The bispecific anti-FGFR1/KLB agonist antibody bFKB1 attenuates non-alcoholic steatohepatitis and atherosclerosis in Ldlr-/-.Leiden mice

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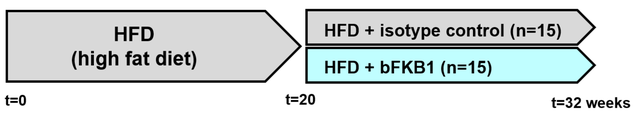
Introduction

Fibroblast growth factor 21 (FGF21) is an endocrine factor that has an important role in regulating whole-body metabolic organ homeostasis and energy balance through heterodimeric receptor complexes comprising FGFR1c, FGFR2c, FGFR3c and β-klotho (KLB). It is considered a promising target for the treatment of obesity-associated metabolic diseases such as NASH and atherosclerosis.

Aim

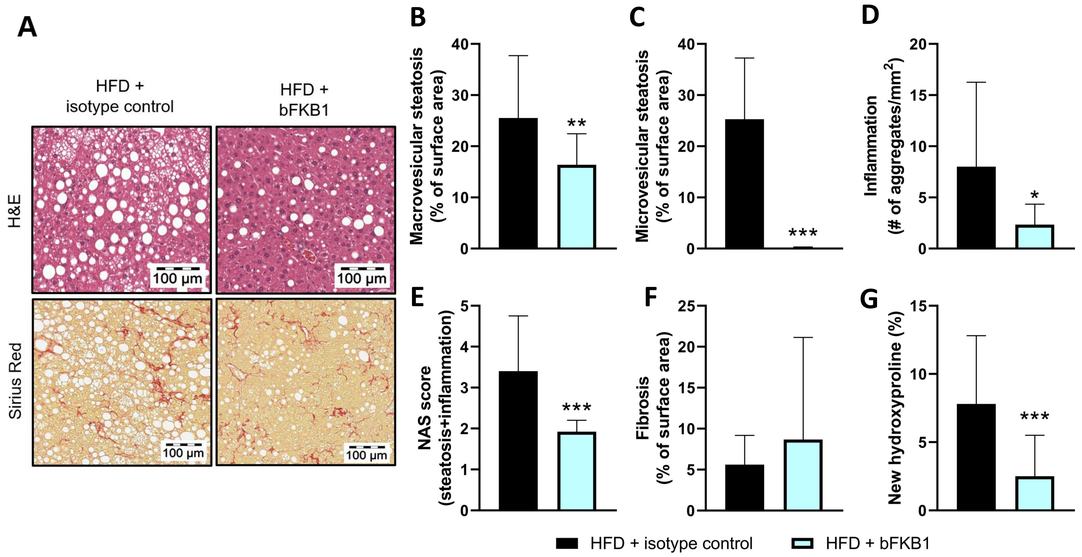
Here, we evaluated the effects of a bispecific antibody (bFKB1) that specifically targets the FGFR1c-KLB co-receptor complex to avoid off-target effects, in a translational preclinical model of obesity-associated NASH and atherosclerosis, to investigate its therapeutic potential against these diseases.

Study design



Effects on NASH and atherosclerosis were assessed histopathologically and biochemically (including D_2O analysis for new collagen formation in liver) in Ldlr-/-.Leiden mice. Underlying mechanisms of the bFKB1 treatment were investigated by hepatic transcriptomics analysis (NGS).

Treatment with bFKB1 improves hepatic steatosis, inflammation and inhibits new collagen formation



Hepatic macrovesicular steatosis (A) was significantly reduced in bFKB1-treated mice compared to those treated with the isotype control (A+B). Microvesicular steatosis (A) on the other hand was completely abolished with the bFKB1 antibody (A+C). Furthermore, bFKB1 treatment reduced the number of inflammatory aggregates in the liver (A+D). The NAS score, calculated as the sum of hepatic steatosis and inflammation was significantly decreased in bFKB1-treated mice. Histologically measured fibrosis (A) was not significantly affected by the treatment (F), though the formation of new collagen was significantly inhibited by bFKB1, as reflected by the newly incorporated hydroxyproline in the liver (G).

bFKB1 inactivates hepatic inflammatory and profibrotic transcriptional pathways

Treatment:	HFD+bFKB1	HFD+bFKB1
Control:	HFD+isotype	HFD+isotype
Param:	Z-score	-logP
Signaling by Rho Family GTPases	-4,3	7,9
Integrin Signaling	-3,7	4,0
GP6 Signaling Pathway	-3,5	4,3
Reelin Signaling in Neurons	-3,5	2,0
Tec Kinase Signaling	-3,2	4,4
Paxillin Signaling	-3,2	2,9
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	-3,2	6,0
Rac Signaling	-2,9	3,4
Actin Cytoskeleton Signaling	-2,8	4,4
Regulation of Actin-based Motility by Rho	-2,8	3,1
Leukocyte Extravasation Signaling	-2,6	7,3
Neuroinflammation Signaling Pathway	-2,5	2,3
Glycolysis I	-2,4	3,1
IL-8 Signaling	-2,2	4,0
Agrin Interactions at Neuromuscular Junction	-2,1	2,4

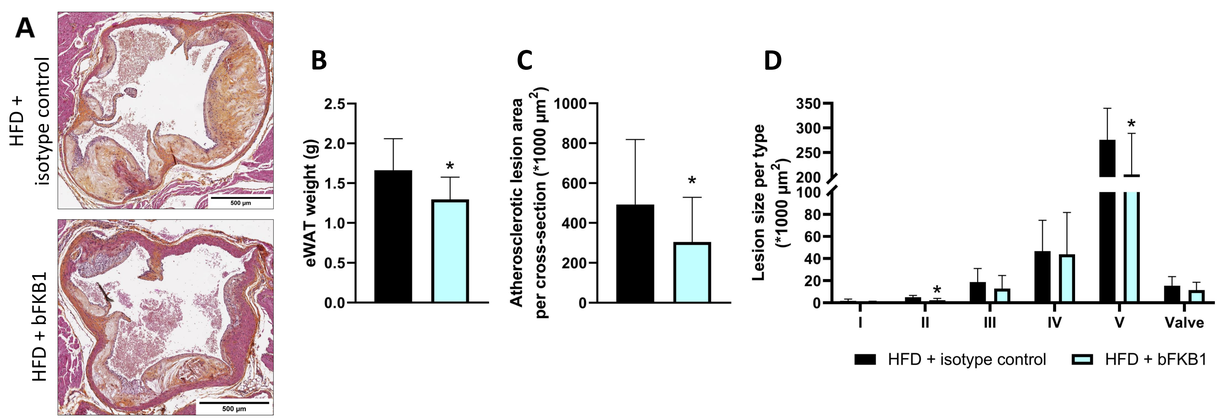
Based on differentially expressed genes in both groups, we determined the effects of bFKB1 on specific biological pathways or processes in which these genes are involved.

In bFKB1-treated mice, 88 pathways were significantly enriched (top 15 shown here). Among these pathways were several inflammatory pathways, for example leukocyte extravasation signaling and IL-8 signaling, that were mostly inactivated by bFKB1 intervention. Other bFKB1-regulated pathways included several lipid/energy metabolism pathways and a number of fibrosis pathways.

bFKB1 improves metabolic parameters and reduces atherosclerotic lesion size and lesion severity

bFKB1 lowered body weight and adipose tissue mass (B) without reducing food intake, lowered plasma insulin and plasma total cholesterol and triglycerides. Plasma ALT, liver weight, liver lipids and hepatic IL-1β protein levels were also decreased with bFKB1 treatment.

In the vasculature, bFKB1 had anti-atherogenic effects, lowering total atherosclerotic lesion area in the aortic root (A+C). This atherosclerosis-lowering effect of bFKB1 was attributable to a reduction in the severe type V lesions (D).



Conclusions

The bispecific anti-FGFR1/KLB agonist antibody bFKB1 has strong metabolic effects in HFD-fed Ldlr-/-.Leiden mice. While no FGFR1c receptor is present in the liver, these beneficial effects are associated with a reduction in liver steatosis and inflammation as well as atherosclerosis. Liver fibrosis was not affected within the treatment period studied, but analysis of new collagen formation and profibrotic transcriptional programs indicate that the treatment may have antifibrotic potential in a longer treatment duration in line with recent clinical results of FGF21 mimetic class of molecules.

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