EPIGENETICS

Misreading the code

A new study has shown that the deregulation of histone methylation at loci that encode differentiation-specific transcription factors is oncogenic, suggesting that misinterpretation of the histone code could be an important mechanism in cancer.

Plant homeodomain (PHD) fingers are evolutionarily conserved protein modules that recognize different states of histone methylation. In some patients with acute myeloid leukaemia (AML), chromosomal translocation can lead to the fusion of the carboxy-terminal PHD finger of *JARID1A* to the transactivating domain of nucleoporin 98 (*NUP98*). To test the oncogenic potential of the *NUP98*–*JARID1A* fusion, David Allis and colleagues transformed mouse haematopoietic progenitor cells with the fusion protein containing either of the two alternative splice forms of

JARID1A — one that contains a PHD finger (NJL) and one in which the PHD motif has been spliced out (NJS). They found that cells transduced with the NJS form of *NUP98*–*JARID1A* or an empty vector proliferated transiently before differentiating into mature cells. By contrast, cells transduced with NJL proliferated indefinitely as undifferentiated progenitors.

When the NJL-transduced progenitors were transplanted into mice, the mice died of AML, whereas NJS-transduced progenitors did not induce leukaemia *in vivo*. Furthermore, deletion of the *JARID1A* PHD finger (*JARID1A*–PHD3) in NJL abolished the NJL-mediated transformation of cells.

How does NJL induce leukaemia? Wang *et al.* found differences in the expression profiles of NJL-transformed cells and control cells. Intriguingly, many genes that were upregulated in the NJL-transformed progenitors were known targets of polycomb proteins or contained a bivalent domain (a region that contains both activating and repressing chromatin marks and is thought to maintain chromatin in a poised state for transcriptional activation or repression) in embryonic stem cells. These features are characteristic of genes that encode developmentally important transcription factors, such as the homeobox (*Hox*) genes, *Gata3*, *Meis1*, *Pbx1* and *Eya1*. Consistent with the importance of deregulation of the expression of these genes by NJL in leukaemogenesis, the enforced expression of *Hox* genes or *Meis1* has previously been shown to induce AML.

What type of histone modification does *JARID1A*–PHD3 recognize? Using pull-down assays, the authors

found that *JARID1A*–PHD3 specifically recognizes histone H3 lysine 4 trimethylation or dimethylation (H3K4me3/2), which is a histone mark associated with gene activation. To test whether deregulation in reading H3K4me3/2 marks at genes that are important in development can lead to oncogenesis, the authors replaced *JARID1A*–PHD3 in the *NUP98* fusion with another H3K4me3/2-recognizing PHD finger. This fusion protein still led to transformation. However, the mutation of residues that interact with H3K4me3/2, or replacement of *JARID1A*–PHD3 with an H3K4me0-binding PHD finger, abolished transformation.

Because recognition of H3K4me3/2 is not sequence specific, it is unclear how NJL specifically upregulates the expression of a subset of developmental genes. Using chromatin immunoprecipitation, the authors found that the polycomb proteins enhancer of zeste homologue 2 (EZH2) and suppressor of zeste homologue 12 (SUZ12) spread throughout *Hoxa* gene clusters during differentiation in control cells, but the binding of these polycomb factors was restricted in progenitor cells transfected with NJL. Therefore, the authors suggest that the NJL fusions compete with polycomb binding, leading to the continued activation of developmentally crucial genes that should normally be silenced by polycomb following differentiation. As there are approximately 200 PHD fingers in the human genome, some of which have been associated with disease, it is possible that histone-misreading mechanisms, such as those described in this study, might have pathogenic roles in other cancers and diseases.

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ORIGINAL RESEARCH PAPER Wang, G. G. *et al.*
Haematopoietic malignancies caused by
dysregulation of a chromatin-binding PHD finger.
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DIGITAL VISION