EPIGENETICS

Pioneering the path from methylation to transcription

Epigenetic marks have a key role in setting up the transcriptional programmes that define specific cell types, but it is not clear how the marks are interpreted to give rise to differential transcription. New research shows that the FOXA1 transcription factor binds to methylated enhancers and opens the chromatin to facilitate access by other transcription factors.

The Forkhead transcription factor FOXA1 is known to be a pioneer factor in the development of several organs and cancers, binding to *cis*-regulatory elements and recruiting other transcription factors to induce transcription. Using **chromatin immunoprecipitation combined with microarray analysis (ChIP-chip)**, Brown and colleagues identified binding sites for FOXA1 in breast and prostate cancer cells. The majority of

sites in both lines were in enhancer rather than promoter regions, were not shared with the other cell type and were associated with genes that are uniquely expressed in that line.

When the authors looked for epigenetic marks that were associated with FOXA1 binding, they found a significant over-representation of the activating H3K4me1 and H3K4me2 marks (histone H3 monomethylated and dimethylated at lysine 4, respectively) around the bound sites. Artificially reducing the levels of these marks by overexpressing a demethylase reduced the levels of FOXA1 binding, showing that this binding occurs in response to the marks rather than causing them. Instead, FOXA1 binding caused an increase in DNase I sensitivity at the sites to which it is recruited, showing that FOXA1 binding leads to an

opening of the chromatin structure — a feature that is associated with increased transcription.

This suggests a model in which FOXA1 acts as the initial reader of the epigenetic signature, and then opens up chromatin to allow the recruitment of other transcription factors that generate the expression programme of the cell. It will be interesting to see if other pioneer transcription factors operate through similar mechanisms.

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ORIGINAL RESEARCH PAPER Lupien, M. & Eeckhoute, J. *et al.* FoxA1 translates epigenetic signatures into enhancer-driven lineage-specific transcription. *Cell* **132**, 958–970 (2008)

FURTHER READING de la Serna, I. L., Ohkawa, Y. & Imbalzano, A. N. Chromatin remodelling in mammalian differentiation: lessons from ATP-dependent remodellers. *Nature Rev. Genet.* **7**, 461–473 (2006)