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STEM CELLS

Close encounters with full potential

Conferring stem-cell potential on mature cells is not easy. A decisive impediment to this process has now been identified, and its elimination allows almost all mature cells to efficiently adopt a stem-cell identity.

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Differentiated cells, such as skin cells or blood cells, are firmly committed to their lifelong vocation. They adopt an alternative fate only with great reluctance and through powerful coercion[1]. Such reprogramming events are typically infrequent (for example, the efficiency[1] of converting skin cells into induced pluripotent stem (iPS) cells is generally less than 1%), hampering the generation of various cell types for research and therapy. Reporting on *Nature*'s website today, Rais *et al.*[2] show that, during reprogramming, cells enter an intermediary purgatory in which positive and negative influences duel to affect successful dedifferentiation. The authors further demonstrate that eliminating a single negative influence, the protein Mbd3, allows reprogramming to iPS cells to occur with almost 100% efficiency. They thus provide salient insight into the molecular events that drive cell-fate changes.

Cellular identity is spearheaded by transcription factors, which dictate what genes should be expressed, and thus cell fate[1,3]. The introduction of just four such stem-cell regulators (Oct4, Sox2, Klf4 and Myc) into skin cells is theoretically sufficient to enkindle stem-cell identity[1], yet in practice this remains a sporadic process. Reprogramming inefficiency has been ascribed to either the absence of crucial activating signals during this process[4,5] or an inability of the cells to surmount inhibitory barriers[6,7]. Therefore, numerous stem-cell regulators have been tested for their ability to maximize reprogramming efficiency[1,4]. Rais *et al.*, however, took a different approach.

Genes active in stem cells are largely dormant in differentiated cells. To induce pluripotency (the ability to differentiate into all cell types of the body), reprogramming factors attempt to resuscitate the expression of these genes. For this, they recruit transcriptional coactivators[5]. But why is this effort ultimately futile in most cases[8]? Rais and colleagues find that, unexpectedly, reprogramming factors also recruit the transcriptional repressor Mbd3 (a member of the NuRD complex[9]), inadvertently directing it to suppress the very stem-cell genes they are trying to reactivate. The authors reasoned, therefore, that ablating Mbd3 — which has been implicated[6] in hindering iPS-cell reprogramming — might improve reprogramming efficiency (Fig. 1). They found that, indeed, deleting the *Mbd3* gene while introducing the reprogramming factors did the trick: when combined with optimal growth conditions[7], mouse skin, blood and brain cells could be reprogrammed with near-complete (more than 90%) efficiency, and even human cells could be reprogrammed with vastly improved efficiency[2].

These data suggest that reprogramming factors act dichotomously, trying to revive pluripotency genes while simultaneously repressing their expression (Fig. 1). This paradoxical transcriptional indecision leads to a power struggle between transcriptional coactivators and repressors (including Mbd3). Therefore, there is only stochastic reactivation of pluripotency genes, which explains why successful iPS-cell generation is such a rare event.

Potentially, after a protracted bout of many months[10], coactivators may eventually prevail. However, Mbd3 seems to be the overarching antagonist of iPS-cell reprogramming across all cell types tested. Its removal resolves these lengthy conflicts, enabling reprogramming factors to unilaterally reactivate stem-cell genes essentially in all cells.

The authors' work unites hitherto irreconcilable findings concerning cell-fate conversions. Reprogramming often yields partially reprogrammed 'pre-iPS cells'; these are an imperfect facsimile of bona fide iPS cells and are stably trapped in a paused state in which they fail to execute the terminal reprogramming events[7,11]. Remarkably, the maturation of these cells into fully fledged iPS cells might be driven by downregulation of reprogramming factors[11,12]. Why these essential reprogramming drivers should be deleterious for the last phase of reprogramming has been unclear. The present findings suggest that sustained overexpression of reprogramming factors in pre-iPS cells might continuously recruit Mbd3 to stem-cell genes, and that curtailing the levels of these factors may relieve Mbd3-mediated inhibition, allowing coactivators to triumph and driving pre-iPS cells to pluripotency.

Teleologically, it is difficult to rationalize

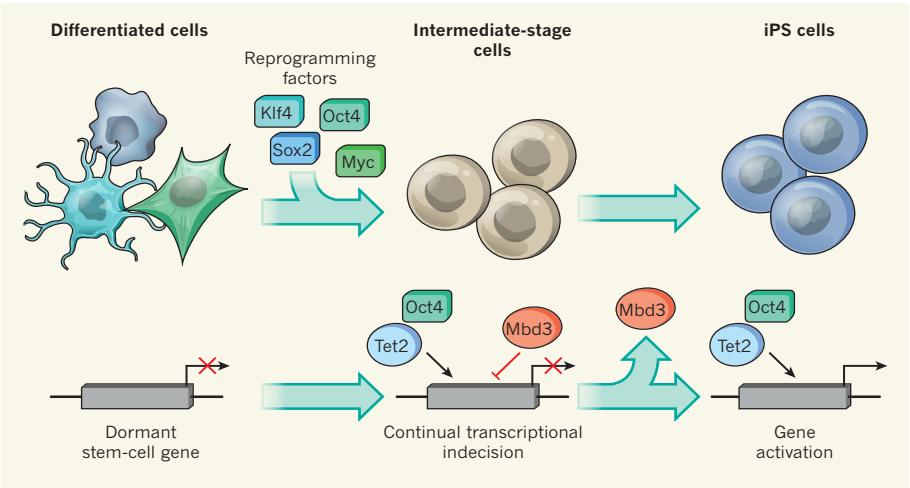

Figure 1 | The battle for pluripotency. The introduction of just four genes encoding transcription factors (*Oct4*, *Sox2*, *Klf4* and *Myc*) into differentiated cells triggers the reprogramming of these cells into induced pluripotent stem (iPS) cells, by reviving the expression of dormant stem-cell genes[1]. This process is highly inefficient, because most cells are halted at a dedifferentiated but not fully reprogrammed stage called the intermediate stage[10] (perhaps akin to pre-iPS-cells). Rais *et al.*[2] show that the reprogramming factors Oct4, Sox2 and Klf4 recruit not only transcriptional coactivators (such as Tet2)[5] to stem-cell genes, but also transcriptional repressors, including Mbd3, which potently inhibit gene reactivation. Eliminating Mbd3 enables the coactivators to efficiently resuscitate dormant stem-cell genes, allowing almost all cells to be converted into stem cells.

why reprogramming factors recruit Mbd3 to hinder their own success. This may be a molecular heirloom of stem cells, in which pluripotency factors interact with Mbd3 to suppress stem-cell genes[9] in order to preconfigure differentiation[3]. Therefore, permanent Mbd3 ablation might deleteriously alter reprogrammed iPS cells by impeding their subsequent differentiation[9]. Technical approaches that transiently inactivate this protein during reprogramming may prove decisive. Whether Mbd3 removal can potentiate the direct conversion of skin cells into other differentiated cell lineages (such as brain or liver cells[1]) also remains a pertinent question.

The exceptional reprogramming efficiencies described by Rais *et al.* are evidence that cellular identity is a surprisingly malleable property that might be reforged — for example, to generate cell types of therapeutic value. Of equal importance is the unprecedented insight provided by this work into the molecular mechanisms that direct stem-cell reprogramming. Knowledge of how developmental decisions are made and revoked may also reciprocally illuminate our understanding of cancer biology, in which differentiated cells similarly relinquish their dedicated vocation and choose another path. ■

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