NGM282 Promotes HDL Biogenesis and Transhepatic Cholesterol Efflux to Prevent Atherosclerosis in Mice

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BACKGROUND AND AIMS

- FG19, an endocrine hormone produced in the gut, acts in the liver to control bile acid synthesis. 1-2
- NGM282 is an engineered, non-tumorigenic analogue of human FG19. 3

In phase 2 clinical trials in patients with non-alcoholic steatohepatitis, administration of NGM282 resulted in rapid and profound reductions in liver fat content, liver inflammation, and fibrosis. 4

However, increased cholesterol levels and the molecular mechanisms that integrate the FG19 signaling with cholesterol metabolic pathways are incompletely understood.

Here, we investigate these mechanisms using a combination of pharmacological, bioinformatics, metabolomics and biochemical approaches.

METHODS

- db/db mice (I62NdKOa) received an intravenous injection of 1 x 10^8 vector genome adeno-associated virus (AAV) carrying FG19, NGM282 or green fluorescent protein (control). Two weeks later, serum levels of cholesterol, HDL-C and LDL-C were measured.
- Livers were collected for transcriptome profiling, QPCR, metabolomics and histological analysis.

- Hepatocyte-specific AQA-deficient mice were obtained by injecting Abca1^−/− mice with AAV-TBG-Cre, which drives Cre recombinase expression under TSG promoter, allowing hepatocyte-specific expression.

- FGFR-deficient mice or wild-type mice received an intravenous injection of 3 x 10^8 vector genome AAV carrying FG19 or green fluorescent protein (control).

- ApoA1-deficient mice were placed on a high-fat, high-cholesterol Western diet (Harlan TD83317) immediately following AAV injection, and this diet was continued ad libitum throughout the study. Mice were euthanized 18 weeks after AAV administration for analysis.

- En face analysis of the ApoA1-deficient mice were conducted at Wake Forest School of Medicine Metabolic Core (Winston-Salem, NC). Aortic lesion area was quantified using Image J software and expressed as percent lesion area relative to total aortic area. All quantifications were carried out by an observer blinded to the sample identity.

- Concentrations of total cholesterol, HDL-C and LDL-C were measured by enzymatic methods on an automated analyzer (COBAS INTEGRA 400 Plus Clinical Analyzer, Roche Diagnostics).

RESULTS

NGM282 Increases Serum Cholesterol in db/db Mice

- Administration of FG19 or NGM282 resulted in elevations in total cholesterol, HDL-C and LDL-C 2 weeks in db/db mice

NGM282 Selectively Activates Hepatic LXR Signaling in db/db Mice

- Transcriptome profiling and Ingenuity pathway analysis revealed that FG19 and NGM282 activate the LXR/RXR pathway.

Deficiency in Hepatocellular ABCA1 Abolishes NGM282-Associated Cholesterol Change

- ApoA1 and NGM282 selectively modulate LXR signaling and upregulate genes in transhepatic cholesterol efflux without causing steatosis.

- However, fibrosis and NGM282-associated cholesterol changes were abolished in mice deficient in LXR.

NGM282-Associated Cholesterol Change is Dependent on FGFR4

- Administration of FG19 or NGM282 resulted in elevations in total cholesterol, HDL-C and LDL-C 2 weeks in db/db mice

NGM282 Protects Against Atherosclerosis in ApoE-deficient Mice

- In dyslipidemic ApoE-deficient mice fed a Western diet, treatment with NGM282 significantly reduced atherosclerotic lesion area in arteries

CONCLUSION

- The endocrine hormone FG19 and its analogue NGM282 have a hitherto unsuspected intrinsic role in promoting transhepatic cholesterol efflux and HDL biogenesis through selectively activating LXR signaling, while ameliorating steatosis and atherosclerosis.

- The selective modulation of LXR by NGM282 may provide additional understanding of the observed cholesterol increases in animals and humans, as well as the cardiovascular benefit in animals.

References:
1. Akhrass et al., Dip Dis 2015; 15:207-221
4. Lee et al., Sci Transl Med 2016; 8:525ra279
5. Harris et al., Lancet 2018; 391:1279-1285
6. Harris et al., Hepatology 2019; 70:1860-1870

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Summary

LXR Agonists Increase Serum LDL-C in Humans

- Activation of LXR signaling is well known to promote reverse transport of cholesterol from peripheral tissues to the liver. 1
- LXR activation reduces the expression of genes involved in cholesterol efflux, facilitates cholesterol esterification by promoting fatty acid synthesis, and exhibits anti-inflammatory effects through inhibition of TLR signaling. 2,3
- The development of LXR agonists as anti-inflammatory agents has been hindered by hepatic defects that accompanies activation of LXR in the liver. 4
- Furthermore, first-in-human testing of LXR agonists revealed LDL-C elevations. 5
- Similarly, administration of NGM282 in patients with non-alcoholic steatohepatitis resulted in elevations in serum LDL-C levels, but reductions in liver fat content. 6

NGM282 BMS-852927 Increases LDL-C in Humans

- In dyslipidemic ApoE-deficient mice fed a Western diet, treatment with NGM282 significantly reduced atherosclerotic lesion area in arteries.