Tbx3: a new trick for an ‘old’ myocyte?

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This editorial refers to ‘T-box transcription factor TBX3 reprogrammes mature cardiac myocytes into pacemaker-like cells’ by M.L. Bakker et al., pp. 439–449, this issue.

Tbx3: a new trick for an ‘old’ myocyte? Well, not quite… Tbx3 is a T-box transcription factor that is expressed in the pacemaking and conduction system myocytes beginning during early embryonic stages of cardiac development.1 When expressed in embryonic atrial chamber myocytes, ectopic induction of spontaneous pacemaking activity in atrial myocardium was observed in vivo, thereby suggesting that Tbx3 can ‘impose’ pacemaking capability upon otherwise unsuspecting working myocytes.2 Bakker et al.3 test the hypothesis that Tbx3 would also be able to induce pacemaker activity in mature adult cardiac myocytes. Like the proverbial ‘old dog’, however, it appears that it is also difficult to teach old myocytes this new trick.

Bakker et al.3 show that while Tbx3 does repress certain genes typically excluded from pacemaking centres such as those encoding the gap junction proteins connexin 40 (Cx40) and connexin 43 (Cx43) in adult mouse atrial myocytes, it failed to induce the pacemaker channel protein encoded by the hyperpolarization-activated cyclic nucleotide-gated 4 (Hcn4) gene. Consequently, no spontaneous sinusoidal action potentials characteristic of those typically observed in sinoatrial node pacemaker myocytes were observed in adult myocytes overexpressing Tbx3. This is not to say, however, that Tbx3 did not have an effect on cellular electrophysiology. The authors show repression of inward rectifier (I\textsubscript{K1}) and sodium currents (I\textsubscript{Na}) in adult myocytes from mice where Tbx3 expression was induced. Such repression is generally consistent with the low or absent levels that mature sinoatrial node pacemaker myocytes.4

In contrast, exogenous or ectopic expression of Tbx3 in neonatal ventricular myocytes in culture1 or in atrial myocytes from late embryonic/fetal stages of development in vivo5 did result in Hcn4 expression and the appearance of spontaneous sinusoidal action potentials. This appears to be one of the major differences affected by Tbx3 in young (immature) myocytes compared with those typically observed in mature sinoatrial node pacemaker myocytes. The latter are indicated, but only the immature myocytes develop true pacemaking capability. How might these results be explained? Tbx3 is a transcriptional repressor that is closely related to Tbx2 and Tbx5 and has been implicated in a diverse array of developmental processes, including those associated with stem cells, cancer progression, and mammary gland, limb, and heart development.6 Within the heart, Tbx3, Tbx2, and Tbx5 show partially overlapping patterns of expression and appear to have similar or partially redundant biological functions.6–9 Tbx3 also appears to work in concert with Tbx18 and Tbx20 to delineate regional cardiac morphological differentiation within the sinoatrial and atroventricular nodes.9,10 Tbx3 has been shown to down-regulate Cx43 gene expression through interactions with Msx1 and Msx2, members of the muscle segment homeobox gene family.7 There is also good evidence indicating that Tbx3 exerts transcriptional repression of the Cx40 and natriuretic precursor peptide A (Nppa) genes.1,2 An important point here is that each of these repressed gene targets (i.e. Cx43, Cx40, and Nppa) normally show little or no expression in mature sinoatrial and atrioventricular nodes,11 although this is an oversimplification because limited expression of Cx40 and Cx43 has been observed within discrete regions of different components of the pacemaking and conduction systems during development and even into maturity.11–13 Still, it is generally true that mature nodal tissue in particular shows only limited expression of these genes, and it is reasonable to surmise from the available evidence that Tbx3 and its cohorts actively contribute to their repression in these regions.

Another important influence exerted by Tbx3 is its apparent role in regulating cell proliferation in the developing heart,5,14 and this likely accounts, in part, for the restricted cell growth and proliferation found in sinoatrial and atroventricular junctions relative to rapidly expanding chamber myocardium during embryonic/fetal periods of heart development. Consistent with this idea, Tbx3 knock-down experiments result in cardiac morphological defects that become manifest during early embryonic/fetal development.8,14 These include outflow tract and ventricular septal defects. Interestingly, however, Tbx3 does not appear to be required for structural/morphological development of the nodes themselves.10 To recap what is known, Tbx3 is a transcriptional repressor that functions to restrict cell proliferation during key points in cardiac development, and it works in conjunction with other transcription factors like Msx1 and Msx2 to repress expression of certain target genes, such as Cx43, Cx40, and Nppa, among others. Within the developing heart, Tbx3 expression is normally confined primarily to pacemaking and conduction system myocardium. Aberrant expression of Tbx3 in atrial

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chamber myocardium leads to induction of ectopic pacemaker activity in early heart development, but adult atrial chamber myocytes only partially convert to a pacemaker phenotype when Tbx3 is introduced exogenously. Conversely, a recent study has shown that selective down-regulation of Tbx3 in adult hearts leads to rather severe conduction system defects and an increased propensity for development of potentially lethal cardiac arrhythmias.15

Thus, it appears that Tbx3 may be a necessary prerequisite for proper development and function of the cardiac pacemaking and conduction system, but it is not sufficient by itself to fully induce this phenotype in mature adult myocytes. It remains to be determined what other factors and/or conditions are needed to activate Hcn4, cyclic intracellular calcium oscillations, and other important physiological characteristics needed to drive cardiac pacemaking, and this promises to be an active area of investigation for some time to come. Who knows, maybe this elusive second component will enable an old myocyte to learn a new trick after all. We shall have to wait and see...!

Conflict of interest: none declared.

References

Figure 1 Differential effects of exogenous Tbx3 on development of pacemaker activity in immature (embryonic/neonatal) and mature (adult) cardiac myocytes.