MOUSE MODELS

Going straight for the heart

A key event in vertebrate heart development is the formation of a wall (septum) that divides the heart into left and right atria and ventricles — failure to do so is one of the main causes of congenital heart defects in newborns and is known as atrioventricular canal defect (AVCD). Using sophisticated mouse genetics, Jiao and colleagues now show that Bmp4 is a key signal from the myocardium to the mesenchyme/endocardium, the levels of which are crucial for complete atrioventricular separation. As well as shedding light on this developmental process, the authors have created an excellent mouse model of this human congenital defect.

Previous expression studies and tissue-culture experiments have established that Bmp4 has a role in heart development. But Bmp4 is essential in early embryonic development, so a direct *in vivo* test of its role in heart development was not possible until now. Jiao *et al.* used a hypomorphic *Bmp4* allele and using the Cre/loxp approach manipulated the levels of Bmp4 specifically in heart muscle cells. The choice of cell type was dictated by their careful expression study in *Bmp4*^{lacZ} mouse embryos, which showed that *Bmp4* is expressed in these cells in the region where the septa are formed.

Whereas cell-type specificity was achieved using a rat troponinT promoter to drive Cre recombinase expression, the different levels of *Bmp4* expression were achieved using different combinations of hypomorphic, wild type and null alleles.

Atrioventricular septation turns out to be highly sensitive to Bmp4 levels — as the levels decrease, septum formation is less and less successful. Interestingly, Bmp4 does not seem to be required for the early events that lead to septum formation, but as Jiao *et al.* suggest, this might be because other Bmps that are expressed in that part of the heart at that time might compensate for the lack of Bmp4.

AVCD commonly occurs in Down syndrome babies. Although mouse models of Down syndrome can be used to study AVCD, Jiao and colleagues have created the first animal model in which AVCD is a primary defect. This is also the first identification of a molecular signal between the myocardium and the mesenchyme/endocardium.

Undoubtedly, overcoming early lethality by using conditional mutants is the way forward for studies of late developmental events such as heart development, and similar approaches are set to provide further valuable insights into the intricacies of heart development.

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References and links

ORIGINAL RESEARCH PAPER Jiao, K. *et al.* An essential role of Bmp4 in the atrioventricular septation of the mouse heart. *Genes Dev.* **17**, 2362–2367 (2003)

FURTHER READING Harvey, R. P. Patterning the vertebrate heart. *Nature Rev. Genet.* **3**, 544–556 (2002)