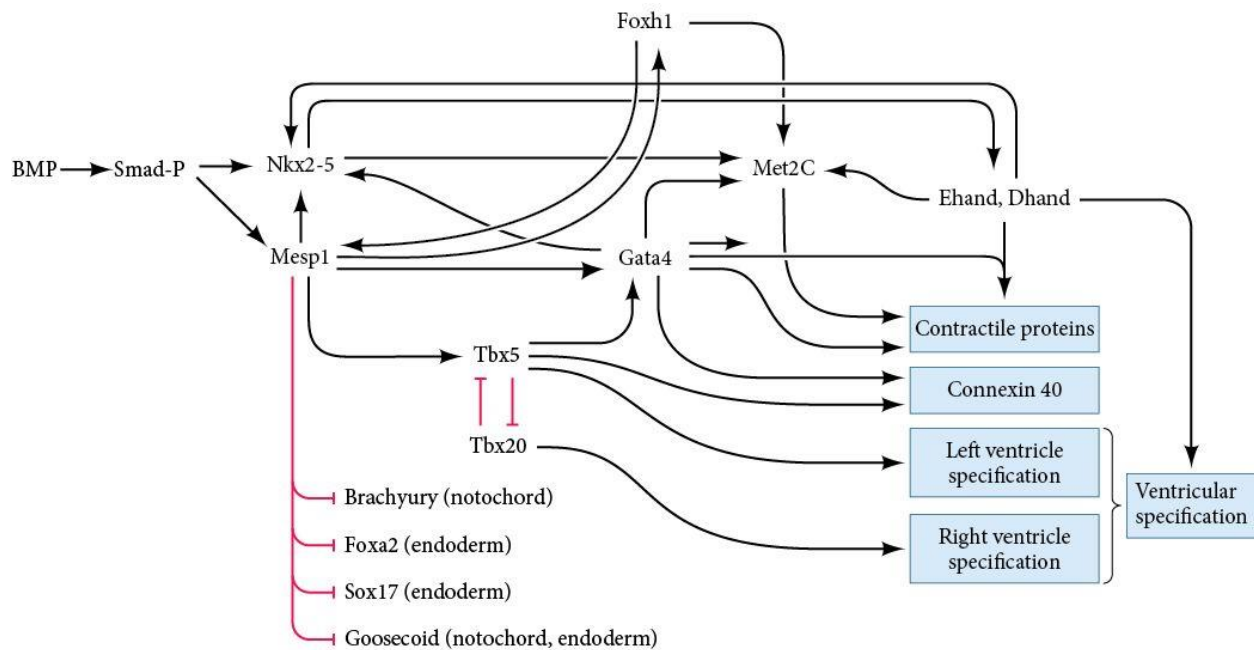


A Self-Sustaining Gene Regulatory Network Differentiates the Heart

Several proteins are expressed very early during heart development (see Figure 1). *Nkx2-5* and *Mesp1* are also critical in initiating a self-sustaining gene regulatory network. One of the genes active in this network encodes the *Gata4* transcription factor, which is first seen in the precardiac cells of chicks and mice when these cells emerge from the primitive streak. *Gata4* is necessary for activating numerous heart-specific genes as well as for activating expression of the gene for N-cadherin, a protein that is critical for both the formation of the cardiac epithelium and the fusion of the two heart rudiments into one tube (Linask 1992; Zhang et al. 2003).



After D. May et al. 2012. Nat Genet 44: 89-93

Figure 1 Model gene regulatory network for the vertebrate heart initiated by BMP signals. BMP signaling activates the pivotal switches *Nkx2-5* and *Mesp1*. These transcription factors act in concert to activate numerous heart-forming genes. *Mesp1* has also been shown to repress genes that would otherwise specify the cell into other fates. The antagonism between *Tbx20* (right side) and *Tbx5* (left side) can also be seen. This model is provisional, as new ChIP-Seq techniques have identified thousands of promoters activated at different stages of heart development. (After May et al. 2012.)

In addition to activating a group of core heart-forming genes, *Mesp1* also helps activate different patterns of protein synthesis in the heart fields on each side of the embryo. *Mesp1* and *Nkx2-5* instruct the cells of the second heart field to express the *Foxh1* gene, which commits these heart precursor cells to become the right ventricle and outflow tract (von Both et al. 2004). In the first heart

field, *Mesp1* activates the *Tbx5* gene, whose product is critical for heart tube and left ventricle development (see Figure 18.16; Koshiba-Takeuchi et al. 2009). In these early cells, *Tbx5* acts with *Gata4* and *Nkx2-5* to activate numerous genes involved in heart specification. Later, *Tbx5* becomes restricted to the atria and left ventricle. The ventricular septum (the wall separating the left and right ventricles) is formed at the boundary between those cells that express *Tbx5* and those that do not. *Tbx5* protein works antagonistically to *Tbx20*, which becomes expressed in the right ventricle. When the *Tbx5* expression domain is ectopically expanded, the location of the ventricular septum shifts to this new location. Moreover, a conditional knockout of the mouse *Tbx5* gene—specifically inactivating it during ventricular development—leads to the formation of a lizardlike ventricle that lacks any septum (Takeuchi et al. 2003; Koshiba-Takeuchi et al. 2009). Thus, *Tbx5* is extremely important in separating the left and right ventricles. Mutations in the human *TBX5* gene cause Holt-Oram syndrome (Bruneau et al. 1999), characterized by abnormalities of the heart and upper limbs.

All the material on this website is protected by copyright. It may not be reproduced in any form without permission from the copyright holder.

© 2023 Oxford University Press