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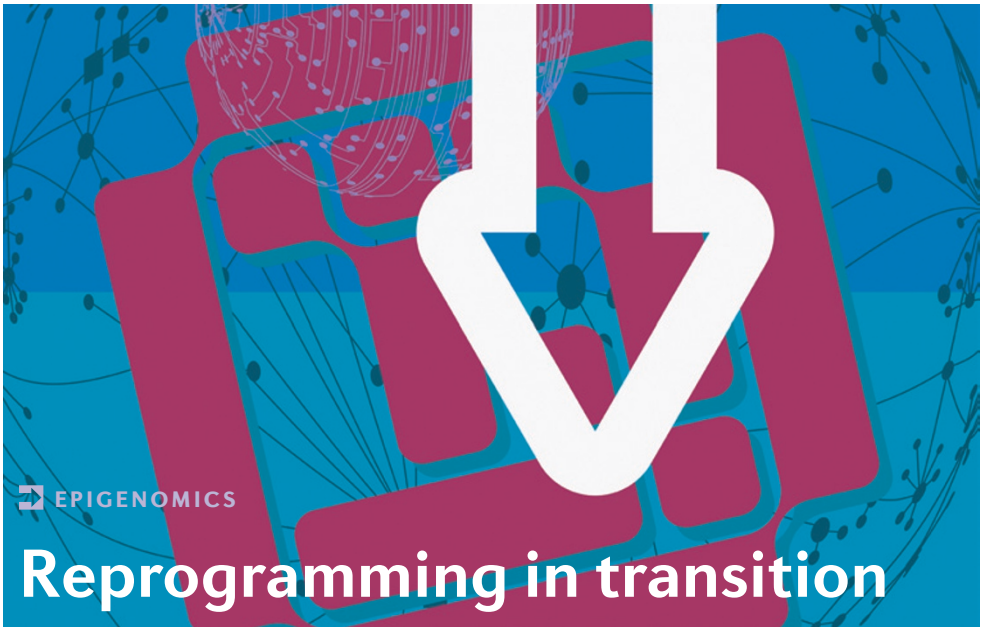

Reprogramming in transition

Reprogramming of the mammalian epigenome has been the subject of intense scrutiny in the contexts of germ cells and stem cells. Now, a new study reveals that epigenome reprogramming is also a crucial feature of epithelial-to-mesenchymal transition (EMT) — an example of extreme cellular plasticity that occurs during normal development and during transformation of cells to malignancy.

Working with cultured mouse hepatocytes, McDonald and colleagues used transforming growth factor-β (TGFβ) to induce EMT. As well as undergoing changes in gene expression and cell shape that are consistent with EMT, these cells also underwent changes in the nucleus, including a shift to a more 'open' chromatin state than that observed in untreated cells. The authors showed that DNA methylation patterns were unchanged during EMT, but western blotting revealed significant changes in bulk levels of three histone modifications. Specifically, levels of the heterochromatic mark dimethylation of histone H3 at lysine 9 (H3K9me2) were reduced, whereas those of H3K36me3 and H3K4me3 — both of which are associated with transcriptionally active chromatin — were increased.

How is this epigenomic reprogramming brought about, and what contribution does it make to the changes in cell characteristics? Using RNAi knockdown, McDonald and colleagues found that the histone demethylase LSD1 (also known as KDM1A) was required for the altered levels of histone modifications that follow TGFβ treatment. LSD1 usually interacts with co-repressors that bring about H3K4 demethylation and promote heterochromatin formation. However, the authors provide evidence that EMT involves a switch to LSD1 interaction with co-activators that instead promote increases in H3K36me3 and H3K4me3. Furthermore, LSD1 was required for the increased motility and chemoresistance of cells following TGFβ treatment — an indication that epigenomic reprogramming is key to altered cell function during EMT.

McDonald and colleagues went on to examine the specific locations in the genome where these epigenetic changes occur. Chromatin immunoprecipitation followed by microarray (ChIP–chip) experiments revealed the importance of large organized heterochromatin K9 modifications (LOCKs), which are lost during transformation of some cancer cell lines. The vast majority of LOCKs showed reduced H3K9me2 following EMT. Furthermore, much of the increase in H3K36me3 was seen at genes that lie at the boundaries between LOCKs. Many of these genes have functions in processes that are highly relevant to EMT, such as cell migration and cell adhesion. Finally, increased H3K4me3 levels were accounted for by the formation of domains of this mark over certain LOCKs.

This study expands the range of contexts in which epigenomic reprogramming is known to be important and fits in well with the theory that EMT involves changes of differentiated cells to a stem-cell-like state. The role of LOCKs in epigenome dynamics will be an important topic for further investigation.

Louisa Flintoft

ORIGINAL RESEARCH PAPER McDonald, O. G. *et al.* Genome-scale epigenetic reprogramming during epithelial to mesenchymal transition. *Nature Struct. Mol. Biol.* 3 Jul 2011 (doi:10.1038/nsmb.2084)
FURTHER READING Plath, K. & Lowry, W. E. Progress in understanding reprogramming to the induced pluripotent state. *Nature Rev. Genet.* **12**, 253–265 (2011)