Comparison of Hepatic Differentiation Potential between Human ES and iPS Cells

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Background: Human embryonic stem cells (hESC) and induced pluripotent stem cells (hiPS) may provide functional hepatocytes for drug discovery, developmental biology, and therapeutic use. In this study, we aimed to compare the capacity of hESC and hiPS to differentiate towards hepatocytes.

Method: Using sequential treatments of embryoid bodies established from hESC and hiPS with various combinations of cytokines and growth factors, we have developed an optimal protocol permitting efficient differentiation towards hepatocytic lineage.

Results: After 4 weeks of treatment, both hESC and hiPS acquired a polygonal shape and differentiated into hepatocyte-like cells as judged by light and electron microscopy, and quantitative RT-PCR analysis. Both hESC- and hiPS-derived hepatocyte-like cells exhibited a time-dependent upregulation of genes associated with early- and late-stage hepatic differentiation, including α-fetoprotein (AFP), CK8, CK18, albumin (ALB), asialoglycoprotein 1 (ASGPR1), tryptophan deoxygenase (TDO), glucose-6-phosphatase (G6P), ornitine carbamoyl transferase (OCT), CYP1A2, CYP3A4, CYP3A7, and CYP7A1. Increased expression of AFP, ALB and ASGPR1 was confirmed by immunostaining, western blotting and FACS analysis. In addition, hESC- and hiPS-derived hepatocytes accumulated glycogen, secreted high levels of albumin and showed signs of indocyanine green uptake indicative of mature hepatocyte function.

Conclusion: hES and hiPS showed a comparable potential to differentiate towards hepatocytes *in vitro*. Transplantation experiments using heptocytes derived from hES and hiPS cultures are underway to formally test their ability to give rise to differentiated hepatocytes in *vivo*.