The therapeutic potential of microRNA-22 in MASH and obesity

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1 INTRODUCTION

MicroRNAs (miRNAs) represent a class of short endogenous non-coding RNAs that play pivotal roles as post-transcriptional regulators, modulating gene expression across diverse biological processes. Their involvement has been elucidated in various human diseases, including cardiometabolic diseases.

We identified microRNA-22 (miR-22) as a key regulator of lipid and metabolic homeostasis using miR-22 knockout and transgenic mice, respectively. Furthermore, miR-22 is upregulated in adipose tissue of individuals affected by obesity, where its levels exhibit a positive correlation with the severity of fibrosis in patients diagnosed with MAFLD/MASH. The therapeutic potential of miR-22 inhibition in MAFLD and obesity was assessed in mice and non-human primates using a systemically delivered anti-miR-22 oligonucleotide compound.

Our findings demonstrate that systemic administration of the anti-miR-22 oligonucleotide compound is both safe and well-tolerated. Furthermore, this intervention effectively suppresses hepatic lipid accumulation and induces weight loss in preclinical models, underscoring its promise as a therapeutic strategy for managing MAFLD and obesity.

2 MATERIALS & METHODS

All experiments were carried out on female wild-type (C57BL/6J), miR-22$^{+/-}$ and miR-22$^{-/-}$ mice (a kind gift from Dr. Da-Zhi Wang), or miR-22 Tg$^{+/+/Albumin}$–Cre mice obtained by crossing a miR-22 Tg with a commercially available Alb-Cre model (The Jackson Laboratory, mouse strain B6.Cg-Speer6-ps1Tg(Alb-Cre)21Mgn/J, Cat. #003574). The mice were given *ad libitum* access to normal chow or a 60% high-fat diet (HFD) and drinking water for the entire duration of the experiment. Mice were kept on HFD and treated with Vehicle, LNA Scramble (SCR) or LNA anti-miR-22 once a week with intraperitoneal injection. All tissues were harvested, washed in PBS and stored on ice or fixed in 4% paraformaldehyde overnight. The anti-miR-22 oligos were designed using a mix-mer strategy to target the seed region of hsa-miR-22-3p.

5 ACKNOWLEDGEMENTS & DISCLOSURES

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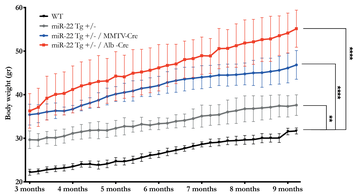
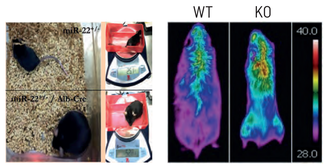
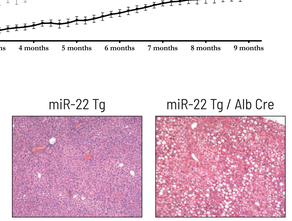
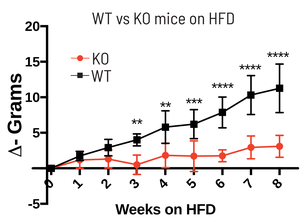
3 RESULTS

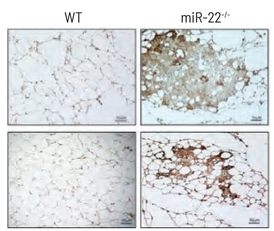
Mice engineered to overexpress miR-22 exhibit pronounced obesity even when maintained on a standard chow diet, accompanied by significant liver steatosis. Conversely, mice lacking miR-22 fail to gain weight when subjected to a HFD (60% of total caloric intake from fat). These mice demonstrate protection against hepatic steatosis, with their WAT displaying positivity for markers characteristic of BAT. Additionally, they exhibit heightened temperature in the intrascapular area, indicative of increased metabolic activity.







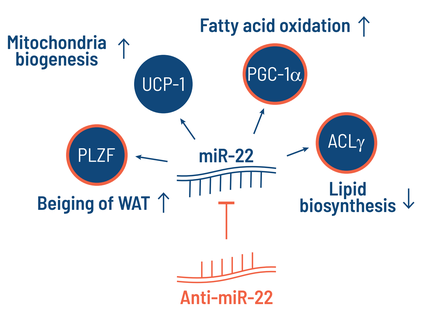




4 CONCLUSION

We identified 3 major metabolic players that are under miR-22 control and that can regulate:

- lipid biosynthesis
- mitochondrial biogenesis
- beiging of white adipose tissue



We designed and tested a therapeutic strategy to pharmacologically inhibit miR-22 *in vivo* and protect against or alleviate obesity and MAFLD. Mice treated with LNA targeting miR-22, as opposed to those treated with a scramble oligo or vehicle alone, exhibited resistance to diet-induced obesity. Anti-miR-22 therapy effectively reduced body weight in obese mice and reversed liver steatosis. Importantly, no discernible differences in food intake were observed among groups deficient in miR-22 expression (genetically and pharmacologically induced). This underscores an orthogonal mechanism to GLP1 agonists and sets the stage for the development of pharmacological inhibitors targeting miR-22 as a promising therapeutic strategy.