Clinical translatability of Ldlr-/-.Leiden mouse model for NASH

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Introduction

NASH is one of the most prevalent chronic liver diseases, which is closely associated with obesity, insulin resistance, dyslipidemia and cardiovascular disease. Preclinical validation of novel drug candidates for the treatment of NASH requires a translational animal model that should recapitulate these hallmarks of the human disease.

Aim

The present study aimed to further investigate the translatability of Ldlr-/-.Leiden mouse as translational NASH model.

Method

Ldlr-/-.Leiden mice fed a translational energy dense high fat diet *without cholesterol supplementation* for 20-24 weeks were compared with human NASH patients on (a) obesity and insulin resistance; (b) lipoprotein profiles, endogenous cholesterol synthesis and de novo lipogenesis (DNL); (c) liver transcriptome and metabolome profile; (d) histological NASH endpoints and (e) atherosclerosis. In addition, the response to treatments for 10 weeks with 10 mg/kg/d obeticholic acid (OCA) or 20 mg/kg/d cenicriviroc via diet admix or 12 weeks with 0.12 mg/kg/d semaglutide via sc injections was analyzed.

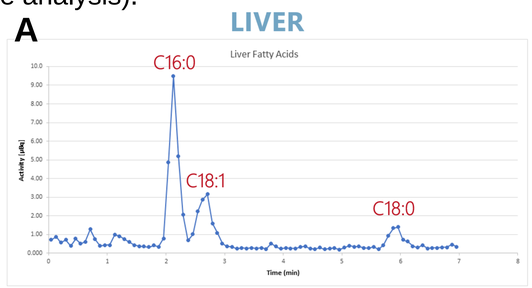
Diet-induced obesity, hyperinsulinemia and dyslipidemia in Ldlr-/-.Leiden mice

At t=24 weeks:	Chow	HFD
Body weight (g)	36.7 ± 1.6	51.8 ± 1.0***
Blood glucose (mM)	6.7 ± 0.3	6.9 ± 0.3
Plasma insulin (ng/mL)	2.0 ± 0.3	20.7 ± 4.3***
HOMA-IR	0.6 ± 0.1	6.3 ± 1.4***
Plasma cholesterol (mM)	7.6 ± 0.6	33.2 ± 2.7***
Plasma TG (mM)	1.3 ± 0.1	4.8 ± 0.8***

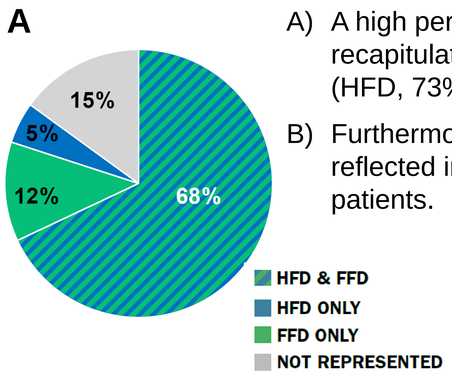
*** P<0.001 vs chow

Ldlr-/-.Leiden mice have an active endogenous cholesterol synthesis and DNL (as in NASH patients)

- Ldlr-/-.Leiden mice have an active endogenous cholesterol synthesis as in humans (measured via balance analysis).
- DNL is upregulated (14C from acetate is incorporated into newly synthesized fatty acids. Fatty acid profiling **(A)** via LC/MS showed that 14C signal was predominantly found in palmitate (C16:0, the primary end-point of DNL).

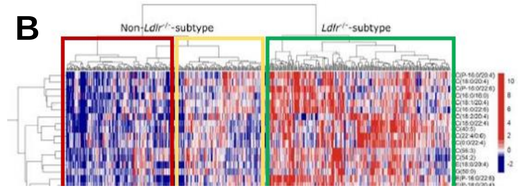


Ldlr-/-.Leiden mice recapitulate human NASH transcriptome and metabolome profiles

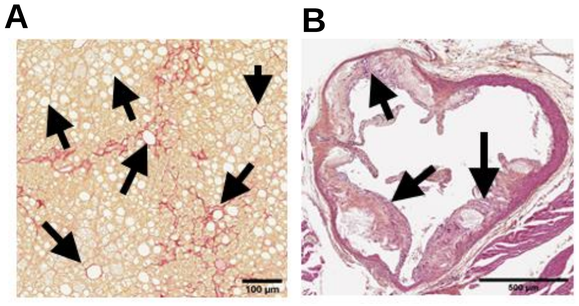


A) A high percentage of human NASH pathways is recapitulated in Ldlr-/-.Leiden mice on a high fat diet (HFD, 73%) or fast food diet (FFD, 80%).

B) Furthermore, Ldlr-/-.Leiden serum metabolome is reflected in a substantial proportion of NASH patients.

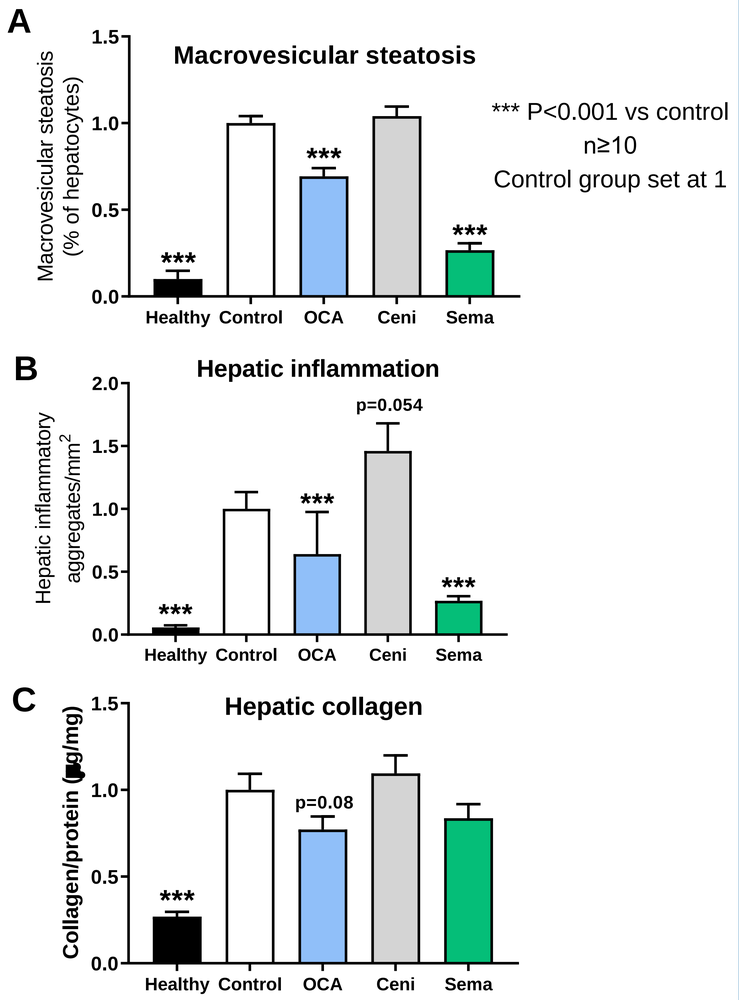


Ldlr-/-.Leiden mice develop NASH with bridging fibrosis and atherosclerosis



After 24 wks on HFD Ldlr-/-.Leiden mice develop **(A)** NASH with macrovesicular steatosis (arrows) and fibrosis (Sirius red staining) and **(B)** atherosclerotic plaques (arrows).

Ldlr-/-.Leiden mice respond to NASH treatments in line with clinical trials



Ldlr-/-.Leiden mice respond to treatments with NASH resolution (OCA & semaglutide, not cenicriviroc) and improvement with fibrosis (OCA tendency only), in line with clinical trials.

Conclusions

Overall, the Ldlr-/-.Leiden mouse model shows good clinical translatability and accurately mimics the etiology and pathology of NASH and fibrosis in humans.