Exciting news: catecholamines in induction and regionalization of the heart

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This editorial refers to ‘Tyrosine hydroxylase is expressed during early heart development and is required for cardiac chamber formation’ by C. López-Sánchez et al., pp. 111–120, this issue.

The heart develops in the anterior half of the vertebrate embryo. Soon after gastrulation has commenced, the heart starts to develop from cells that are part of the splanchnic layer of the lateral plate mesoderm (Figure 1).1 The identification of molecules involved in cardiac induction in the embryo is of great interest, since these are same as those that would be required to efficiently control cardiac differentiation in stem cells. Thus, the knowledge gained in embryos appears to be directly relevant for regenerative medicine.2

Despite its evolutionary distance to mammals, the chick embryo is a valuable model system to work out the mechanisms of cardiac specification. The embryo is large and accessible, and therefore, manipulations at the time of cardiac specification and early heart formation are easily performed. Research in the last 15 years utilizing this model organism has identified several signalling molecules that are important for cardiac induction.1 Heart formation depends on the presence of the foregut endoderm in the vicinity. If this endoderm is experimentally removed, no heart will develop.7 Moreover, the foregut endoderm is able to instruct mesoderm, which normally would differentiate into blood, to change its fate, and instead develop into cardiac tissue.8 The inducing factors present in the foregut endoderm are not species-specific since co-culture of avian foregut endoderm with murine embryoid bodies results in extensive cardiac differentiation.5

Several signalling factors have been identified that act as cardiogenic inducers and are expressed in the foregut endoderm at the time of cardiac induction (Figure 1).1 These include BMP2,4–8 FGF8,3 and secreted antagonist of canonical Wnt signalling.9 Less well defined is the contribution of the factors Sonic hedgehog and Nodal in cardiac induction.1 Some other cardiogenic factors such as Wnt11 are expressed in the cardiac mesoderm itself and probably act in an auto-regulatory loop to enhance and maintain cardiac specification.10

The identification of a novel signalling factor is reported that has heart-inducing activity.11 The authors report that tyrosine hydroxylase (TH), which is the rate-limiting enzyme in catecholamine biosynthesis, is strongly expressed in the cardiac mesoderm. Biochemical analysis reveals that in the early chick embryo, the only catecholamines present are L-DOPA (predominant) and dopamine, while noradrenaline is not produced. Inhibition of TH activity or forced expression resulted in a loss or ectopic induction of cardiac tissue, respectively. These data suggest that TH activity is essential for heart development. However, the actual mechanism of how TH modulates cardiac recruitment at the molecular level is presently unexplored. An attempt was made to link L-DOPA signalling to the well-established cardiogenic BMP2 pathway, and it was found that exogenous L-DOPA enhanced BMP2 expression. This suggests that TH might, via L-DOPA production, positively feed back and enhance cardiogenic signalling in the foregut endoderm. If TH activity was an essential element of early heart development, one would expect this pathway to be evolutionarily conserved. Indeed, TH mRNA expression can be found in the murine embryo at the right time. However, loss of TH, although lethal due to foetal cardiovascular failure, does not affect early cardiovascular development.12

Although there always remains the argument of genetic redundancy to explain the differing outcomes of the experiment in the chick and the mouse, it is therefore possible that this pathway may not be important in mammals. The ultimate test in this context will be to apply L-DOPA and interfere with TH activity in murine stem cell cultures and study cardiac differentiation under these conditions.

Interestingly, TH has another role in the developing heart. TH is also involved in the regionalization of the heart. The allocation of cells to the atrial and ventricular lineages is known to be regulated by the retinoic acid signalling pathway (RA).13 Gain-of-function of RA results in the suppression of ventricular fate and an increase in atrial identity, whereas the reverse outcome is the result of the loss-of-function experiment.14 It is now demonstrated by López-Sánchez11 that RA at least partially acts through TH. Since the molecular pathway involved in controlling atrial-specific gene expression has been defined and cis-acting promoter elements and trans-acting factors are known, it will be interesting and also important to define the molecular mechanism utilized by L-DOPA in this context.

The fact that modulating TH activity also induces cardiac arrhythmias in the chick embryo suggests that in the early heart, L-DOPA may be an important modulator of cardiac pacemaker activity. At present, little or nothing is known about dopamine receptor

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expression in the early heart. Moreover, the pharmacology of pacemaker activity in the early embryo is a neglected research area. Thus, this new study provides many exciting and stimulating insights in the role of catecholamines during early cardiac development.

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References