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The early heart remodelled

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Abstract

What factors direct the formation of heart muscle in the developing embryo? Unexpectedly, a chromatin-remodelling protein complex turns out to be a crucial determinant of cardiac-cell fate.

The chances are that many of us will develop heart disease at some point in our lives. So understanding how heart muscle, heart valves and other heart structures regenerate is particularly important. The work published by Takeuchi and Bruneau in this issue (page 708)¹ takes us a step closer to achieving this goal, and also provides us with intriguing insights into the role of chromatin-remodelling complexes in the developing heart.

ATP-dependent chromatin-remodelling complexes are multi-protein machines that use the energy of ATP hydrolysis to modify the structure of chromatin (the complex of DNA and histone proteins), thereby activating or repressing genes. The vertebrate chromatin-remodelling BAF complexes resemble the yeast chromatin-remodelling complexes SWI/SNF, RSC and SWR. However, whereas each yeast complex is probably made up of an invariant set of protein subunits, in BAF complexes, combinatorial assembly of subunits produces distinct functional complexes. For example, mouse BAF complexes consist of 11 subunits; one of these is the Baf60 subunit, which is encoded by three genes, *Baf60a*, *Baf60b* and *Baf60c* (ref. ²). BAF complexes usually repress their target genes, whereas yeast SWI/SNF activates all known targets^{3,4}, implying that there are mechanistic as well as structural differences between BAF complexes and SWI/SNF. So far, how these complexes regulate gene expression is a matter of speculation.

Takeuchi and Bruneau¹ focused on BAF complexes because these proteins have been implicated in cardiac development — a screen conducted in early mouse embryos found that *Baf60c* was expressed selectively in tissues that give rise to the heart⁵. Notably, when *Baf60c* was depleted experimentally, heart formation was defective⁵. Takeuchi and Bruneau reasoned that, as *Baf60c* is selectively expressed in mouse embryonic cardiac tissue, it might contribute to heart formation if injected into the embryo outside the heart developmental fields. Indeed, when the authors inject *Baf60c* together with the cardiogenic transcription factor *Gata4* outside the heart fields, these tissues express heart-specific genes¹. Baf60c and *Gata4* also induce expression of another transcription factor, *Nkx2-5* (ref. ¹). Thus, it seems that *Gata4* cooperates with Baf60c to set up a gene-expression program that drives heart development. And from what we know about BAF complexes, it seems likely that the transfected Baf60c assembles with the other ten subunits to form a cardiogenic BAF complex (Fig. 1). Remarkably, addition of yet another transcription factor, *Tbx5*, transforms non-cardiac embryonic cells into beating heart muscle¹.

So how do *Gata4* and Baf60c cooperate to induce the expression of cardiac-specific genes? On the basis of results obtained from chromatin immunoprecipitation studies (a technique

that detects the binding of proteins to DNA using antibodies), the authors propose that Gata4 binds directly to Baf60c (Fig. 1). They also find that Baf60c doesn't function by interacting with the general transcriptional apparatus. Instead, it is required for Gata4 binding to DNA (Fig. 1), consistent with its apparently instructive role in this model system. Interestingly, this is the opposite to the situation in yeast, in which the SWI5 transcription factor first binds to DNA and then recruits the SWI/SNF complex to its target promoter⁶. BAF complexes contain domains that can interact with modified histones and DNA; hence, in the absence of a transcription-factor 'guide', they might find their targets by multivalent recognition of a specific genetic locus⁷.

Apparent cooperation between chromatin-remodelling complexes and tissue-specific transcription factors is not unique to the developing heart. A similar process occurs in embryonic stem cells, in which a variant of the BAF complex that is apparently found only in these cells (esBAF) interacts with Oct4 and Sox2 transcription factors⁸. esBAF complexes are essential for embryonic-stem-cell formation and also for formation of the inner cell mass — the part of the embryo that is pluri-potent, giving rise to all cell types. The distinctive subunit composition of esBAF⁹ seems to produce its biological specificity, similar to the way that letters are combined into words with specific meanings. Indeed, misspelling the esBAF 'word', by incorporating incorrect subunits, results in a loss of pluripotency.

There are also specialized chromatin-remodelling complexes in neural progenitors (npBAF) and neurons (nBAF), and misspelling the 'word' in these cells, for instance by genetic ablation of one subunit and replacement with another, leads to lethal defects in the developing nervous system¹⁰. In each neural complex there seems to be specific interactions between the chromatin-remodelling complex and the specific cellular transcription factors.

The instructive role of BAF complexes in cellular differentiation is unexpected, as previous biochemical studies had suggested that the complexes have a nonspecific role in transcription, either functioning as part of the general transcriptional machinery or directing the binding of TBP (a transcription initiation factor) to promoters. But even in yeast, the association of SWI/SNF with general transcription factors or with transcription-associated RNA polymerase has not been consistently reproduced. Takeuchi and Bruneau's findings are, however, consistent with the observation that two subunits of the npBAF complex, Baf45a and Baf53a, can direct the division of neural stem cells in places in the developing nervous system where these cells don't usually proliferate¹¹.

The emerging model of the genetic circuitry that drives heart development^{1,12} (Fig. 2) now suggests that Baf60c may be near the top of the hierarchy. This instructive role is not due to its tissue-specific expression, because it is also found in npBAF complexes^{11,13}. Perhaps Baf60c has some general role in the control of multipotent cells, by modifying chromatin structure and allowing genes to remain accessible for later activation. Alternatively, it could achieve its specificity by combining with other BAF subunits that have restricted expression, generating an assembly of subunits found only in the regions of the embryo that give rise to the heart.

The details of assembly of the cardiogenic BAF complex (let's call it cBAF) suggest that Takeuchi and Bruneau's strategy¹ for generating heart tissue might work even better if they could reduce expression of the competing non-cardiogenic Baf60 subunits (Baf60a and Baf60b), which might have instructive roles for other tissues. Additional biochemical studies will be required to determine the subunit composition of this complex or family of complexes — a challenging task, given the tiny number of cells that are involved in initially specifying the heart.

Clearly, the next step will be to determine if skin or blood cells can be transformed directly into beating heart muscle using Baf60c and its co-regulators. An alternative approach might be to use induced pluripotent stem cells — cells from adult tissue that have been reprogrammed into stem cells — and to exploit our clearer knowledge of the genetic network involved in cardiac development^{1,12} to control heart formation. These strategies might allow direct regeneration of defective or diseased heart muscle using a patient's own tissue, without the need for immunosuppression.

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Figure 1. A chromatin-remodelling complex instructs heart development

Takeuchi and Bruneau¹ induced the expression of the cardiac-specific Baf60c subunit and the transcription factor Gata4 in mouse embryonic tissues outside the heart developmental fields. **a**, Transfected Baf60c probably assembles with the other ten BAF subunits to form a cardiogenic BAF complex (cBAF). Baf60a and Baf60b are not incorporated into cBAF. **b**, cBAF seems to bind to target loci, perhaps by multivalent recognition through histone- and DNA-binding domains. **c**, cBAF recruits Gata4 through a presumed interaction between Baf60c and Gata4, which results in the expression of heart-specific genes. The arrangement of subunits in the BAF complex is not yet established.

Figure 2. The genetic circuitry regulating heart development

In mammals, extracellular signals act directly or indirectly to produce localized expression of the BAF complex subunit Baf60c and the transcription factor Gata4 in the area of the embryo that gives rise to the heart. Baf60c and Gata4 work together with another cardiogenic transcription factor, Tbx5, to activate genes encoding other regulators of heart development — Mef2, Nkx2–5, Hand and Isl1. These directly activate certain muscle-specific genes. Additional steps, requiring Tbx5, organize synchronous activity of cardiac muscle cells, giving rise to beating heart muscle. (Modified from ref. ¹².)