UNRAVELING ADIPOSE TISSUE – LIVER CROSSTALK BY PROFILING MICRORNA SECRETOME IN PORTAL VEIN PLASMA OF NON-ALCOHOLIC STEATOHEPATITIS PATIENTS

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INTRODUCTION & AIM

MicroRNAs can trigger hepatocyte apoptosis, hepatic stellate cell activation and NF-κB signaling. Here they could potentially promote the progression from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH). In this study we investigate the microRNA secretome in the portal vein plasma of NALFD patients and characterize the influence of miR-29a in vitro after palmitic acid treatment.

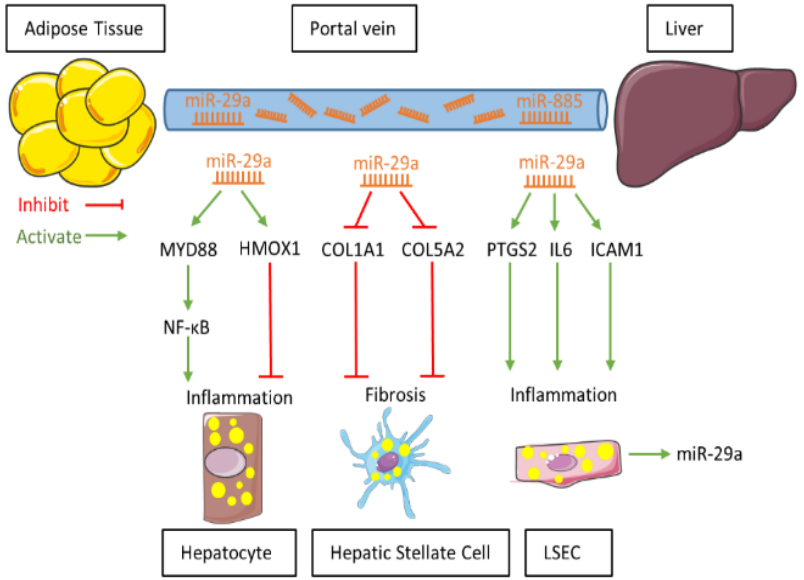
METHODS

MicroRNAs were screened in portal vein plasma samples of obese, NAFL and NASH patients. We also investigated the microRNA-mediated changes in pro-fibrogenic and pro-inflammatory gene expressions within hepatic cells by exposing them to palmitic acid and transfecting with mock or miR-29a mimics. Expressions were screened with TaqMan Array Human MicroRNA A Cards v2.0 and measured by real-time PCR.

CONCLUSION

NASH patients derived portal plasma had increased miR-29a and miR-885 levels. Additionally, transfection with miR-29a resulted in increased pro-inflammatory and decreased pro-fibrogenic gene expression.

Our results point towards a potential adipose tissue-liver crosstalk mechanism involving miR-29a in patients with NASH. Identifying the source of miR-29a and the direct target genes in the liver is of utter importance as it may give us novel insights on how NAFLD progression is regulated.

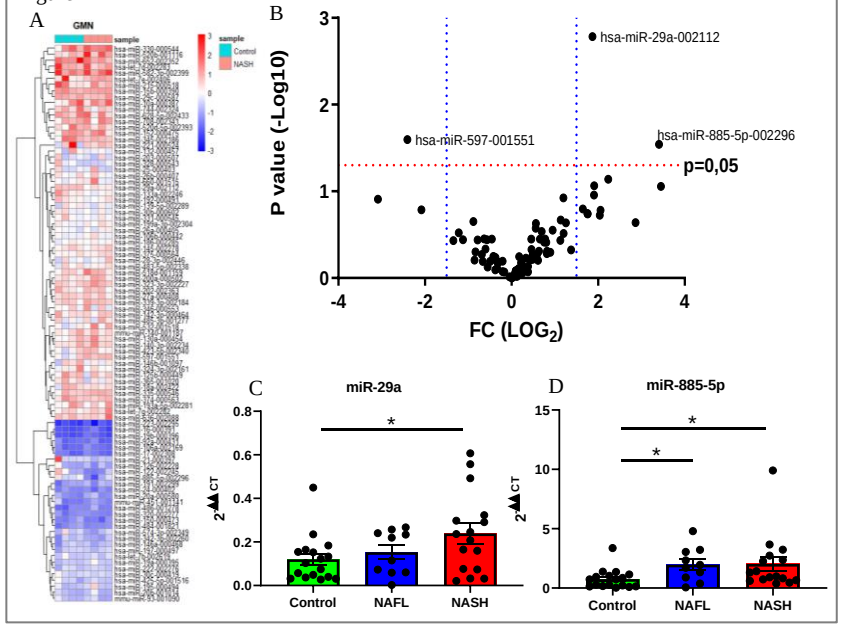


RESULTS - I

Increased microRNAs in portal plasma of NASH patients

- miR-29a and miR-885 were differentially expressed in the portal vein plasma of NASH patients relative to controls (miR-885-5p fold change=9.62, p=0.008; miR-29a fold change=2.86, p=0.035) **(Fig.1 A-B).**
- By including an independent cohort, the above result was further validated since significantly increased levels of miR-29a and miR-885 could be detected in NASH patients **(Fig.1 C-D).**
- These results suggest a possible mechanism whereby secreted adipose tissue-derived factors can directly influence gene expression in the liver.

Figure 1

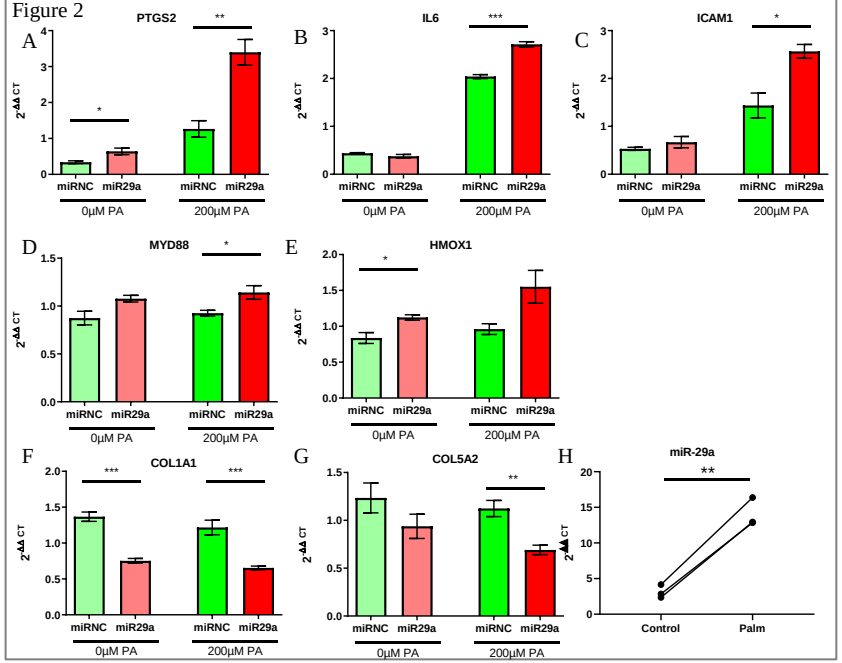


RESULTS - II

miR-29a affecting hepatic gene expression

- Transfecting SK-HEP1 cells with miR-29a mimics led to increased expression of pro-inflammatory genes *PTGS2*, *ICAM1* and *IL6* **(Fig.2 A-C).** Interestingly, SK-HEP1 cells also showed increased miR-29a release after palmitic acid exposure **(Fig.2 H).**
- miR-29a in hepatocytes led to an increase in pro-inflammatory *MYD88* and anti-inflammatory *HMOX1* **(Fig.2 D-E).**
- Finally, fibrosis-related transcripts *COL1A1* and *COL5A2* were decreased in hepatic stellate cells after exposure to miR-29a mimic **(Fig.2 F-G).**

Figure 2



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