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Human embryonic stem cells as a research model for human biology and diseases

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As a pluripotent and unlimited cell source, human embryonic stem (hES) cells offer the promise to develop new transplantation therapies and to characterize early events of human cell development and diseases. We have developed a novel method to generate a broad range of hematopoietic cells including immune modulating leukocytes from hES cells in culture. This study provides the first evidence that differentiated hES cells can generate functional APCs in addition to other myeloid and erythroid cells in culture (*Zhan, Lancet, 2004*). In addition to cell culture-based methods, we are also exploring the transgene expression approach to enforce and enhance hematopoietic differentiation from hES cells *in vitro*. We have been working on the role of two signaling pathways, Wnt/beta-catenin and Notch/CBF1/Hes1, for hematopoietic differentiation as well as self-renewal or maintenance of undifferentiated hES cells. Both pathways are greatly activated in differentiating hES cells induced by a variety of methods. Our data point to a role of the Wnt/beta-catenin activation in promoting cell proliferation (essential for both HES cell selfrenewal and differentiation), instead of hES cell maintenance (*Dravid, Stem Cells, 2005; Cai, Cell Res, 2007*). Notch signaling activation is not required for self-renewal or maintaining undifferentiated hES cells or trophoblast differentiation, but required for differentiation commitment to the 3 embryonic germ layers. We conclude Notch signaling is important for hES cells to exit from the undifferentiated state and/or enter to certain differentiated states (realizing differentiation potential or pluripotency), but not necessarily self-renewal of the undifferentiated state.

We have started to use hES cells as a genetic/developmental model for human diseases lacking functional products of a defined gene. To this end, we have established hES cell lines deficient in PIG-A, which is required for GPI-anchored cell surface protein synthesis and mutated in hematopoietic stem cells in PNH patients. We found that PIG-A deficient hES cells were capable of self-renewal or committing differentiation into the 3 embryonic germ layers after differentiation induction. However, hES cells deficient in PIG-A and GPI-anchored proteins failed to form trophoblasts induced by embryoid body formation or BMP4, a unique characteristic of hES cells different from mouse ES cells. The defect in trophoblast formation was due to reduced BMP4 signaling in the PIG-A deficient hES cells (*Chen, submitted*). The effects of PIG-A and GPI-anchored protein deficiency in hematopoiesis from hES-derived hematopoietic precursors will be discussed. These studies highlight the excitement that hES cells provide an unprecedented and much needed research tools for understanding the development and function of human cells and tissues, complementing or validating studies using murine or other small animal models.

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