E-cadherin, a new mixer in the Yamanaka cocktail

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Dramatic changes in cell fate occur in development, cancer and reprogramming to the pluripotent state (induced pluripotency). Cells are morphologically defined *in vivo* by their epithelial or mesenchymal nature. During development, some cells undergo epithelial-to-mesenchymal transitions (EMTs) or mesenchymal-to-epithelial transitions (METs) as a natural step in the adoption of particular cell fates in most tissues (Acloque *et al*, 2009). A characteristic of epithelial cancers is an EMT and subsequent invasion of the underlying mesenchyme as a prerequisite for the malignant phenotype (Acloque *et al*, 2009). Shinya Yamanaka first demonstrated that fibroblasts—typical mesenchymal cells—can be reprogrammed to a pluripotent state (atypical epithelial) by expression of transcription factors associated with pluripotency (Takahashi & Yamanaka, 2006). This discovery was followed by the observation that a MET event occurs early in the reprogramming process (Stadtfeld *et al*, 2008).

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As the precise steps and mechanisms of reprogramming to the pluripotent state are mostly obscured in a 'black box', it is important to uncover the mechanisms of MET that underlie this process. For decades, proteins such as E-cadherin (E-cad) have acted as markers of the epithelial state and are known to be downregulated during an EMT. E-cad is a transmembrane protein that dimerizes with cadherin molecules on adjacent cells to form adherens junctions. It also interacts with various proteins inside the cell including α -catenin, β -catenin and p120, which then interact with the

cytoskeleton (Perez-Moreno *et al*, 2003). Therefore, E-cad is thought to act as a bridge between the cell-adhesion machinery and the cytoskeleton, and provide cells with a compass that orients them in tissues such as stratified epithelia. In EMTs associated with malignancy, E-cad and/or its adhesion partners are degraded, allowing for the physical separation of cells from their epithelial sheet into the underlying mesenchyme (Acloque *et al*, 2009). Furthermore, this degradation has a functional role in EMTs, and blocking the degradation of proteins like E-cad prevents epithelial invasion.

Recent evidence suggests that E-cad and other cell-adhesion molecules also have functional roles in METs. In this issue of *EMBO reports*, the Besser group provide evidence that expression of E-cad with three of the Yamanaka factors—SOX2, KLF4 and c-MYC—induces reprogramming

of murine fibroblasts, without the need for OCT4 (Redmer *et al*, 2011). Previously, Samavarchi-Tehrani and colleagues used functional genomics to determine which gene changes occur during the early, middle and late stages of reprogramming (Samavarchi-Tehrani *et al*, 2010). This analysis identified the induction of a microRNA family (miR-200) as important mediators of BMP signalling responsible for the induction of MET and E-cad upregulation, at the earliest stages of reprogramming. Li and co-workers have also previously shown that blocking MET or promoting EMT could decrease reprogramming efficiency (Li *et al*, 2010). In addition, KLF4, a member of the original Yamanaka cocktail, was found to induce expression of E-cad and other epithelial markers in the target fibroblasts, outlining a role for this transcription factor in induced pluripotency (Li *et al*, 2010). Furthermore,

Fig 1 | A summary of changes occurring during reprogramming from a fibroblast to a pluripotent stem cell. The figure depicts a summary of recent work showing that as fibroblasts are reprogrammed, they quickly lose their mesenchymal nature and undergo a mesenchymal-to-epithelial transition. Later in the process, pluripotency genes are induced, while various mechanisms, such as induction of c-MYC expression, block senescence pathways.

this group showed that specifically ablating E-cad expression dramatically inhibited reprogramming, suggesting that the MET required for induced pluripotency required the activity of E-cad, and that it was not just a marker of fate change (Li *et al*, 2010).

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The new study by Redmer and colleagues takes this work a step further and shows that E-cad has an even more significant role than was previously appreciated. The authors confirm previous findings implicating a functional role for E-cad in reprogramming by showing that the loss of E-cad expression drives pluripotent stem cells to differentiate. In addition, they show that the forced expression of a Yamanaka cocktail including E-cad is able to drive induced pluripotency, even in the absence of OCT4. This is important because although many groups have shown that most members of the Yamanaka cocktail of reprogramming factors—OCT4, SOX2, KLF4 and c-MYC—can be omitted or replaced by various manipulations, there have been few instances of reprogramming to the pluripotent state proceeding in the absence of OCT4. The results of Redmer and co-workers emphasize that the spatial and mechanical input provided by E-cad has an important role in altering cell fate.

Perhaps these results should not be surprising, as previous work has demonstrated that forced expression of E-cad in cells facilitates the transition of an alternative type of pluripotent stem cell (FAB-SC) to become *bona fide* embryonic stem cells (Chou *et al*, 2008). Conversely, considering their different biological activities, it is unlikely that E-cad functionally replaced OCT4 in the experiments carried out by Redmer and colleagues. Perhaps the pertinent question is how the addition of E-cad to the Yamanaka cocktail was able to drive reprogramming in the experiments by the Besser group. The most likely scenario, considering the work of Li and colleagues (2010), is that E-cad and KLF4 acted to drive and maintain a MET early in reprogramming. Then, as SOX2 and KLF4 are known to drive transcription of highly overlapping patterns of pluripotency genes (Sridharan *et al*, 2009), these two factors sufficed to initiate the pluripotency programme, despite the lack of OCT4. As

c-MYC is known to act on metabolic and proliferation pathways (Sridharan *et al*, 2009), this protein could have facilitated the conversion to a self-renewing state and prevented the onset of senescence pathways (model summarized in Fig 1).

The data presented by Redmer and colleagues reinforce the idea that MET is necessary for, but not sufficient to induce, pluripotency in mesenchymal cells such as fibroblasts. Other groups have shown that reprogramming epithelial cells such as keratinocytes that already express E-cad to the pluripotent state is quicker and more efficient (Aasen *et al*, 2008); this is thought to be due to the lack of a requirement for MET, although this has not been formally tested. Should that be true, it could be illustrative to determine whether the transcriptional and epigenetic transitions that occur in mesenchymal target cells are conserved or distinct from those in epithelial cells on their way to the pluripotent state. Finally, it is clear from these data and previous work (Chou *et al*, 2008; Li *et al*, 2010) that reinforcement of an epithelial state is crucial to the stability of pluripotent stem cells, but it does not address the reason that this might be the case. This work was performed in murine cells, which are capable of surviving at clonal density, whereas human pluripotent stem cells are not. Do murine and human induced pluripotent stem cells

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maintain similar epithelial characters and do they need polarity signals from proteins such as E-cad, or do they simply need to maintain the epithelial state? Considerable effort will be required to tease apart these possibilities, but it is necessary to achieve an understanding of not only pluripotency, but also the process by which the Yamanaka factors induce a complete remodelling of cell fate.

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A new postal code for dendritic mRNA transport in neurons

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The controlled sorting and transport of proteins has long been accepted as the basic regulatory mechanism responsible for establishing polarized structures in most cell types, whereas the subcellular sorting and transport of messenger RNAs (mRNAs) has been considered to be a special feature of highly polarized cells, such as the neurons of the central nervous system. The concomitant idea that proteins can be synthesized in specific cellular compartments—under local control in dendritic spines in response to the activation of neighbouring synapses—was thought to be

the exception to the rule. This view, however, has changed. It has been shown that the majority of mRNAs are not evenly distributed in the cells of *Drosophila* embryos (Lécuyer *et al*, 2007), indicating that the controlled subcellular transport and sorting of mRNAs is at least as common as protein sorting, even in early cells, long before they differentiate into highly polarized neurons or other specialized cell types.

In a paper published in this issue of *EMBO reports*, Subramanian *et al* (2011) enhanced our understanding of neuronal mRNA transport. They found that a guanine