LIPOTOXIC LIVER SYSTEM RECAPITULATES THE NASH PHENOTYPE

- Non-alcoholic fatty liver disease (NAFLD) is the most prevalent of liver diseases affecting >30% of the population and can progress to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). It is currently unknown which factors promote progression along the spectrum of NAFLD-NASH-Fibrosis-HCC.
- Currently there are no approved treatments for NASH, but two compounds with different mechanisms of action are currently in Phase 3 clinical trials – obeticholic acid (OCA, FXR agonist) and GFT505 (farnesyl pyrophosphate phosphatase, FPPS, inhibitor).

OBJECTIVE: To gain a mechanistic understanding of the ability of OCA and GFT505 to impact pathways known to be relevant for the development of NASH.

OCA AND GFT505 GLOBAL EFFECTS

- Global transcriptomic (RNAseq) analyses of hepatocytes revealed a clear separation of healthy (HTY) and lipotoxic (LTX) treatment groups along two principle components (Figure 3A). Regression (RPG) was able to move the phenotypes back to a HTY state, OCA separated more efficiently than GFT505 along the axis of principle component 2 (Figure 3A).
- The LX mice treated with a robust transcriptomic response in hepatocytes (Figure 3B). RPG reversed this response; OCA was better at reverting the LX-mediated response (Figure 3B).
- OCA and GFT505 exhibited on-target effects, OCA, an FXR agonist, and GFT505, a FPPS inhibitor, activated FXR- and FPPS-dependent gene response, respectively (Figure 3C). OCA also exhibited on-target upregulation of hepatic secretion of FGF19 (Figure 3C).

FIGURE 3.

OCA AND GFT505 IMPACT ON NASH-ASSOCIATED BIOLOGY

- OCA and GFT505 administered to NASH-modeling mice are capable of reversing lipotoxic effects (Figure 4).
- Secreted Lf and MCP1 (CCL2) were downregulated by GFT505 (Figure 4B). In the context of a LX-mediated response, OCA was also able to reduce secretion of Lf and MCP1 (data not shown).
- Expression of these genes was not detected by RNAseq in hepatocytes, however, NPC gene expression corroborated secretion of Lf and MCP1 (Figure 4B).
- These NPC’s may be the major contributor of Lf and MCP1 secretion.

FIGURE 4.

CONCLUSIONS

- Our in vitro human liver lipotoxic system recapitulates key biological signaling pathways of NASH and interrogates the mechanism of action of two compounds, OCA and GFT505, in a dose-response study for the treatment of NASH.
- Our results indicate that GFT505 may have a greater impact on reducing intracellular lipid accumulation and alleviating inflammation and fibrosis when compared to OCA.
- Furthermore, OCA may have a greater impact on restoring glucose homeostasis.
- Our results also provide supporting evidence for the reported increase in patient cholesterol and LDL levels when treated with OCA.
- This work was supported by SBIR R44 DK101036 (NIDDK).

FIGURE 5.

FIGURE 6.

FIGURE 7.

FIGURE 8.