Molec lar Cell
Previews

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Pl ri o en cell hen f ed i h oma ic cell ha e he dominan a ili o re rogram he oma ic genome Work Piccolo e al (3) ho ha he Te and Te h dro la e are im or an for DNA me h la ion re rogramming of l ri o enc gene and aren al im rin

Experimental reprogramming has captured the imagination of biologists and medical practitioners alike because of the inherent fascination and scientific interest with turning one cell type into another and the implications this has for understanding disease processes and developing new ideas for therapy. Cloning by somatic cell nuclear transfer, induced pluripotency, and fusion of somatic cells with embryonic stem cells (ESCs) or embryonic germ cells (EGCs) can reprogram specialized cells (or their nuclei) to pluripotent ones that can potentially regenerate all of the differentiated cell types in an adult organism (Yamanaka and Blau, 2010). Although these techniques work (which sometimes still feels like a miracle), they are inefficient (typically one in a thousand to one in a hundred attempts succeed), and reprogramming is often incomplete. A number of bottlenecks to successful reprogramming have been identified, including some that are epigenetic, which appear to be critical. Hence, the epigenome of somatic cells needs to be reprogrammed into that of pluripotent cells (which is very different). For example, the promoters of pluripotency transcription factor genes such as *Oct4* or *Nanog* are DNA methylated in somatic cells and need to be demethylated during reprogramming. Insights into naturally occurring epigenetic reprogramming in primordial germ cells (PGCs), early embryos, and ESCs have indeed informed and resulted in improvements of experimental reprogramming. In a fascinating study by Piccolo et al. (2013), this thinking has now been applied to cell fusion reprogramming using ESCs and EGCs.

EGCs, derived from PGCs, are pluripotent and similar to ESCs in most respects; however, many EGC lines possess erased DNA methylation in imprinting control regions (ICRs) when they are derived from gonadal PGCs, which have undergone genome-wide demethylation (including in ICRs). Interestingly, these cells—when fused with somatic cells to form heterokaryons—can reprogram the somatic nuclei to a pluripotent state and erase methylation in the *Oct4* promoter and ICRs (Tada et al., 1997, Piccolo et al., 2013). ESCs, by contrast, dominantly reprogram somatic cell nuclei in fusions, but ICRs maintain their methylation, just as they do in preimplantation

may be more dynamic than we think. A major unresolved question is how EGCs can reprogram ICRs while ESCs cannot, despite the same expression of Tets and all other relevant modifiers of DNA methylation. Perhaps the subtlety lies in factors that target Tets to their locations in the genome or, conversely, in factors that protect from demethylation such as Stella or Zfp57.

These new findings have interesting implications for both experimental and natural reprogramming. First, the Tet1 and Tet2 hydroxylases are also important for induced pluripotent stem cell (iPSC) reprogramming, in part because of how they may be targeted to the genome (Costa et al., 2013). Second, *Tet1* knockout mice do not appear to have problems with demethylating ICRs in their PGCs (while *Tet1*/*Tet2* double knockouts have a partially penetrant ICR erasure defect), and *Tet2* knockouts develop normally to adulthood (hence, without any apparent pluripotency defect). Nor does combined *Tet1*/*Tet2* deficiency abolish genome-wide erasure of methylation in PGCs, which seems to occur largely by a passive mechanism (