STEM CELLS

Modelling genetic diseases with iPS cells

Pluripotent stem cells induced from skin fibroblasts have recently attracted considerable attention as an alternative to embryonic stem cells for potential applications in disease modelling, drug screening and regenerative medicine. Svendsen and colleagues now describe how induced pluripotent stem (iPS) cells from a child with spinal muscular atrophy (SMA) can be differentiated into motor neurons that maintain the disease genotype and phenotype, providing a pioneering demonstration of the potential of human iPS cells for modelling a genetic disorder and for drug screening.

SMA is an autosomal recessive genetic disorder that is caused by mutations in the survival motor neuron (SMN) genes, which lead to motor neuron degeneration and progressive paralysis. The authors generated iPS cells by infecting fibroblasts from the patient with SMA and his unaffected mother with viral vectors encoding the transcription factors OCT4 (also known as POU5F1), SOX2, NANOG and LIN28, which have previously been shown to reprogramme human somatic cells to a pluripotent state. Both cells from the patient (iPS-SMA cells) and cells from the unaffected control (iPS-WT cells) were able to generate teratomas harbouring tissue from the three primary embryonic germ layers (ectoderm, mesoderm and endoderm), but the iPS-SMA cells showed markedly lower levels of SMN1 than the iPS-WT cells.

Given that the lack of SMN proteins specifically affects the viability of motor neurons, the authors differentiated these iPS cells into motor neurons using various growth factors, including retinoic acid and sonic hedgehog. Differentiation was confirmed by checking for the expression of motor neuron transcription factors (HOXB4, OLIG2, ISL1 and HB9 (also known as MNX1)) and markers of mature motor neurons (SMI-32 and choline acetyltransferase). Although similar numbers of motor neurons were initially generated from the WT and SMA iPS cultures, after 6 weeks of differentiation there was a decrease in the size and number of the motor neurons differentiated from the iPS-SMA cultures. Furthermore, after 8 weeks in culture the iPS-SMA-derived cells did not exhibit punctate synapsin staining, suggesting that presynaptic maturation was impaired.

Finally, the authors examined whether compounds that are known to increase the levels of SMN proteins, namely valproic acid and tobramycin, were able to induce the formation of SMN gems (naturally forming aggregates of SMN proteins) in the cytoplasm and nucleus of the SMA-iPS-derived motor neurons. They found a significant increase in gems in the SMN-deficient cells after 2 days of drug treatment, confirming that these cells could be useful for drug screening.

Until now, studies of SMA have relied on animal models of the disease, which involve knockdown or overexpression strategies, or SMA patient fibroblasts, which do not show the same vulnerability as motor neurons. This paper validates the use of human iPS cells to model a genetically inherited neurological disease, highlighting its immediate potential for studying the mechanisms of SMA and drug screening in a more relevant setting.

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ORIGINAL RESEARCH PAPER Ebert, A. D. *et al.* Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature* 21 Dec 2008 (doi:10.1038/nature07677)