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Methylome and Transcriptome Profiling of Hepatocytes Derived from Human Pluripotent Stem Cells

Akademisk avhandling
Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Biotech Center plan 5, Arvid Wallgrens Backe 20, fredagen den 16:e mars 2018, klockan 13:00

av Nidal Ghosheh

Fakultetsopponent:
Professor Laura Suter-Dick
University of Applied Sciences Northwestern Switzerland

Avhandlingen baseras på följande delarbeten

I. Ghosheh N, Olsson B, Edsbagge J, Küppers-Munther B, Van Giezen M, Asplund A, *et al.* Highly Synchronized Expression of Lineage-Specific Genes during In Vitro Hepatic Differentiation of Human Pluripotent Stem Cell Lines. Stem Cells Int. 2016; 2016:8648356.

II. Ghosheh N, Küppers-Munther B, Asplund A, Edsbagge J, Ulfenborg B, Andersson TB, *et al.* Comparative transcriptomics of hepatic differentiation of human pluripotent stem cells and adult human liver tissue. Physiol Genomics 2017: doi:10.1152/physiolgenomics.00007.2017

III. Ghosheh N, Küppers-Munther B, Asplund A, Andersson C. X, Björquist P, Andersson TB, Caren H, *et al*. Novel transcriptomics targets for functional improvement of hepatic differentiation of human pluripotent stem cells. (manuscript).

IV. Ghosheh N, Ulfenborg B, Küppers-Munther B, Asplund A, Andersson C. X, Andersson TB, *et al.* Identification of hypermethylated genes involved in hepatic functionality in human pluripotent stem cell-derived hepatocytes. (manuscript).

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Abstract

Six hundred million people suffering from liver diseases worldwide of which the lethality is two million. Freshly isolated hepatocytes from the liver have been used for transplantation purposes and are extensively used to recapitulate drug metabolism. However, they lack stem cell ability and therefore cannot multiply, and will vary depending on each donator. Toward this, hepatocytes derived from human pluripotent stem cells (hPSC-HEP) recapitulate many features of their *in vivo* counterparts. However, the establishment of fully functional mature hepatocytes *in vitro* is still lacking. Abnormal DNA methylation emerging in *in vitro* cultured cells may underlie the immature functionality of hPSC-HEP and might explain the observed transcriptional differences between the *in vitro* generated hepatocytes and their *in vivo* counterparts. The aim of the thesis was to investigate the transcriptome and methylome of hPSC-HEP to identify their similarities and differences with human adult liver tissues.

Interestingly, on the transcriptome level, the results revealed stronger correlation and higher similarity of hPSC-HEP to adult liver than to fetal liver. Moreover, genes important for the functionality of hepatocytes with deviating expression and DNA methylation patterns, including a protein module consisting of seven drug-metabolizing enzymes that were downregulated in hPSC-HEP compared to adult liver, were identified.

In conclusion, the thesis shed light on significant deviations in the transcription and methylation of genes that are critical for the hepatic functionality. Further in-depth investigation and manipulation of these genes and their regulators in the differentiation protocol will pave the way for the generation of more functional hepatocytes *in vitro*.

Keywords: human pluripotent stem cells, gene transcription, gene regulation, DNA methylation, transcriptome, hepatocytes

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