The cell cycle and pluripotency
Is there a direct link?

Michael J. Edel1 and Juan Carlos Izpisua Belmonte1,2,*

1Center of Regenerative Medicine in Barcelona; Aigüader; Barcelona, Spain; 2Gene Expression Laboratory; Salk Institute for Biological Studies; La Jolla, California USA

Growing scientific evidence is accumulating suggesting the tantalizing possibility that a push to the cell cycle is all we need to achieve pluripotency and define cell fate.1-8 Recent work published in Genes and Development last month has shown that manipulation of the cell cycle of human embryonic stem cells (hESCs) regulates pluripotency and self-renewal.1 It is obvious that the cell cycle plays a major role in maintaining and sustaining pluripotency of cells because modification of it will cause cell cycle crisis and later apoptosis. However the question remains if there exists a direct mechanistic link between the plasticity of cells and the cell cycle.

The work we have recently performed demonstrates that Rem2 GTPase, a known suppressor of the p53 pathway,9 also controls cyclin D1 localization in hESCs that in turn regulates pluripotency by forcing the pluripotent cells to form more ectoderm at the expense of mesoderm under general differentiation conditions in vitro.1 Further work published in this issue of Cell Cycle demonstrates that knocking out Rem2 GTPase gene expression in the zebra fish embryo causes loss of neural tissue resulting from a decelerated cell cycle and increased apoptosis. This supports the notion that control of the cell cycle by Rem2 GTPase is critical for maintaining proper embryogenesis towards neurons (Figure 1).

Evidence linking cell cycle to pluripotency was made clear by evidence demonstrating that loss of p53 function can enhance the efficiency of reprogramming, suggesting that the cell cycle is an important function in attaining a pluripotent cell state.3-8 These papers collectively conclude that the road to pluripotency involves a first step to increase proliferation rate of cells that then “switches on” pluripotency genes in a second step. Other work linking pluripotency to cell cycle has been that Nanog regulates S phase entry and that downregulation of Nanog can be rescued by Cdc25A and CDK6 overexpression, two important cell cycle regulators.10 A further link was established with the finding that the Oct4/sox2-regulated miR-302 targets cyclin D1 in hESC.11 Finally, A recent in vivo study functionally demonstrated that Cyclin A, a core cell cycle regulator, is specific for mESC survival but not differentiated fibroblasts, suggesting a role for the cell cycle in maintaining pluripotency.12 However, does modifying the rate of the cell cycle directly result in the modification of pluripotency of cells? To shine light on this question, Edel et al. show in their Genes and Development paper that manipulation of a single cell gene during early reprogramming, namely cyclin D1 or Rem2 GTPase, can increase the percentage of SSEA3, SSEA4 or TRA-1-60 positive cells emerging from early reprogramming cells.1 Therefore, by instating an embryonic stem cell-like proliferation profile in somatic cells the number of pluripotent cells increase during early reprogramming events. Moreover, by overexpressing a cyclin D1 mutant that localizes in the wrong cell compartment induces cell cycle crises and apoptosis severely reducing the ability to form pluripotent cells.1 If we accept that manipulation of single cell cycle gene by gain of function is a “gold standard” for determining function of a gene, it could be concluded that the cell cycle directly regulates pluripotency. However, further evidence would be welcomed in order to cement this point. This could come in the form of a recent paper on TBX3, known to suppress p19ARF expression, a major cell cycle regulator.13 They show that TBX3 can enhance pluripotency, suggesting that the cell cycle is directly linked to pluripotency, although its role in development separate to cell cycle cannot be ruled out in those experiments.14 Therefore, despite all this evidence, experiments that can rule out the pleiotropic effects of manipulating cell cycle genes while studying the effect of cell cycle on pluripotency are lacking before we can define exactly the role of the cell cycle in pluripotency.

References

*Correspondence to: Juan Carlos Izpisua Belmonte; Email: belmonte@salk.edu and izpisua@cmrb.eu
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Figure 1. Schematic model of Rem2 GTPase function during developing embryo. Rem2 GTPase is essential for hESCs self-renewal and pluripotency by controlling proliferation and apoptosis (1). This model proposes that during embryo development that "high" level of Rem2 expression is needed to maintain the formation (survival) of the inner cell mass (ICM), which embryonic stem cells are derived. Rem2 levels decrease in most cells after the ICM stage that then differentiate towards other cell lineages. It is known that Rem2 is regulated and mediates FGF2 signaling (1). The model proposes that those cells that maintain high levels of Rem2 expression respond differently to the changing microenvironment during development (such as FGF2 levels) and are directed specifically towards a neuronal cell fate. The presence of high levels of Rem2 may also enable survival of those cells. Therefore Rem2 is essential during the early stages of ICM development and then again at a later stage of development for the proper development of neurons. Note that the inserts are photos of PCR for Rem2 mRNA levels of hESCs differentiated specifically towards neurons or under general conditions of differentiation (on gelatin coated plates with 20%FCS).