

Transcriptional profiling of human embryonic stem cells and their functional derivatives

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen försvaras i Karl Kyhlberg salen, Medicinaregatan 7, Göteborg, torsdagen den 28 oktober kl 13.00

av

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Avhandlingen är baserad på följande artiklar:

- I. **Jane Synnergren**, Theresa L. Giesler, Sudeshna Adak, Reti Tandon, Karin Noaksson, Anders Lindahl, Patric Nilsson, Deidre Nelson, Björn Olsson, Mikael C.O. Englund, Stewart Abbot, Peter Sartipy (2007) Differentiating human embryonic stem cells express a unique housekeeping gene signature. *Stem Cells*, 25(2): 473-480.
- II. **Jane Synnergren**, Karolina Åkesson, Kerstin Dahlenborg, Hilmar Vidarsson, Caroline Améen, Daniella Steel, Anders Lindahl, Björn Olsson, Peter Sartipy (2008) Molecular signature of cardiomyocyte clusters derived from human embryonic stem cells. *Stem Cells*, 26(7): 1831-1840.
- III. **Jane Synnergren**, Nico Heins, Gabriella Brolén Gustav Eriksson, Anders Lindahl, Johan Hyllner, Björn Olsson, Peter Sartipy, Petter Björquist (2010) Transcriptional profiling of human embryonic stem cells differentiating to definitive and primitive endoderm and further towards the hepatic lineage. *Stem Cells Dev*, 19(7): 961-978.
- IV. **Jane Synnergren**, Caroline Améen, Anders Lindahl, Björn Olsson, Peter Sartipy. Expression of microRNAs and their target mRNAs in human stem cell derived cardiomyocyte clusters and in heart tissue. Accepted for publication in *Physiol Genomics*, 2010 Sep 14. [Epub ahead of print]

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Abstract

Human embryonic stem cells (hESCs) represent populations of pluripotent, undifferentiated cells with unlimited replication capacity, and with the ability to differentiate into any functional cell type in the human body. Based on these properties, hESCs and their derivatives provide unique model systems for basic research on embryonic development. Also, industrial *in vitro* applications of hESCs are now beginning to find their way into the fields of drug discovery and toxicology. Moreover, hESC-derivatives are anticipated to be promising resources for future cell replacement therapies. However, in order to fully utilize the potential of hESCs it is necessary to increase our knowledge about the processes that govern the differentiation of these cells. At present, some of the major challenges in stem cell research are heterogeneous cell populations, insufficient yield of the differentiated cell types and immature derivatives with limited functionality. To address these problems, a better understanding of the regulatory mechanisms that control the lineage commitment is needed. The aim of this thesis has been to increase the knowledge of the global transcriptional programs which are activated when cells differentiate along specific pathways, and to identify key genes that show differential expression at specific stages of differentiation. The results indicate that hESCs express a unique set of housekeeping genes that are stably expressed in this specific cell type and in their derivatives, which highlights the importance of proper validation of reference genes for usage in hESCs. Furthermore, an extensive characterization of hESCs and differentiated progenies of the cardiac and hepatic lineages has been conducted, and sets of differentially expressed genes were identified. Two different protocols, which mediate definitive and primitive endoderm respectively, were studied, and important discrepancies between these two cell types were identified. Moreover, the global expression profile of hESC-derived cardiomyocyte clusters were thoroughly investigated and compared to that of foetal and adult heart. To further study regulatory mechanisms of importance during stem cell differentiation, the global expression of microRNAs (miRNAs) was also investigated. Putative target genes of differentially expressed miRNAs were identified using computational predictions, and their mRNA expression was analysed. Notably, an interesting correlation between the miRNA and mRNA expression was observed, which supports the general notion that miRNAs bind to and degrade their target mRNAs, and thus act as fine-tuning regulators of gene expression. Taken together, the results described in this thesis provide important information for further studies on regulatory mechanisms that control the differentiation of hESCs into functional cell types such as cardiomyocytes and hepatocytes.