

## Differentiation of Human Embryonic Stem Cells: Prospects for Development Biology and Cell Therapy

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The great interest in the clinical value of human ES cells rests predominantly on data generated with mouse ES cells. Of the many problems still to be resolved in the quest to make clinical use of human ES cells, perhaps the most fundamental is to isolate a specific cell type of clinical value in high yield. Experience with mouse ES cells suggests that this is possible but we must directly demonstrate this point in the human system. Transplantation into the blastocyst stage of embryonic development shows that mouse embryonic stem (ES) cells are pluripotent, capable of differentiating into all of the adult lineages including the germ line. For ethical reasons, the pluripotency of human ES cells cannot be defined in this way and the uncertainty about the pluripotency of human ES cells is at the center of the controversy over the value of the human cell lines. ES cells are regarded as equivalent to the inner cell mass, cells of the blastula that give rise to the major cell types of the body through the process of gastrulation. However, when ES cells differentiate in vitro, the exquisite order of the early embryo is absent and very little is known about the differentiation of cell types in the absence of the normal organization of the embryo. Here we show that human ES cells can rapidly form embryoid bodies (EBs), cell aggregates that contain the major embryonic and extra-embryonic cell types. The proportion of early cell types can be regulated by application of simple external signals giving EBs that are highly enriched in specific cell states.