



Chronic exposure to per- and polyfluoroalkyl substances (PFAS) increases intracellular cholesterol accumulation and TGF- β activation in Huh7 cells



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Introduction

- PFAS are being considered as environmental endocrine-disrupting chemicals (EDCs).
- Non-alcoholic fatty liver disease (NAFLD) is a liver disease with disrupted hepatic lipid metabolism.
- Previous studies found a positive correlation between serum PFAS level and the incidence or severity of NAFLD.
- We aim to investigate the mechanism underlying the association between chronic exposure to PFAS and development of NAFLD.

Methods

- Huh7 cell culturing and treatment with 0.08% DMSO, 0.4 μ M or 4 μ M different PFAS species for 4 weeks.
- Intracellular triglyceride and cholesterol measurement.
- Transcriptionally quantification of cholesterol metabolism genes and TGF- β .

Figures

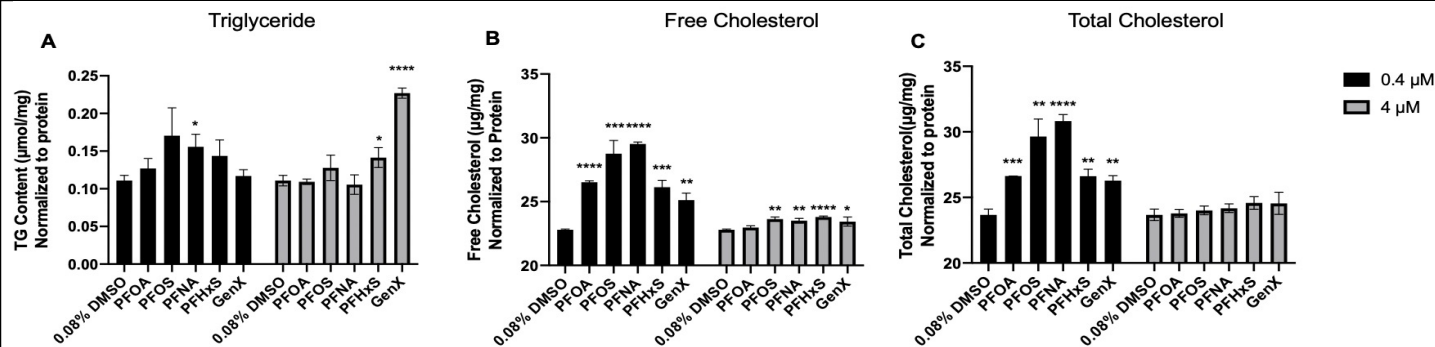


Figure 1. Intracellular lipid content after 4 weeks of PFAS treatment. A) Triglyceride level. B) Free cholesterol and C) Total cholesterol level. Error bar represents SD. The significance level was indicated as follows: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

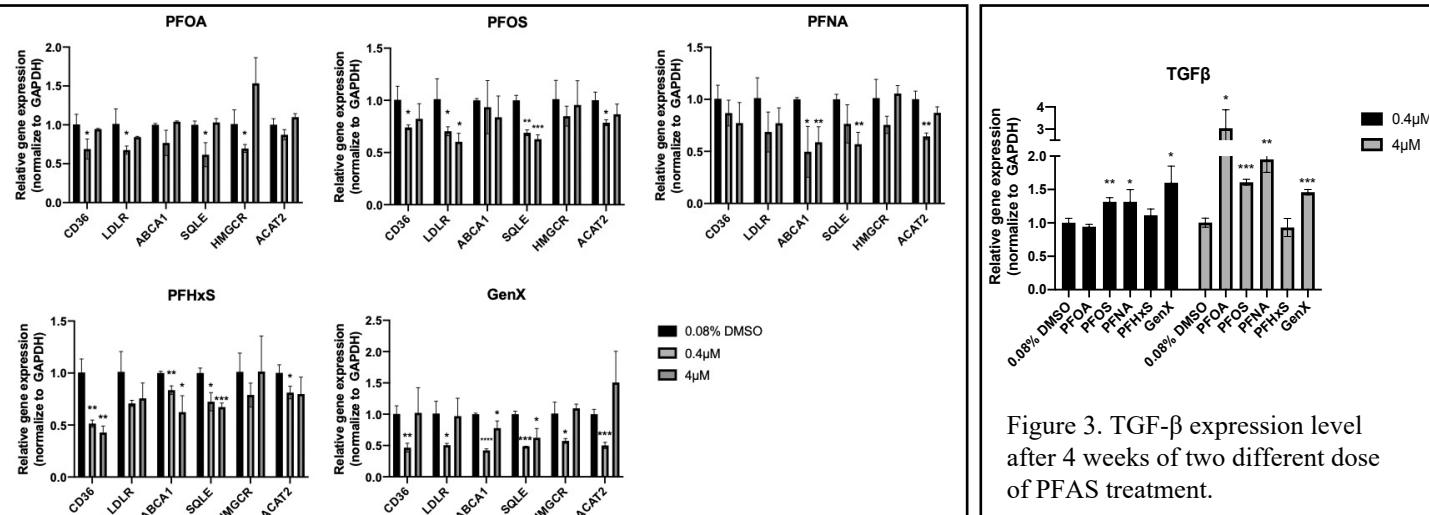


Figure 2. Transcriptional level of genes involved in cholesterol metabolism after 4 weeks of different treatment.

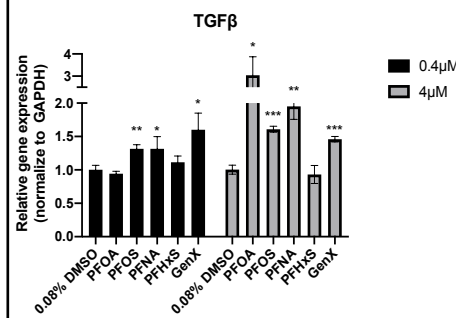


Figure 3. TGF- β expression level after 4 weeks of two different dose of PFAS treatment.

Results

- While only a few PFAS species treatments showed TG elevating effect, all 5 PFAS treatments exhibited increasing intracellular FC and TC, though not in a dose-dependent manner (Figure 1).
- Suppressed expression of cholesterol uptake (CD36, LDLR) and biosynthesis gene (SQLE, HMGCR) in the 0.4 μ M PFAS treated group might be the result of feedback regulation due to increased cholesterol content in cells (Figure 2).
- TGF- β expression is increased after the 4-week treatment with most PFAS species in a dose-dependent manner (Figure 3).

Conclusion and Discussion

- TGF- β plays a critical role in hepatic stellate cell (HSC) activation. Accumulated FC is thought to trigger inflammation and fibrosis in the liver. Further investigation is warranted.
- The effects of PFAS on intracellular TG and TC levels are not in a dose-dependent manner. This may be due to that PFAS have multiple targets, e.g., PPAR α , PXR, whose activation might exert different effects on lipid metabolism. This explanation needs to be supported by more data.

Acknowledgements

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