Modelling heart valve formation

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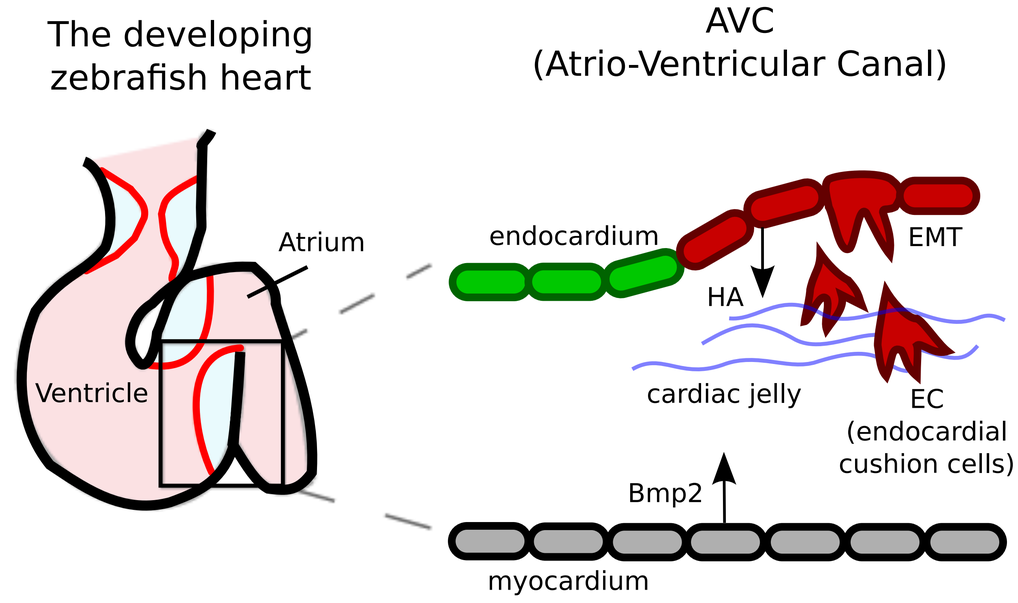
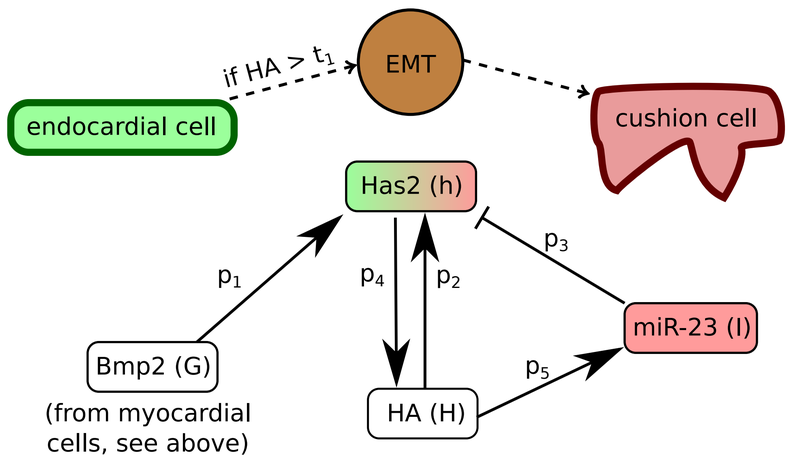
Morphology of heart valve formation

In the developing embryo heart valves emerge from the endocardium, the inner lining of the heart tube, due to an increased extracellular matrix (ECM) production at well defined positions. One of the main ECM components in this process is glycosaminoglycan hyaluronan (**HA**), secreted by the endocarial cells. After undergoing a so-called endothelial-mesenchymal transition (**endo-MT, EMT**), endocardial cells colonize the excess ECM scaffold, called endocardial cushion, forming the heart valves (see illustration on the right). This process requires the regulated secretion of HA. Expression of the main HA synthase, **Has2**, is regulated both negatively through micro-RNAs (eg: **miR-23**), and positively, through HA itself.



Model: the signaling network



...in words...

Bmp2 secreted from the myocardium upregulates the production of **Has2** in endocardial cells. Has2 synthesizes **HA** that induces the production of Has2, creating a **positive feedback loop**. Once the accumulated HA reaches a threshold value $\mathbf{t_1}$, endocardial cells become endocardial cushion (EC) cells. EC cells express **miR-23** that **downregulates** Has2 production.

... and equations

$$\frac{dG(t,r)}{dt} = D_G\nabla^2 G(t,r) - d_G G(t,r) + f(t,r) \quad (1)$$

$$\frac{dh(t,i)}{dt} = -d_h h(t,i) + \frac{p_1 G(t,i) + p_2 H(t,i)}{1 + p_3 I(t,i)} \quad (2)$$

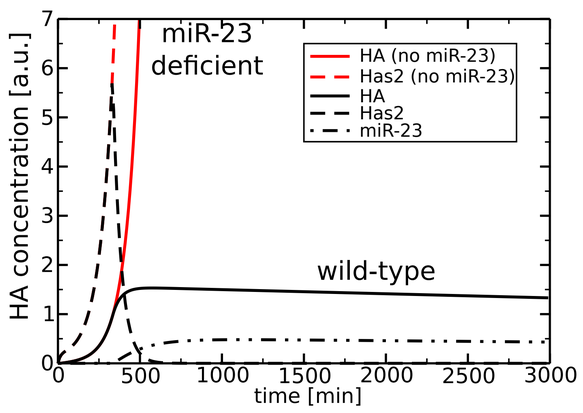
$$\frac{dH(t,r)}{dt} = D_H\nabla^2 H(t,r) - d_H H(t,r) + p_4 h(t,r) \quad (3)$$

$$\frac{dI(t,r)}{dt} = D_I\nabla^2 I(t,r) - d_I I(t,r) + p_5 g(i) H(t,r) \quad (4)$$

The mechanisms shown above are reminiscent of a **reaction-diffusion system**, and can be extended to such a system by allowing the diffusion of the inhibitor miR-23 ($D_I > 0$).

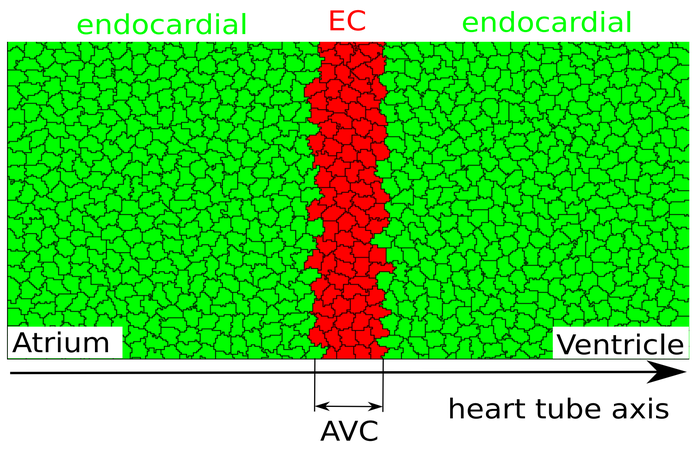
Simulation results

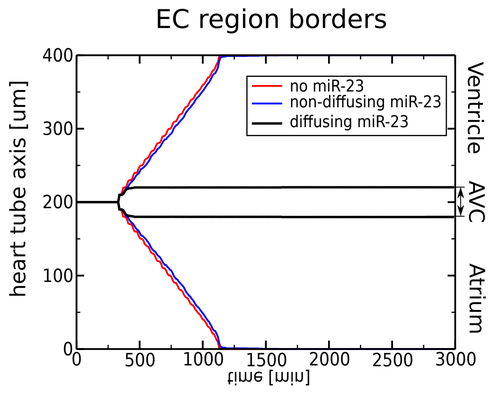
1.

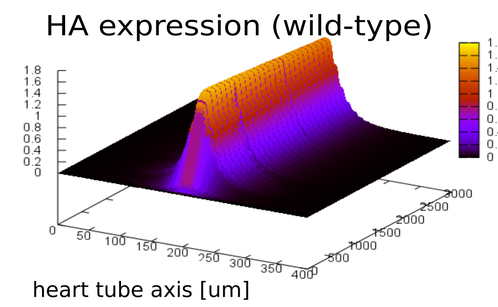


In agreement with experiments, **HA expression level in the AVC region** is relatively stable in the wild-type case (black curves), and increase significantly in the miR-23 deficient case.

2. Using a **spatially extended model**, we show that the system can produce a **localized expression of HA**, but only if the inhibitory signal (miR-23) is transfered to adjacent cells:







Conclusion:

1. Producing both Has2 and miR-23 in the endocardium can qualitatively explain the observed HA expression levels.

2. The model results suggest that miR-23 is exported from the endocardial cells. We hypothesize that miR-23 might be transported in exosomes.

Reference: Anne Karine Lagendijk, András Szabó, Roeland M.H. Merks and Jeroen Bakkers. (*in press*) Hyaluronan: A critical regulator of endothelial-to-mesenchymal transition during cardiac valve formation. *Trends in Cardiovascular Medicine.*

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