Insulin induces *de novo* lipogenesis in human skin stem cell-derived hepatic cells

**Introduction**

Non-alcoholic fatty liver disease (NAFLD) ranges from simple steatosis to hepatocellular carcinoma. Among 25% of the global population suffers from NAFLD. A strong correlation with the metabolic syndrome (insulin resistance, obesity, dyslipidemia,...) is observed. Due to interspecies differences and ethical concerns, the use of laboratory animals to investigate this disorder is discouraged. Therefore, human-relevant *in vitro* NAFLD models are urgently needed by the pharmaceutical industry. Postnatal human skin precursor cells, differentiated towards hepatic cells (hSKP-HPC), proved already their potential to mimic *in vivo* toxicological responses to steatosis-inducing drugs. Here, we investigate whether insulin is able to induce triglyceride accumulation in hSKP-HPCs and mimic hepatic steatosis as observed in subjects suffering from the metabolic syndrome. The mechanisms by which insulin influences intracellular triglyceride accumulation are summarized in Figure 1.

**Methods**

hSKP-HPCs were generated according to an earlier established in-house protocol [1]. Subsequently, the cells were exposed to 100 nM insulin for 24h. The expression of lipogenic (*ACC1, FASN, PPAR-γ, SCD1* and *SREBP-1c*) and lipid metabolism-related genes (*APOB, CD36, ACADSB, CPT1a, PPAR-α, DGAT1, DGAT2* and *GPAT1*) was evaluated by RT-qPCR. Additionally, 72h exposure was carried out to assess intracellular lipid accumulation. Hereto, the cells were stained with LipidTOX green for neutral lipids and examined by fluorescence microscopy.

**Results**

- Increased intracellular lipid load was confirmed by fluorescence microscopy (Fig. 2).
- Upregulation of three *de novo* lipogenic genes (*ACC1, FASN* and *SCD1*), upregulation of *DGAT2* which is responsible for the final esterification step and decreased triglyceride export by VLDL (very low-density lipoprotein) due to downregulated *APOB* (Fig. 3).
- Other tested genes (*PPAR-γ, SREBP-1c, CD36, ACADSB, CPT1a, PPAR-α, DGAT1* and *GPAT1*) were not significantly modulated.

**Conclusion**

Insulin induces intracellular triglyceride accumulation in hSKP-HPCs by increasing *de novo* lipogenesis, increasing triglyceride esterification and decreasing triglyceride export. Therefore, hSKP-HPCs may serve as a promising human-relevant *in vitro* model to study hepatic lipid-metabolism related disorders.