

Somatic coding mutations in human induced pluripotent stem cells.

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Public Summary:

Adult stem cells or human induced pluripotent stem (hiPS) cells are generated by expressing defined factors in fibroblast cells from adult patients in a process called reprogramming. These cells have great promise for regenerative medicine as they maintain the genome of the original donor, thus reducing the possibility of immune system rejection in stem cell therapies. One concern with hiPS cells, however, is whether the reprogramming process could introduce genetic modifications, or mutations, in hiPS cells that are not present in the original donor cells. To address this concern, we investigated whether hiPS cells have a high rate of mutation by sequencing the protein coding regions of the hiPS cell genomes and comparing these sequences to the donor fibroblast cells. We sequenced 22 hiPS lines and found that they did, in fact, have more mutations than the parent fibroblasts suggesting that the reprogramming process and subsequent culture steps may not maintain complete genomic integrity. The mutations discovered in these cell lines were more common in genes involved in cancer, although no cell line had the same number of mutations, suggesting that some lines may be more affected than others. Given the tremendous potential of these cells for therapeutic use, it is important to continue research on mutation rates in hiPS, develop rigorous standards to test for genomic integrity, and perform extensive genetic screening on cell lines intended to be used clinically for cell therapy.

Scientific Abstract:

Defined transcription factors can induce epigenetic reprogramming of adult mammalian cells into induced pluripotent stem cells. Although DNA factors are integrated during some reprogramming methods, it is unknown whether the genome remains unchanged at the single nucleotide level. Here we show that 22 human induced pluripotent stem (hiPS) cell lines reprogrammed using five different methods each contained an average of five protein-coding point mutations in the regions sampled (an estimated six protein-coding point mutations per exome). The majority of these mutations were non-synonymous, nonsense or splice variants, and were enriched in genes mutated or having causative effects in cancers. At least half of these reprogramming-associated mutations pre-existed in fibroblast progenitors at low frequencies, whereas the rest occurred during or after reprogramming. Thus, hiPS cells acquire genetic modifications in addition to epigenetic modifications. Extensive genetic screening should become a standard procedure to ensure hiPS cell safety before clinical use.

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