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miR-22 REPRESENTS A KEY REGULATOR OF LIPID HOMEOSTASIS

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1 INTRODUCTION

Obesity is a growing public health problem, affecting almost 2 billion people worldwide. It is associated with increased risk of type 2 diabetes, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and cancer.

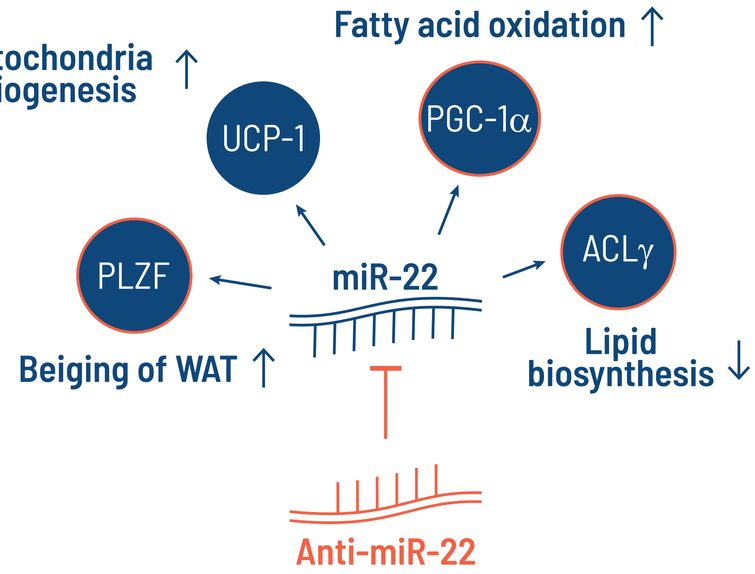
Here we identify microRNA-22 (miR-22) as an essential rheostat involved in the control of lipid and energy homeostasis as well as the onset and maintenance of obesity, using two different mice models. We demonstrate miR-22 overexpression promotes obesity and hepatic steatosis while its loss-of-function protects against these phenotypes even when mice are fed with high fat diet (HFD). Genetic ablation of miR-22 favors metabolic rewiring towards higher energy expenditure and browning of white adipose tissue.

Our findings thus identify a critical non-coding RNA that can control multiple metabolic relevant phenotype as a single genetic factor.

2 MODE OF ACTION

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

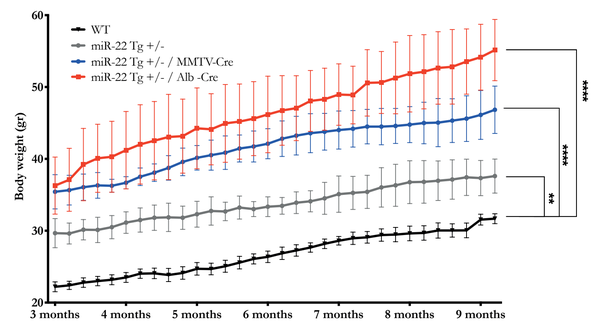
- lipid biosynthesis
- mitochondrial biogenesis
- beiging of white adipose tissue

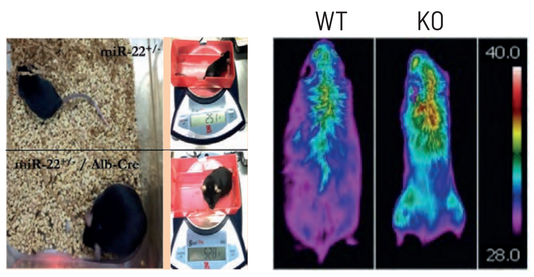


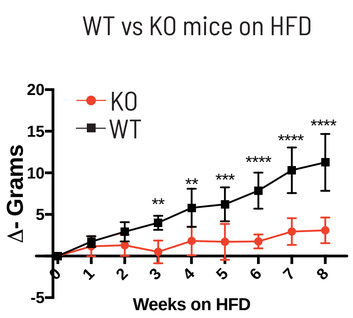
3 RESULTS

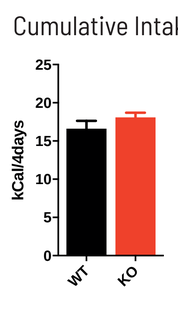
Mice overexpressing miR-22 are profoundly obese on regular chow diet and display a strong liver steatosis.
miR-22 null mice fail to gain weight when challenged with a HFD.

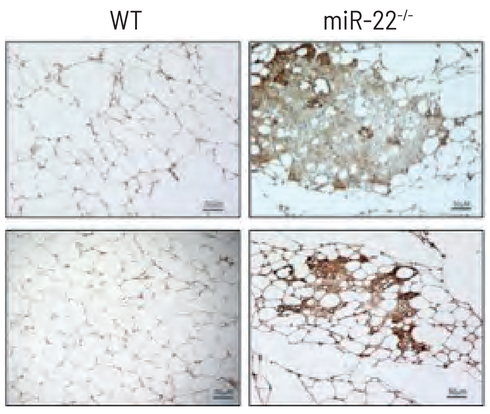
- Livers were protected from steatosis
- WAT stained positive for BAT markers
- Increase in temperature in the intrascapular area

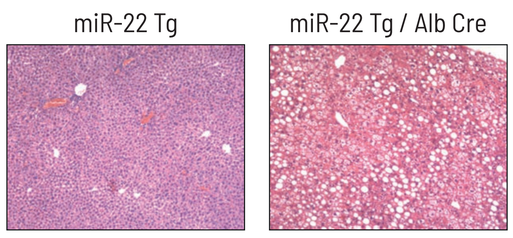


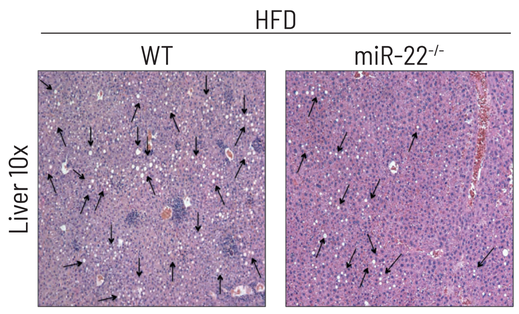










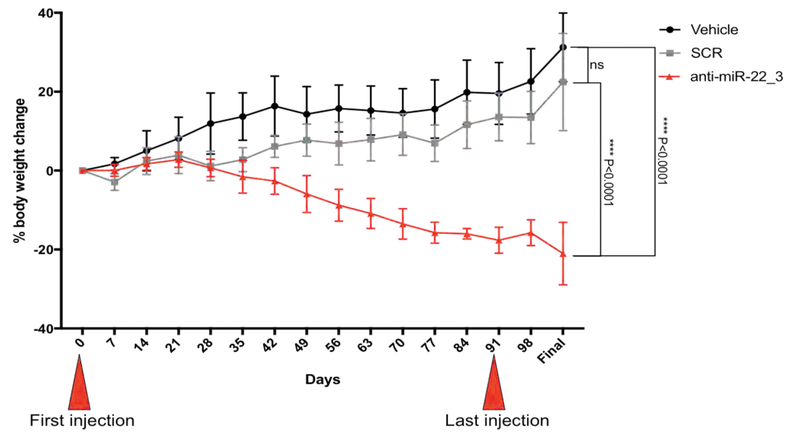


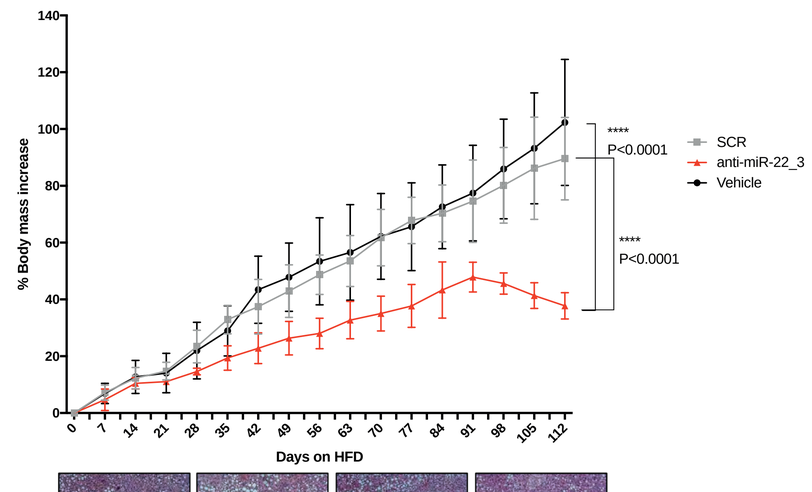
4 RESULTS

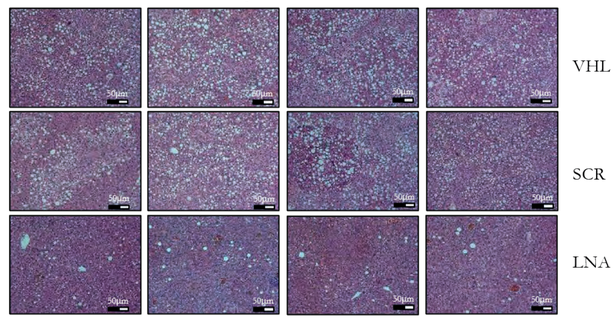
Pharmacological inhibition of miR-22 *in vivo* to protect or cure from obesity and NAFLD:

- Mice treated with LNA against miR-22, contrary to mice treated with a scramble oligo or with vehicle, were protected from becoming obese when fed with HFD.
- Anti miR-22 therapy was effective in reducing weight in already obese mice and revert liver steatosis.
- No difference between miR-22 deficient groups (both genetic and pharmacological induced) in food intake.

This approach provides an orthogonal mechanism to GLP1 agonists and paves the way for the development of pharmacological anti-miR-22 inhibitors as therapeutic strategy.







5 MATERIALS & METHODS

All experiments were carried out on female wild-type (C57BL/6J), miR-22$^{+/-}$ and miR-22$^{-/-}$ mice[1], or miR-22 Tg$^{+/+/Albumin}$-Cre mice obtained by crossing a miR-22 Tg with a commercially available Alb-Cre model[2]. The mice were given *ad libitum* access to normal chow or 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.

[1] a kind gift from Dr. Da-Zhi Wang
[2] The Jackson Laboratory, mouse strain B6.Cg-Speer6-ps1Tg(Alb-Cre)21Mgn/J, Cat. #003574

6 ACKNOWLEDGEMENTS & DISCLOSURES

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