HIGHLIGHTS

DEVELOPMENTAL BIOLOGY

A balancing act

Heart development requires a delicate balance of proliferation and differentiation that is underpinned by the finely tuned execution of genetic programmes. Chen *et al.* and Shin *et al.* now identify and characterize a new mouse homeobox gene, *Hop*, which, although unable to bind DNA, modulates cardiac-specific gene expression by interacting with known major players in cardiogenesis.

Both groups isolated *Hop* from a mouse EST database while searching for new homeobox genes expressed in the heart. Sequence and experimental analysis of Hop's homeodomain revealed that this 73 amino-acid protein is unlikely to have retained its DNA binding ability.

Not surprisingly, *Hop* is expressed in the heart. Its expression in the embryonic heart starts shortly after that of *Nkx2-5* — a principal activator of heart-specific transcription — suggesting that it might be one of its targets. The fact that *Hop* expression is downregulated in *Nkx2-5*-null mice confirmed this prediction. Chen *et al.* also found Nkx2-5 consensus binding sites upstream of *Hop* and showed that Nkx2-5 binds them *in vitro*, again confirming that *Hop* is a direct target of Nkx2-5.

Approximately half of the *Hop*-null homozygotes generated by both groups have abnormal myocardium and die during embryogenesis from heart failure. Shin *et al.* found that $Hop^{-/-}$ embryos that died had thin, often ruptured ventricle walls, whereas $Hop^{-/-}$ adults had thickened ventricle walls, mainly as a result of increased numbers of cardiomyocytes. The authors explain this paradoxical observation by evoking a dual role for Hop in heart development — first it acts to expand the myocardium, whereas later it restricts its proliferation.

Hop seems to fulfil its functions by modulating a subset of heart-specific genes. Although it cannot bind directly to their promoters, it can affect their expression by binding to another crucial transcription regulator in the developing heart, Srf (serum response factor), therefore preventing it from activating genes downstream.

Both groups showed that Hop — which might be vertebrate specific — seems to be involved in a balance between myocardial expansion and restriction that is necessary for proper heart development. We now know that it achieves this by modulating the action of Srf, but what of its other targets? Shin *et al.* have already made the first step towards addressing this question by using microarray analysis to look at the differences in gene expression between $Hop^{-/-}$ and wild-type mice. Among many future directions of research is Hop's involvement in heart disease — understanding Hop function might be relevant to continuing efforts to regrow heart muscle by manipulating the transition of myoblasts from proliferation to terminal differentiation.

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References and links

ORIGINAL RESEARCH PAPERS Chen, F. *et al.* *Hop* is an unusual homeobox gene that modulates cardiac development. *Cell* **110**, 713–723 (2002) | Shin, C. H. *et al.* Modulation of cardiac growth and development by HOP, an unusual homeodomain protein. *Cell* **110**, 725–735 (2002)