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To establish and maintain pluripotency, cells must tightly regulate gene expression. Protein Arg N-methyltransferase 5 (PRMT5) is crucial for the development of primordial germ cells, and there have been suggestions that it might also be involved in embryonic stem (ES) cell pluripotency. Now, Tee *et al.* find that PRMT5 is involved in maintaining pluripotency in ES cells by di-methylating cytosolic histone H2A on Lys3 (H2ARme2) prior to its deposition on chromatin, leading to repression of key differentiation genes.

The authors initially observed that PRMT5 loss is embryonic lethal, owing to a failure to establish pluripotency in cells of the blastocyst. On closer inspection they found that its localization is dynamically regulated during mouse development: it localizes to the nucleus during early development but by embryonic day 6.5 it is upregulated and found in the cytoplasm of the pluripotent epiblast cells of the inner cell mass — the cells used to derive ES cells. Depletion of *Prmt5* by RNA interference (RNAi) in ES cells led to loss of H2ARme2, with kinetics that suggest that PRMT5 methylates H2A in the cytoplasm; reduction of PRMT5 resulted in loss of pluripotency and upregulation of key differentiation genes.

Methylosome protein 50 (MEP50) is a known cofactor of PRMT5; however, Tee *et al.* found that the knockdown phenotype of MEP50 in ES cells is, although similar to that of PRMT5, less severe. This indicates that PRMT5 may have additional roles that are independent of MEP50, perhaps in methylating non-histone proteins. Furthermore, the authors found a physical interaction between PRMT5 and signal transducer and activator of transcription 3 (STAT3), the latter of which has an established role in the control of pluripotency through LIF signalling. The STAT3 pathway does not seem to be perturbed in *Prmt5*-depleted cells, nor is there any alteration in the expression of genes activated by STAT3. However, the genes that are upregulated in response to *Prmt5* depletion are known direct targets of STAT3 repression. Thus, how PRMT5 and STAT3 cooperate to control pluripotency remains to be determined. It is clear, however, that signalling pathways can interact with chromatin through direct action in the cytoplasm to regulate pluripotency.

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ORIGINAL RESEARCH PAPER Tee, W. W. *et al.* Prmt5 is essential for early mouse development and acts in the cytoplasm to maintain ES cell pluripotency. *Genes Dev.* **24**, 2772–2777 (2010)