



MEETING ABSTRACT

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FGF signalling inhibition in ESCs drives rapid genome-wide demethylation to the epigenetic ground state of pluripotency

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Genome-wide erasure of DNA methylation takes place in primordial germ cells (PGCs) and early embryos and is linked with pluripotency. Inhibition of Erk1/2 and Gsk3 β signalling in mouse embryonic stem cells (ESCs) by small molecule inhibitors (called 2i) has recently been shown to induce hypomethylation. We show by whole-genome bisulphite sequencing that 2i induces rapid and genome-wide demethylation on a scale and pattern similar to that in migratory PGCs and early embryos. Major satellites, intracisternal A particles (IAPs) and imprinted genes remain relatively resistant to erasure. Demethylation involves oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), impaired maintenance of 5mC and 5hmC and repression of the *de novo* methyltransferases (Dnmt3a, Dnmt3b) and Dnmt3L. We identify a Prdm14 and Nanog binding *cis*-acting regulatory region in *Dnmt3b* that is highly responsive to signalling. These insights provide a novel framework for understanding how signalling pathways regulate reprogramming to an epigenetic ground state of pluripotency.

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