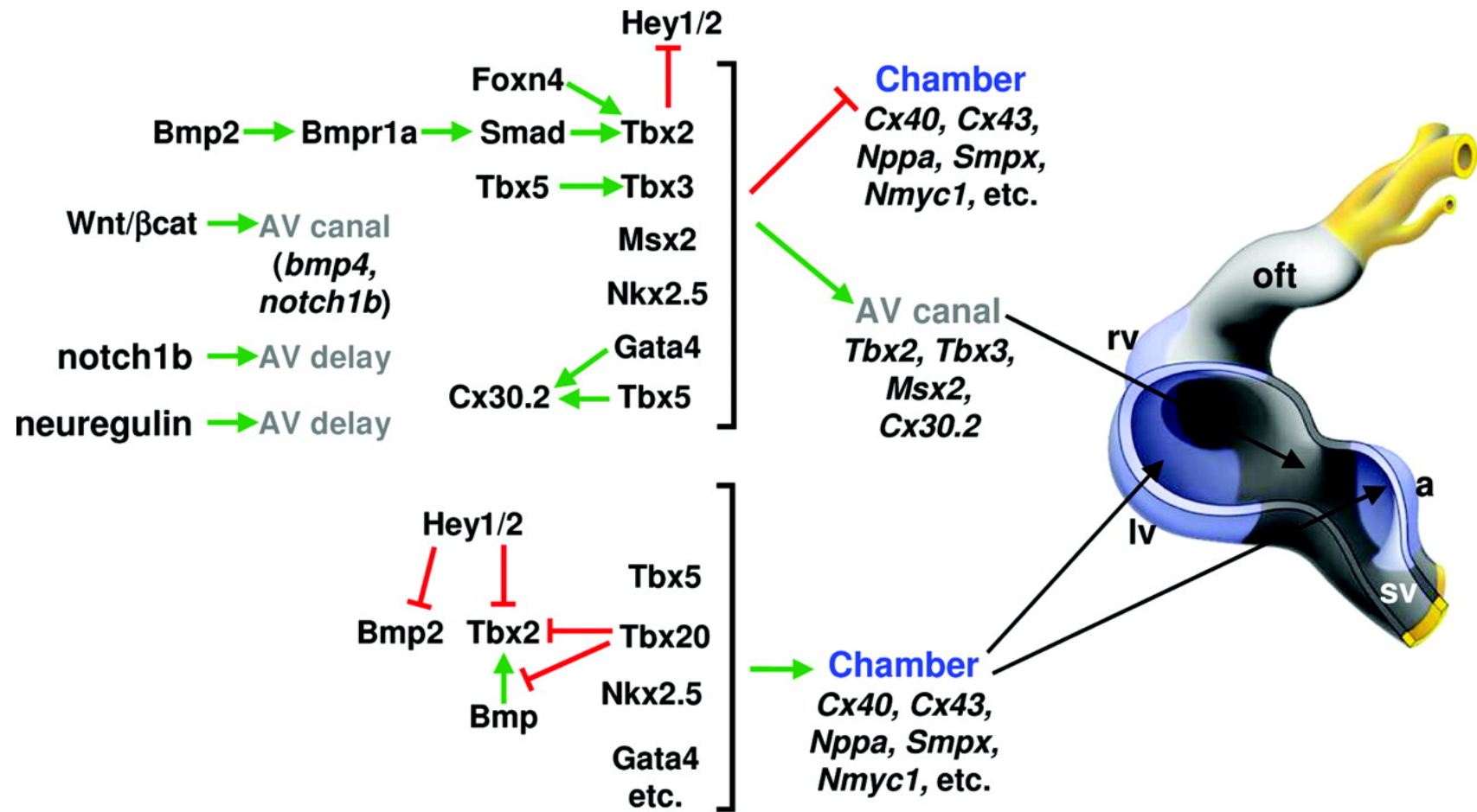
Development of the cardiac conduction tissue



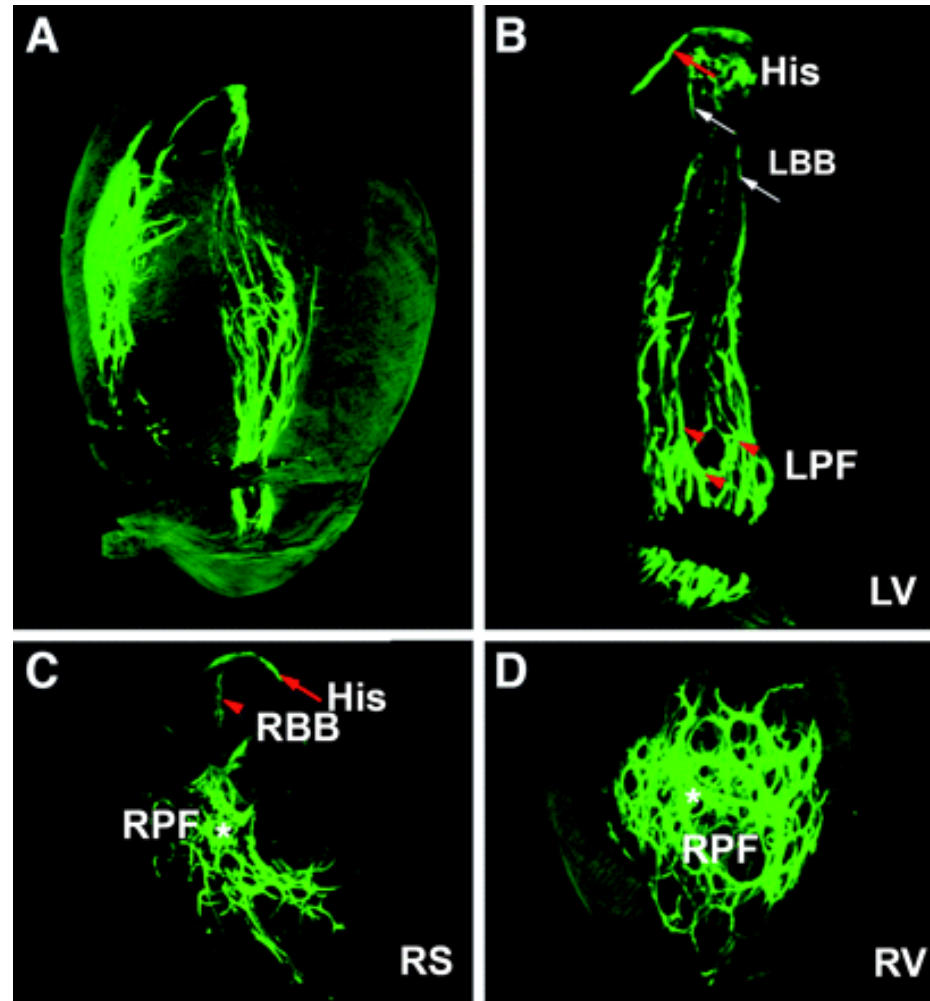
The expression domain of Tbx3 demarcates the cardiac conduction tissue



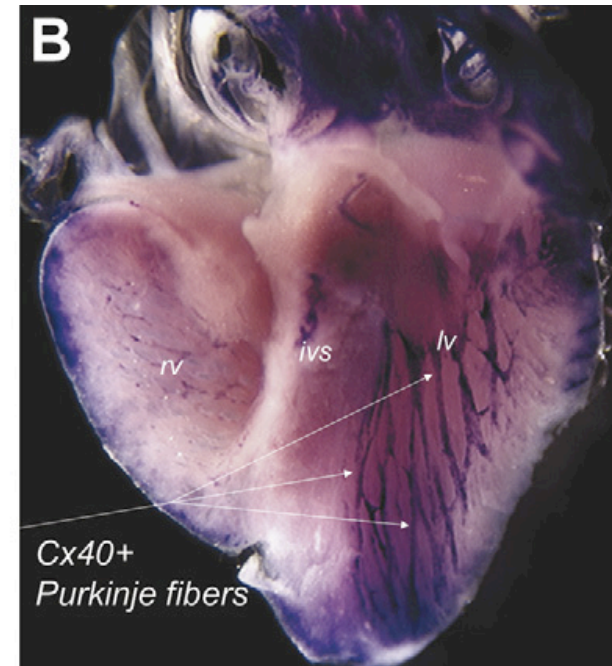
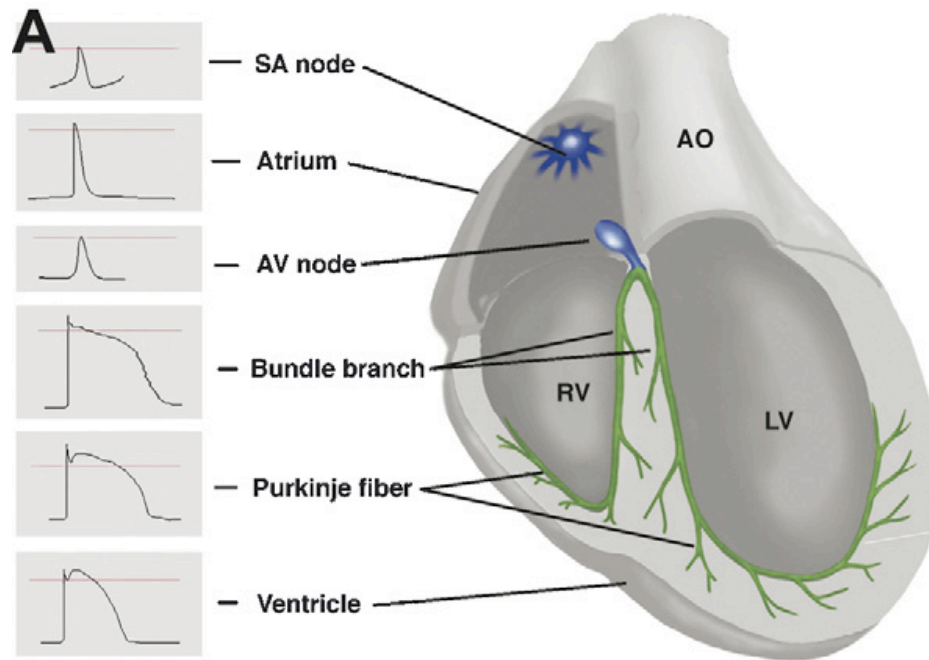
Molecular pathways that regulate cardiac conduction tissue development



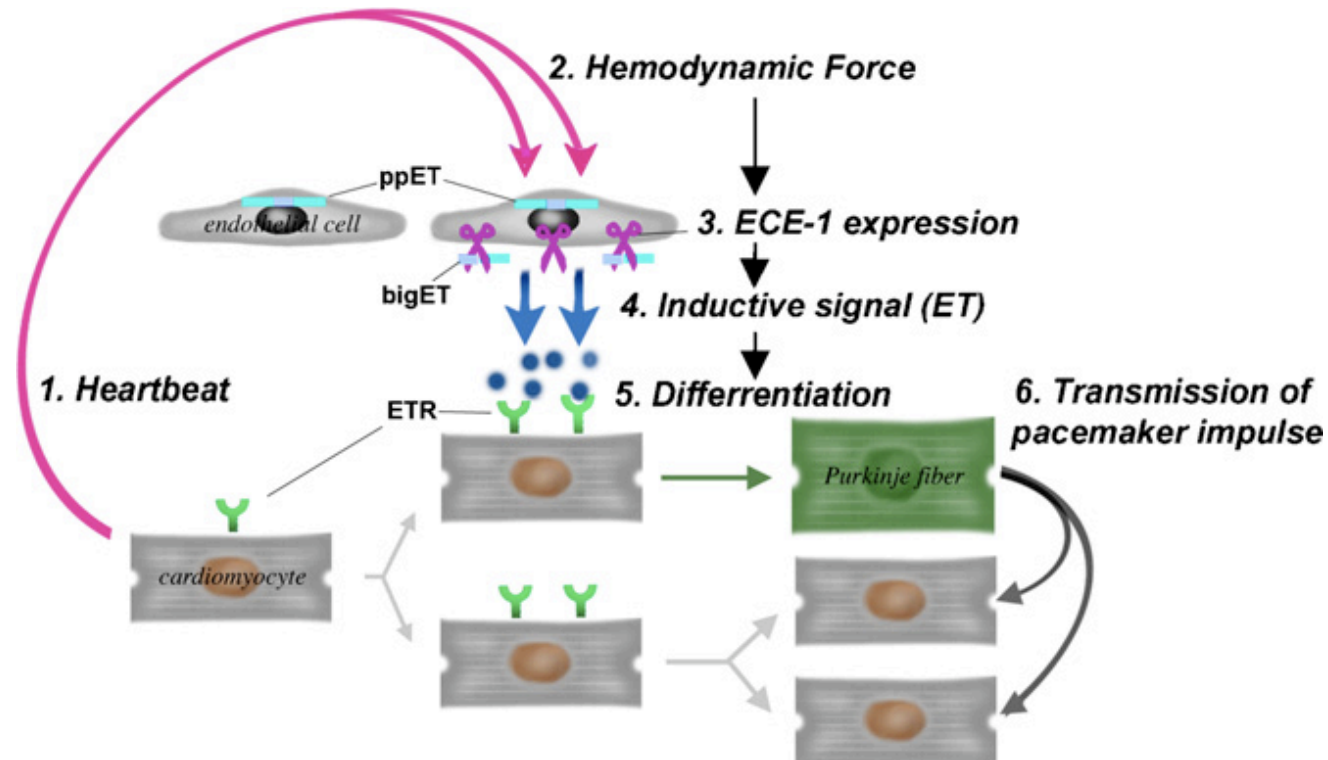
The bundle branches and the Purkinje fibre network



Purkinje fiber network in the ventricle



Endothelin plays a role in inducing cardiac Purkinje fiber cells



In mammals the signaling molecule neuregulin appears to promote purkinje fibre development.

Summary

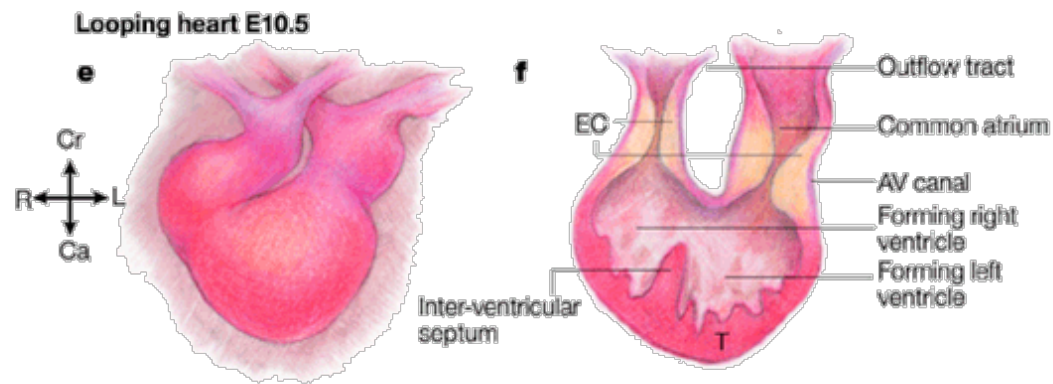
- The cardiac conduction tissue is made of different parts. There are two nodes, the sinus node and the atrioventricular node. These nodes are the primary and secondary pacemaker of the heart. Within the ventricle, rapid conduction of the electrical signal from apex to base is mediated by rapidly conducting Purkinje fiber cells.
- The nodes are characterized by the lack of a resting membrane potential, instead a pacemaker potential is present, which is formed due to a specific set of ion channels that are only present in nodal cells.
- Initially at the tubular heart stage the entire myocardium has a node-like character. The primary pacemaker is localized in the most recently formed cardiac myocytes at the venous pole.
- Subsequently after chamber formation is initiated, the expression of Tbx2 and Tbx3 demarcates the nodular tissue. These cells are hindered to mature into chamber myocardium and thereby retain the primitive characteristics of the tubular heart.
- Purkinje fiber cells in the chick embryo are believed to be induced by endothelin and hemodynamic factors, while neuregulin has been implicated in the murine system.

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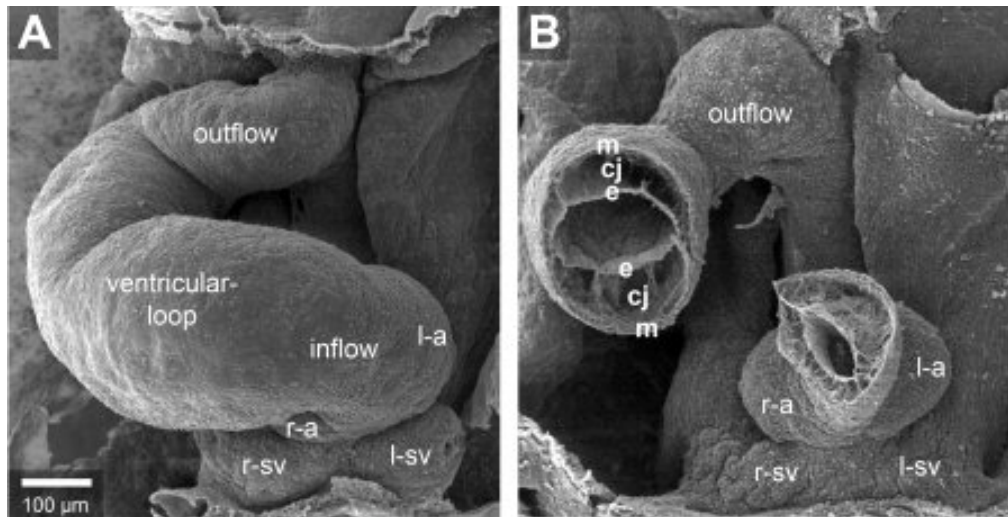
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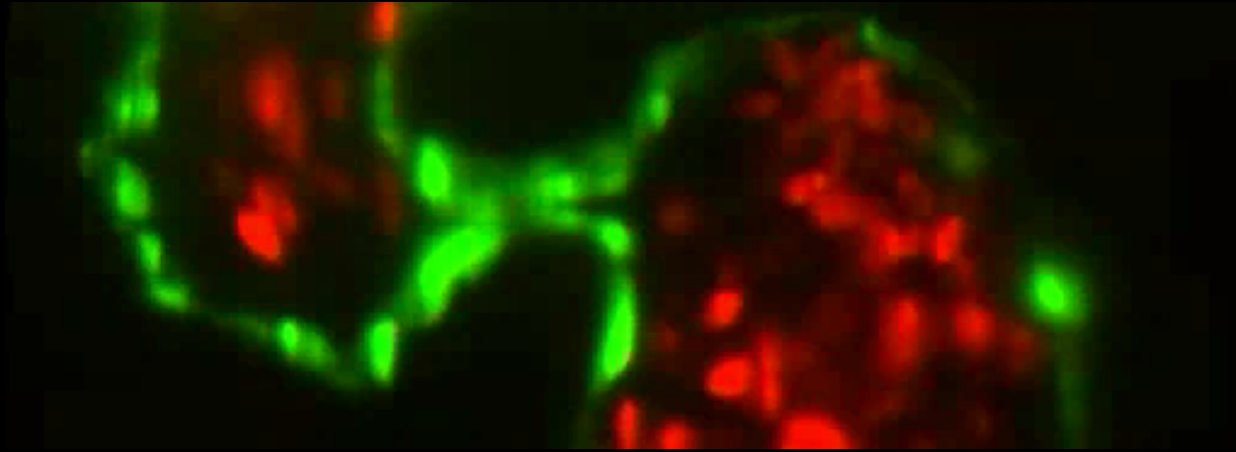
Valve development



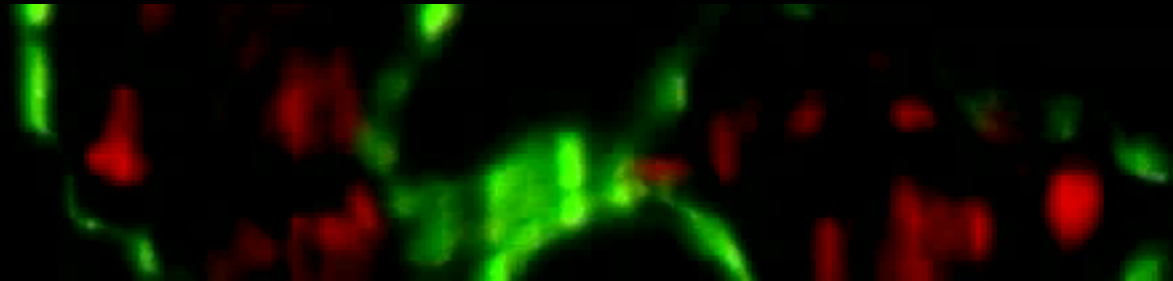
The early embryonic heart achieves unidirectional pumping without valves



ZEBRAFISH VALVE DEVELOPMENT

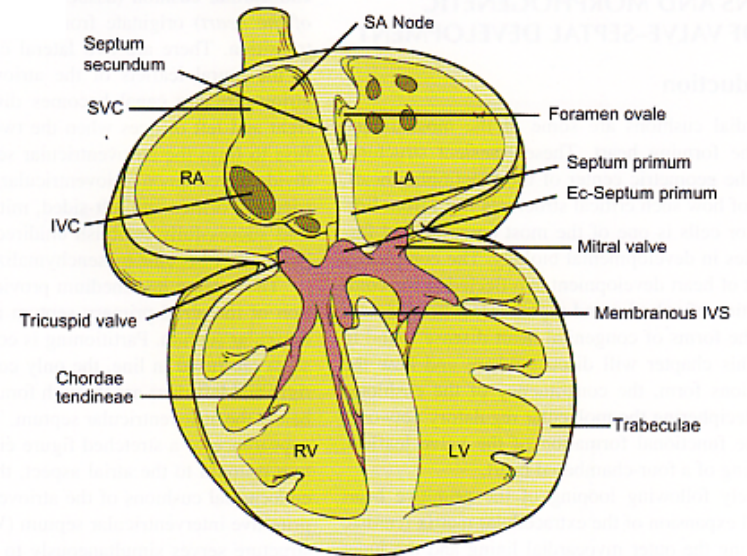
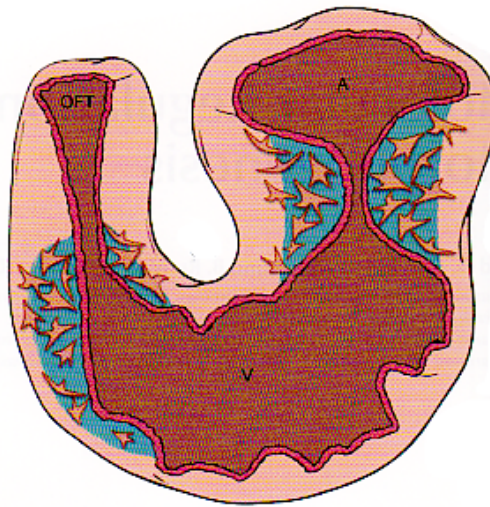
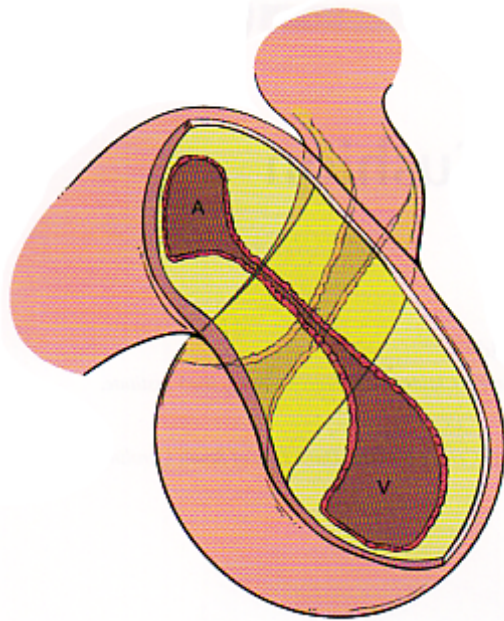


55 hpf



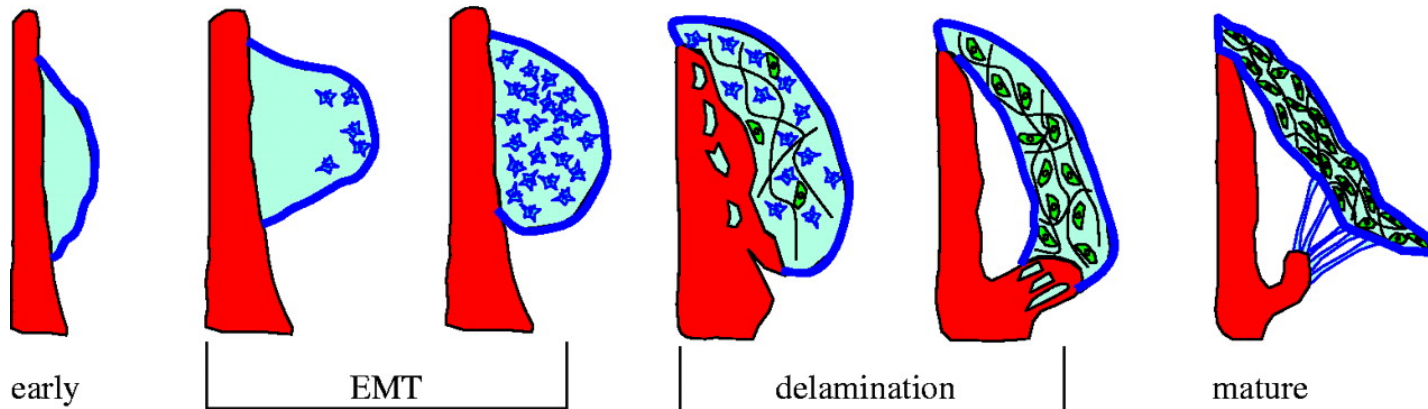
96 hpf

HEART VALVE DEVELOPMENT

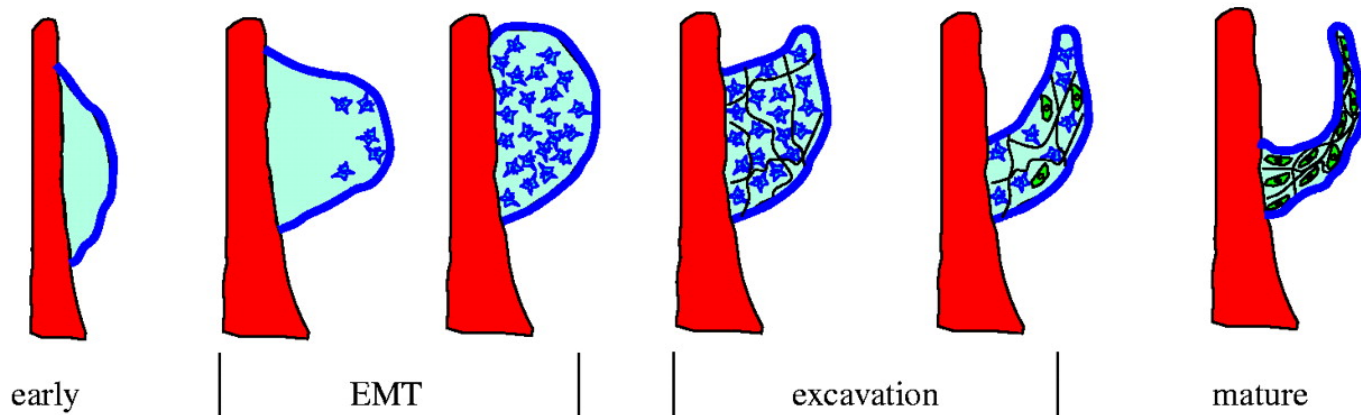


Cardiac cushions are the precursors of the cardiac valve

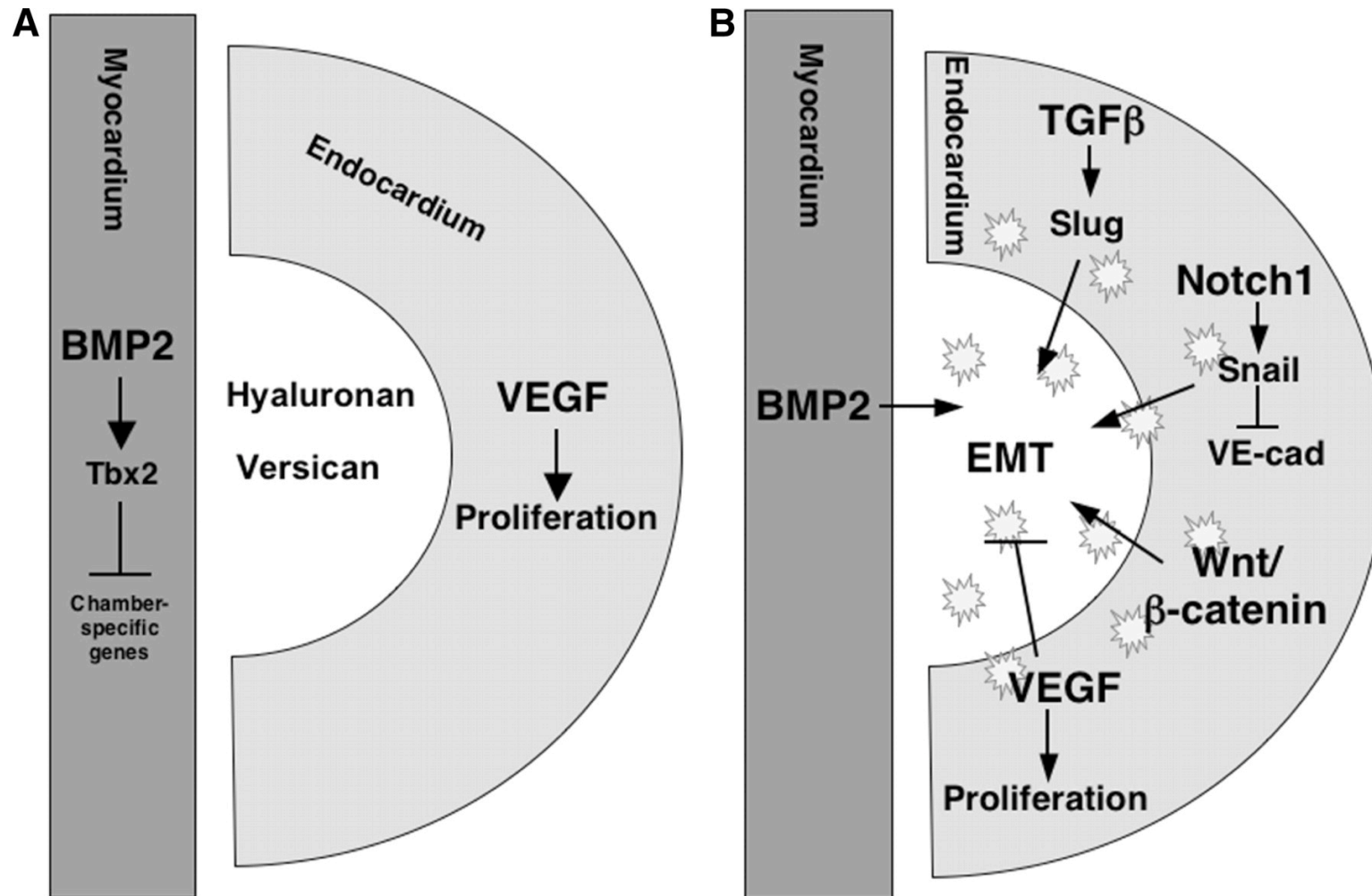
atrioventricular valves



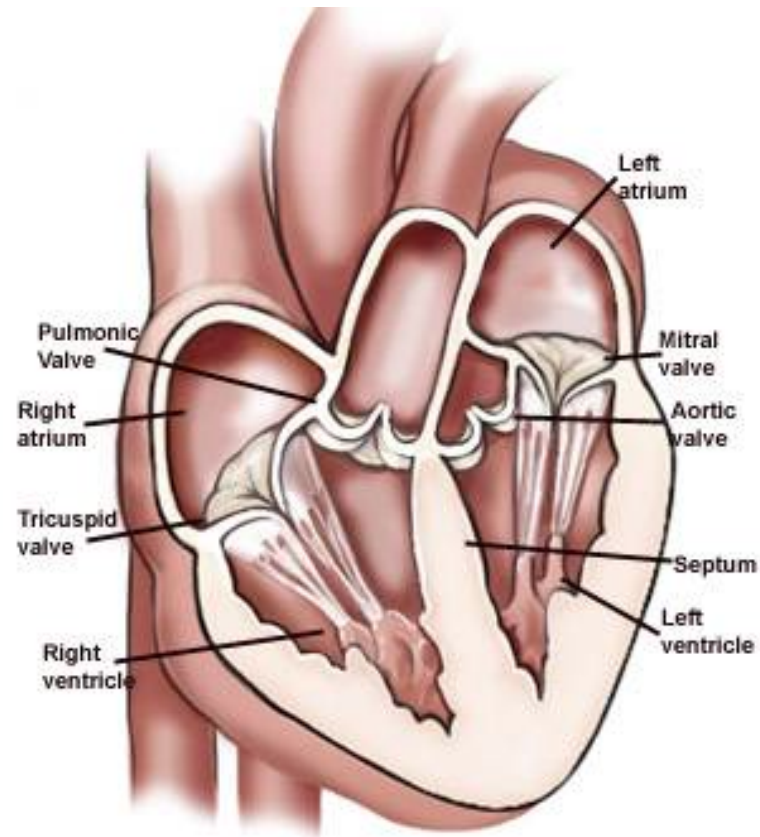
semilunar valves



Signaling pathways that are involved in controlling EMT during cushion development



The adult valvular apparatus



Summary

- Valves are formed initially by EMT of endocardial cells that migrate into the cardiac jelly in the region of the AV-canal and in the OFT.
- The signalling that induces EMT by the AV endocardium is a specific property of the AV canal myocardium and involves BMP2, TGF β , Notch, Wnt, VEGF signaling events with each of which have a specific role in cushion formation.
- Cushion formation however is more complex and involves the immigration of cells but also involves remodeling of the forming valve structure.

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