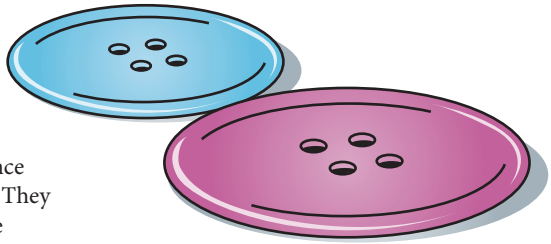
STEM CELLS

The same, but different



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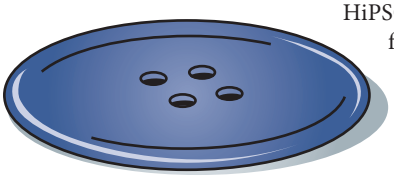
The development of human induced pluripotent stem cells (HiPSCs) has been hailed as a great ethical step forwards in regenerative medicine, because in principle these cells reduce the need to obtain and study human embryonic stem cells (HESCs). However, three papers published in *Nature* indicate that these cell types are not the same at the genomic and the epigenomic levels.

Previous studies have indicated that HiPSCs harbour regions of gene amplification and loss, despite the fact that, biologically, these cells behave identically to HESCs. These aberrations can be lost during prolonged culture *in vitro* and are not dependent on the methods used to produce the HiPSCs. These findings have been verified and extended by Samer Hussein, Nizar Batada and colleagues in early and intermediate HiPSCs, the fibroblasts from which they were derived, and HESCs. They used high-resolution single nucleotide polymorphism arrays to investigate copy number variations (CNVs). The early passage HiPSCs had higher numbers of CNVs than their cells of origin or HESCs, but most of these changes did not provide a proliferative advantage in culture. Importantly, these authors verified that the CNVs were mostly new mutations that occur during the reprogramming process. The genetic mosaic of HiPSCs pools is reduced with continued culture as HiPSCs with a genome that more closely resembles that of HESCs become dominant.



Athurva Gore, Zhe Li and colleagues probed deeper into the genome of HiPSCs to look for the presence of protein-coding mutations. They sequenced the majority of the protein-coding exons in 22 HiPSCs, which were generated from nine fibroblast cell lines using different reprogramming methods, and looked for single base changes, splice variants and small insertions or deletions. These authors estimated that each HiPSC exome had approximately six somatic coding mutations (single base changes and splice variants), and further analyses indicated that some of these changes arose during reprogramming and that others were present at low frequencies in the fibroblasts from which the HiPSCs were created. Importantly, many of these mutations were present in genes that are mutated in human cancers. One HiPSC line cultured over 40 passages retained its seven initial coding mutations and gained four new mutations, indicating that these small coding changes are not lost from the population, unlike CNVs.

Ryan Lister, Mattia Pelizzola and colleagues analysed genome-wide DNA methylation patterns at the single base level in five HiPSC lines, as well as HESCs, somatic cells, and differentiated HiPSCs and HESCs. On a genome-wide scale, the methylomes of HiPSCs and HESCs closely resembled each other and were distinct from those of somatic cells. However, a comprehensive analysis of CG methylation patterns identified a number of differentially methylated CG regions (CG-DMRs) between HiPSCs and HESCs. Interestingly, almost 50% of these CG-DMRs were similar to methylation patterns in the somatic cells from which the HiPSCs were derived, indicating the persistence of what has been termed somatic memory. Moreover, just over 50% of the DMRs were exclusive to HiPSCs (iDMRs). Many of these changes (memory CG-DMRs and iDMRs) remained when HiPSCs were induced to differentiate into trophoblast cells, and a few of the iDMRs were common to all five HiPSC lines, suggesting that there are aberrant methylation hotspots that arise during reprogramming. DMRs of non-CG sequences were also evident in HiPSCs, especially in large DNA regions close to centromeres and telomeres.

All three of these papers clearly indicate that much more needs to be understood about the reprogramming process and that the biological consequences of these genomic and epigenomic changes need to be investigated.

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ORIGINAL RESEARCH PAPERS Hussein, S. M. *et al.* Copy number variation and selection during reprogramming to pluripotency. *Nature* **471**, 58–62 (2011) | Gore, A. *et al.* Somatic coding mutations in human iduced pluripotent stem cells. *Nature* **471**, 63–67 (2011) | Lister, R. *et al.* Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. *Nature* **471**, 68–73 (2011)
FURTHER READING Ben-David, U. & Benvenisty, N. The tumorigenicity of human embryonic and induced pluripotent stem cells. *Nature Rev. Cancer* 10 Mar 2011 (doi:10.1038/nrc3034)