MiR-22 differentially regulates energy metabolism in normal versus hepatic cancer cells

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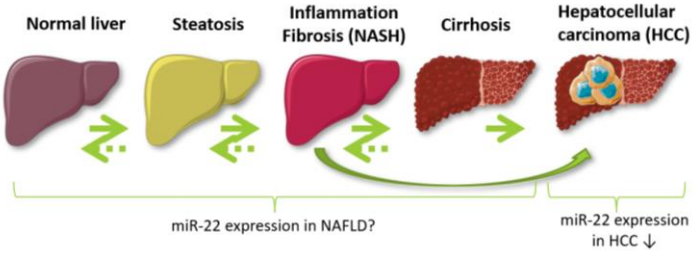
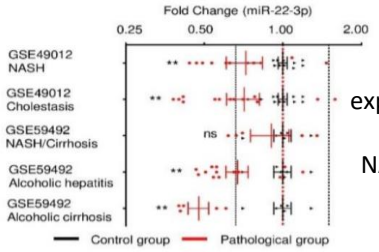
Linear progression of non-alcoholic fatty liver disease (NAFLD) and hepatic cancer



MiR-22 is one of the most abundant miRNAs in the liver and alterations of its hepatic expression have been associated with the development of NAFLD and cancer.

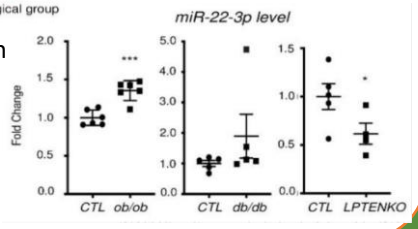
MiR-22 expression is decreased in HCC, but not in early stages of NAFLD in patients

Mir-22 was reported decreased in HCC (PMID 20842113, 23766411)



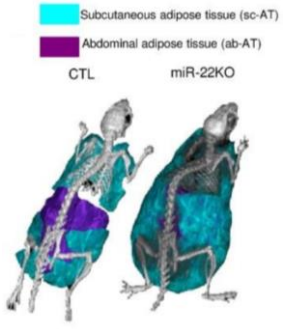
Hepatic miR-22 expression is inconsistent in human cohorts of NASH patients (in silico, GSE datasets).

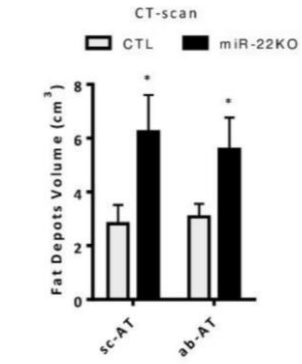
Hepatic miR-22 expression also varies in different mouse models of hepatic steatosis (ob/ob, db/db, LPTENKO mice).

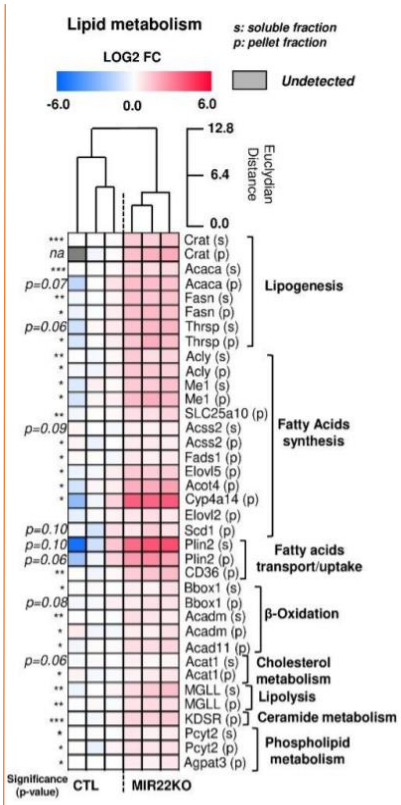


Hepatic miR-22 deficiency exacerbates diet-induced obesity and steatosis in vivo

CT scans (panels below) of fat depots in diet-induced obese control and total miR-22KO mice indicate obesity exacerbation with miR-22 deficiency.

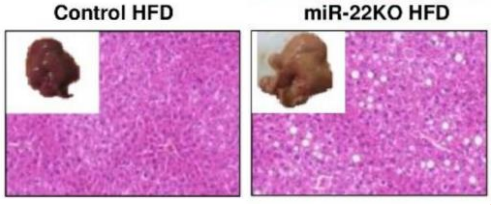




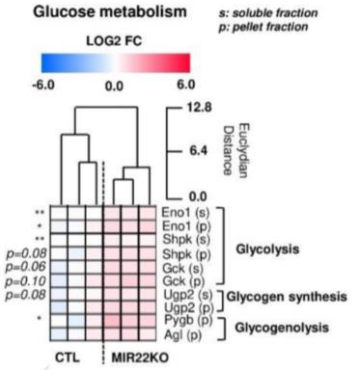


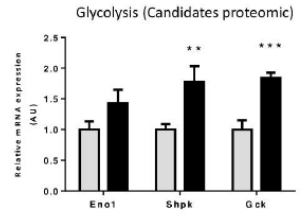
Proteomic analysis revealed upregulation of lipid synthesis and uptake in the livers of obese miR-22KO mice (panel above).

Histology analysis of control and miR-22KO livers showed stronger hepatic steatosis in miR-22KO mice.



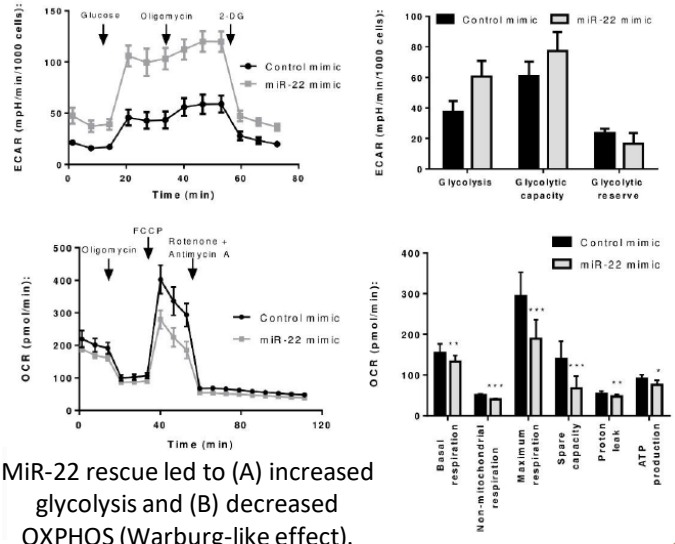
MiR-22 deficiency in vivo triggered hepatic glycolysis, whereas its rescue in hepatic cancer cells induced a Warburg-like effect





Proteomic analysis in miR-22KO livers indicated upregulation of glycolysis (left panel), confirmed by PCR analysis (panel above).

MiR-22 rescue was performed in hepatic cancer cells to assess the therapeutic potential of miR-22 overexpression in hepatic cancer.



MiR-22 rescue led to (A) increased glycolysis and (B) decreased OXPHOS (Warburg-like effect).

Conclusion: MiR-22 function is relevant on a whole-body level, as its ablation led to a striking exacerbation of diet-induced obesity and hepatic steatosis. MiR-22 deletion further led to a metabolic reprograming in the liver (glycolysis and lipogenesis ↑). Nevertheless, its rescue (overexpression) in a hepatic cancer cell line resulted in a Warburg-like metabolic switch, calling for caution when considering this miRNA as a therapeutic target in HCC.

Gjorgjieva et al., JPM, 2020