Anti-inflammatory effects of a chemokine receptor mimicking peptide in obesity-associated MASH and atherosclerosis in Ldlr−/− Leiden mice

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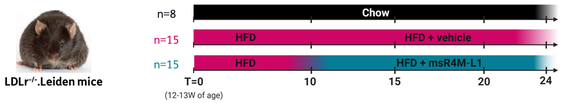
1. Introduction

Inflammation is one of the driving forces in obesity-associated MASH and atherosclerosis progression. msR4M-L1 is novel peptide with potential anti-inflammatory effects, by selectively inhibiting the pro-inflammatory MIF/CXCR4 axis while sparing the dichotomic CXCL12/CXCR4 and cardioprotective MIF/CD74 axis.

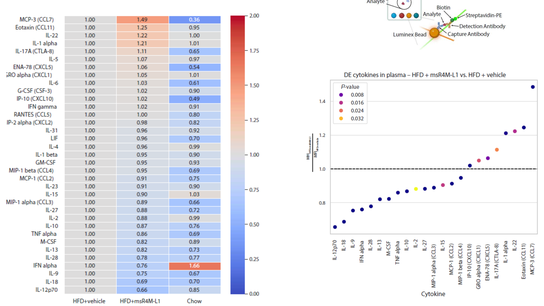
2. Study aim and design

To study potential anti-inflammatory effect of a novel peptide-based chemokine receptor ectodomain mimic, msR4M-L1, as a treatment for obesity-associated MASH and atherosclerosis.

Ldlr−/− Leiden mice were fed a high-fat diet (HFD) for 10 weeks to induce obesity, dyslipidemia, atherosclerosis and MASLD features and subsequently treated for 14 weeks with msR4M-L1 (3x/week via i.p.) or vehicle (3x/week saline via i.p.) while continuing HFD feeding.

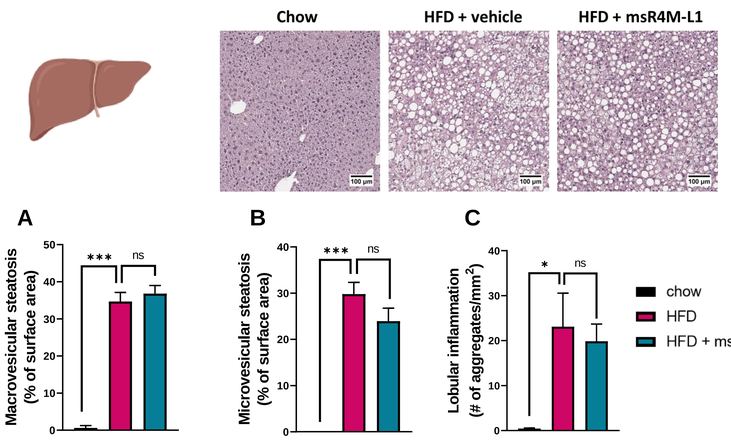


3. msR4M-L1 reduced circulating inflammatory factors



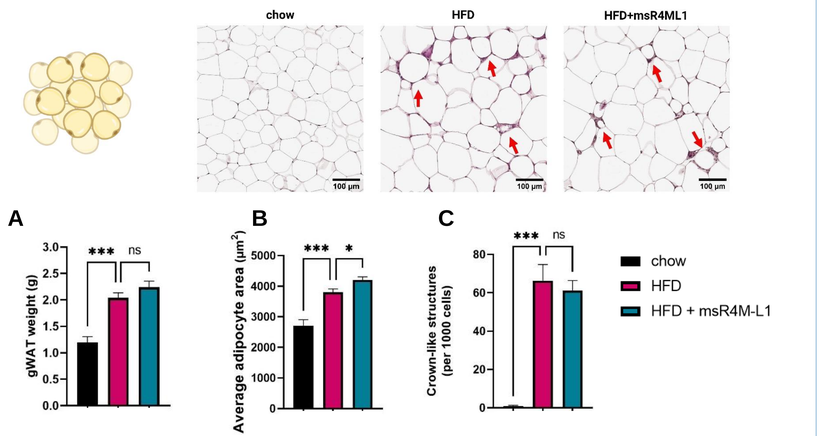
Plasma biomarker profiling by Luminex-based multiplex showed that msR4M-L1 attenuated HFD-induced increase in circulating inflammatory factors.

4. msR4M-L1 did not affect MASH



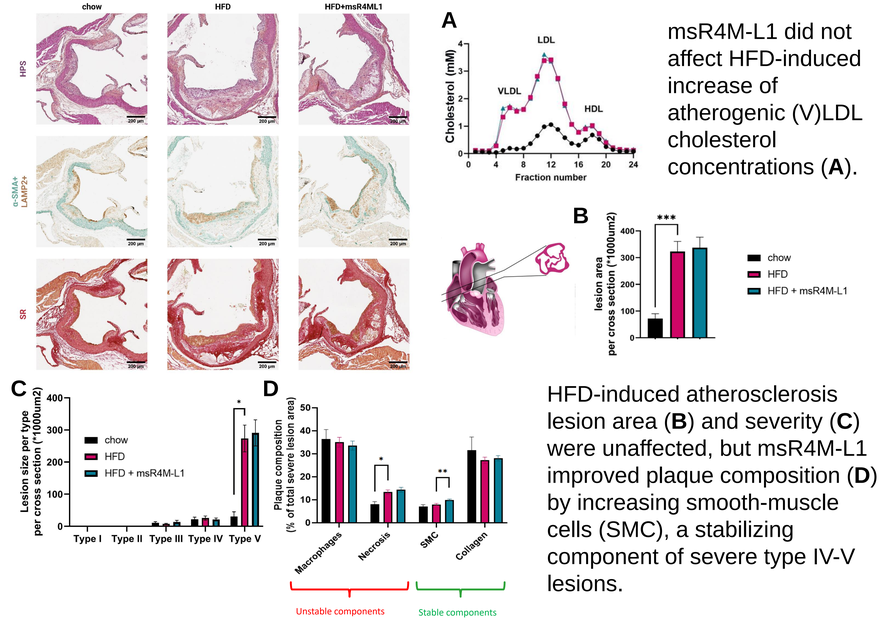
HFD + msR4M-L1 treatment did not significantly affect HFD-induced macrovesicular steatosis (**A**), microvesicular steatosis (**B**) or lobular inflammation (**C**).

5. msR4M-L1 increased average adipocyte size without affecting WAT inflammation



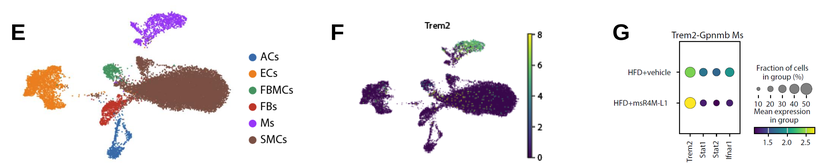
HFD-induced obesity associated with increased gWAT weight (**A**), enlarged adipocytes (**B**) and inflammation which was scored by the number of crown-like structures (CLS; indicated with red arrows in figure **C**). HFD + msR4M-L1 treatment increased adipocyte size but not inflammation.

6. msR4M-L1 improved atherosclerotic plaque composition



msR4M-L1 did not affect HFD-induced increase of atherogenic (V)LDL cholesterol concentrations (**A**).

HFD-induced atherosclerosis lesion area (**B**) and severity (**C**) were unaffected, but msR4M-L1 improved plaque composition (**D**) by increasing smooth-muscle cells (SMC), a stabilizing component of severe type IV-V lesions.



Nuclei from Ldlr–/–.Leiden aorta were sequenced using 10x and scRNA-seq profiles visualized in figure **E.** Subclustering of aortic macrophages (**F**) revealed that msR4M-L1 upregulated Trem2 positive macrophages (**G**). Trem2 is a lipid-sensing receptor regulating myeloid cell functions which is thought improve plaque stability by promoting lipid uptake and macrophage survival, and anti-inflammatory gene expression.

7. Conclusion

Specifically targeting the MIF/CXCR4 axis attenuated HFD-induced low-grade inflammatory state within the vasculature and improved atherosclerotic plaque composition by increasing plaque-stabilizing SMCs and increasing TREM2 positive macrophages, suggesting an overall atheroprotective role.

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