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Histocompatible embryonic stem cells

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Embryonic stem (ES) cells represent an inexhaustible source of precursor cells that can be differentiated into specific cell lineages. As with conventional organ transplants, ES cell-based therapies will face immunologic barriers. Genetically matched pluripotent embryonic stem cells generated via nuclear transfer (ntES cells), or parthenogenesis (pES cells), are a possible source of histocompatible cells and tissues. In a proof of principle experiment, we have shown that customized ntES cells can be used to repair a genetic immunodeficiency disorder in mice (Rideout *et al*., *Cell* 2002). However, generation of ES cells by nuclear transfer remains inefficient, and to date has not been achieved with human cells. ES cells with defined histocompatibility loci can be generated at much higher efficiency by direct parthenogenetic activation of the unfertilized oocyte (Kim *et al*., *Science* 2007). Subsequently, cell lines can be genotyped and selected for MHC identity to the oocyte donor. Cell lines with homozygous MHC haplotypes can also be identified, and tissues from such cells engraft in MHC heterozygous recipients. Compared to ES cell lines from fertilized embryos, pES cells display comparable *in vitro* hematopoietic activity, and blood derivatives can repopulate hematopoiesis in irradiated adult mouse recipients. These experiments establish murine models for generating histocompatible ES cell-derived tissue products, and suggest the theoretical feasibility of ES cell banking to enable off-the-shelf cell therapies. Current efforts are aimed at applying human and interspecies nuclear transfer, parthenogenesis, and direct reprogramming with defined genes to generate pluripotent human stem cells.
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