Maternal factor NELFA drives a 2C-like state in mouse embryonic stem cells

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Abstract

Mouse embryonic stem cells (ESCs) sporadically transit into an early embryonic-like state characterized by the expression of 2-cell (2C) stage-restricted transcripts. Here, we identify a maternal factor—negative elongation factor A (NELFA)—whose heterogeneous expression in mouse ESCs is coupled to 2C gene upregulation and expanded developmental potential in vivo. We show that NELFA partners with Top2a in an interaction specific to the 2C-like state, and that it drives the expression of Dux—a key 2C regulator. Accordingly, loss of NELFA and/or Top2a suppressed Dux activation. Further characterization of 2C-like cells uncovered reduced glycolytic activity; remarkably, mere chemical suppression of glycolysis was sufficient to promote a 2C-like fate, obviating the need for genetic manipulation. Global chromatin state analysis on NELFA-induced cells revealed decommis-sioning of ESC-specific enhancers, suggesting ESC-state impediments to 2C reversion. Our study positions NELFA as one of the earliest drivers of the 2C-like state and illuminates factors and processes that govern this transition.

Figure

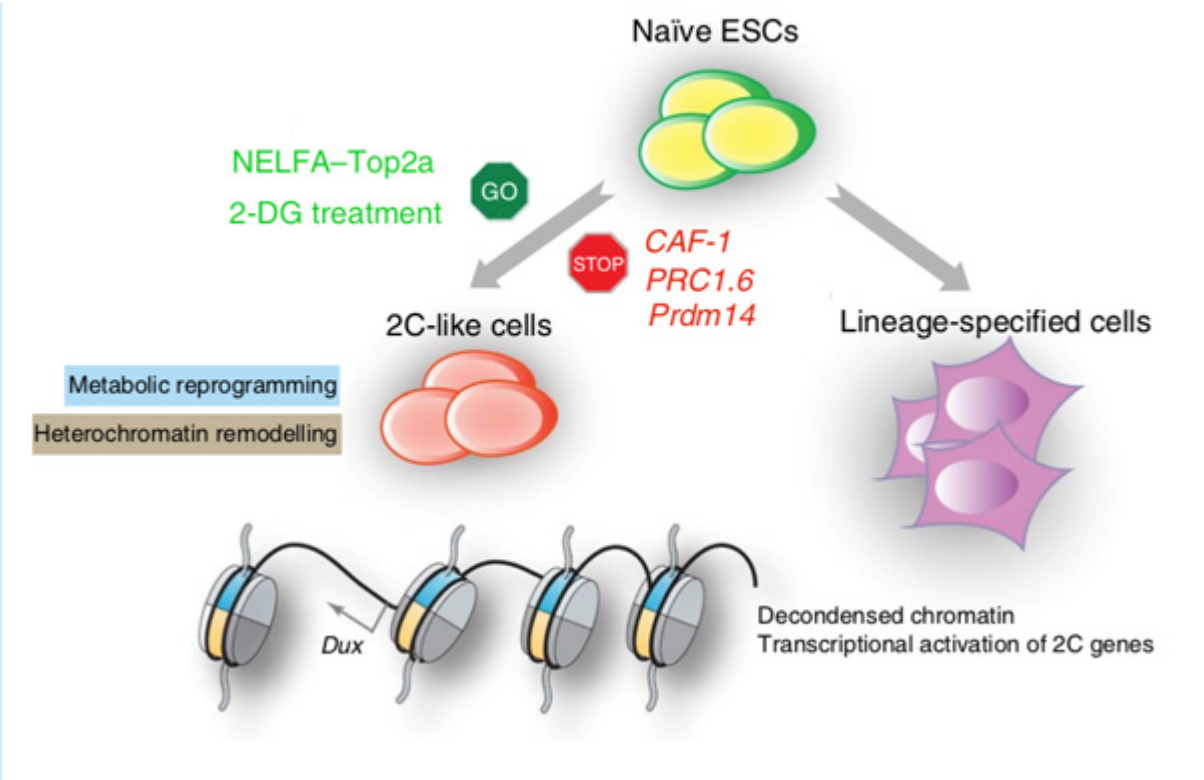

Figure legend: Model of 2C activation.

NELFA induction and 2-DG treatment promote 2C gene expression and the ESC-to-2C-like transition, characterized by extensive chromatin state changes and metabolic reprogramming. In particular, NELFA partners with Top2a to promote *Dux* activation, leading to expression of other downstream 2C genes. An exit from naïve pluripotency via ESC-specific enhancer decommissioning (for example, *Prdm14* enhancer) is also necessary for this transition.