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STEM CELLS

The different flavours of iPS cells

The use of induced pluripotent stem (iPS) cells for studying genetic variants that underlie human diseases is complicated by the fact that individual iPS cell lines are genetically and phenotypically heterogeneous. Kilpinen *et al.* now provide a detailed overview of the genetic and phenotypic variability of 711 iPS cell lines that they have generated; these cell lines are now available for research as part of the human induced pluripotent stem cell initiative (HipSci), and all of the data are freely available.

The authors generated 711 iPS cell lines from the fibroblasts of 301 healthy donors and analysed them using genetic, epigenetic, proteomic and cell morphological approaches. For quality control, gene expression data were obtained for all cell lines, and pluripotency was verified *in silico* using the PluriTest assay, which looks at gene expression profiles. Pluripotency and differentiation markers were also assessed by using a cellular differentiation assay. Together, these data suggest that almost all of the 711 newly derived iPS cell lines are pluripotent.

Next, the authors assessed copy number alterations (CNAs): compared with their progenitor fibroblasts, 41% of all iPS cell lines generated (and 18% of a subset of these cell lines that were genetically more stable and are thus most suitable for future distribution) contained at least one CNA, the majority of which were unique to individual iPS cell lines. CNAs occurred more frequently than expected for a uniform genetic distribution across 35 regions, and the authors show that deletion or duplication of several genes in regions with CNA is likely to provide a selective advantage. Furthermore, when comparing iPS cell lines with and without CNAs from the same donor, the duplication of chromosome 17 was associated with changes in the expression of 1,098 genes. These findings enabled the authors to generate a high-resolution map of the CNAs that reoccur in iPS cells.

To determine what underlies heterogeneity in iPS cells, the authors quantified the variance attributed to differences between individuals ('donor effects') as compared to the variance attributed to factors such as gender and cell culture conditions. Donor effects accounted for 5–46% of the variation in iPS cell phenotypes such as pluripotency, mRNA abundance and cell morphology. Furthermore, donor effects were prominent at expression quantitative trait loci (eQTLs) — that is, at sequence variants that affect the expression of a gene — suggesting that donor variance translates to genetic differences.

Mapping eQTLs further, the authors found that 2,131 eQTLs were specific to iPS cells (and not expressed in somatic cells from tissues obtained through the Genotype-Tissue Expression (GTEx) Consortium). These eQTLs were enriched in active enhancers, poised promoters and binding sites for pluripotency factors. Furthermore, statistical colocalization identified 233 loci that seemed to be responsible for both an iPS cell eQTL and an association with one of 14 complex traits; 45 of these loci were specific to iPS cells. Thus, common genetic differences between individuals, including disease risk variants, may influence gene expression in early development.

In short, this study "provides a detailed picture of the genetic and phenotypic variability in human pluripotent stem cells, including the major drivers of this variation," conclude the authors.

Katharine H. Wrighton

> "these cell lines are now available for research as part of the human induced pluripotent stem cell initiative"

ORIGINAL ARTICLE Kilpinen, H. *et al.* Common genetic variation drives molecular heterogeneity in human iPSCs. *Nature* http://dx.doi.org/10.1038/nature22403 (2017)

WEB SITE

HipSci: http://www.hipsci.org/