MICRORNA CAUSES DYSFUNCTIONAL PROCESSES IN MITOCHONDRIA IN NAFLD

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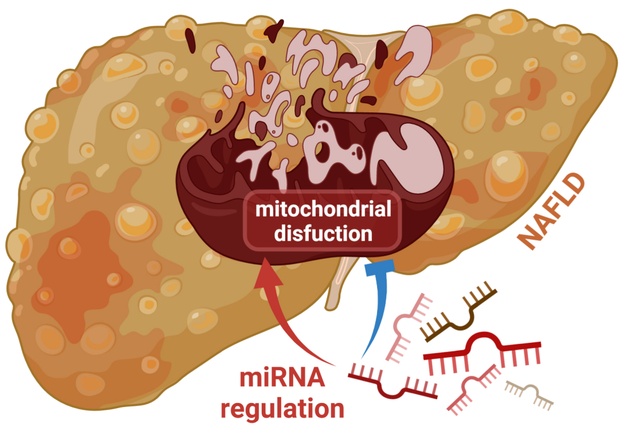
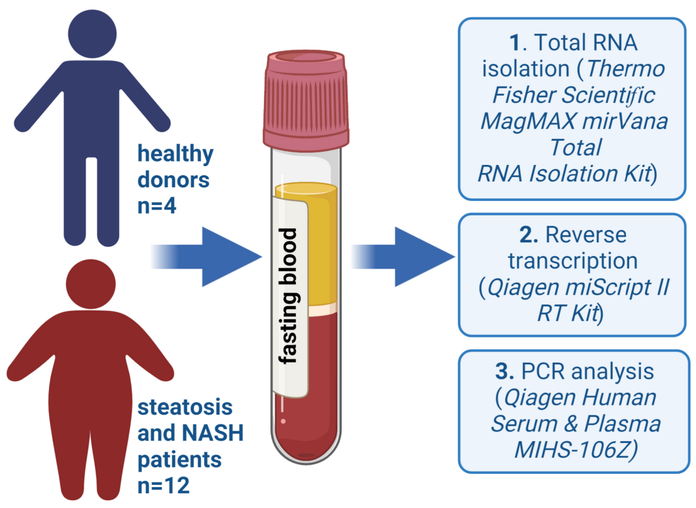
INTRODUCTION



Non-alcoholic fatty liver disease (NAFLD) is emerging as one of the most common chronic liver diseases worldwide, and mitochondrial dysfunction plays a prominent role in the development of this pathology. Research on the involvement of miRNAs in NAFLD is also becoming increasingly important. We aimed to combine knowledge from both fields to better understand how miRNAs cause the dysfunctional processes in mitochondria in NAFLD.

METHODS



Statistical Analysis of Experimental Data
PCR data were analyzed using miScript miRNA PCR Array Data Analysis Tool software (Qiagen, Hilden, Germany). The normal distribution was checked by Shapiro-Wilk test. If the sample fitted the normal distribution Student's t-test was used. Otherwise Mann-Whitney test was applied. Differences were considered significant at $p < 0.05$.

Search for experimentally confirmed targets of DEMs
The experimentally confirmed targets for 24 differentially expressed miRNAs were found in miRTarBase (version 8.0)[1]. The official database website has been down for some time. However, the miRNet 2.0[2] resource contains the miRTarBase dataset, so it was used to obtain information on targets.

RESULTS

1. **24 DEMs were identified** *(DEM – differentially expressed miRNA, at least twofold expression change and $p < 0.05$) (Fig.1).*
2. Mining for experementally confirmed targets of **19* DEMs** in miRTarBase[1] (accesed by miRNet[2]).
3. Comparison of the found experimentally confirmed targets of DEMs with the pathway **"Nonalcoholic fatty liver disease"** (Wikipathways)[3] and highlighting mitochondrial proteins among them (mitochondrial proteins defined by MitoProteome[4]) *(Fig.2).*

* mirTarBase showed - via miRNet - targets for 19 miRNAs from all DEMs. This is most likely due to the fact that we are looking for specific -3/-5p forms, and these are sometimes not indicated in mirTarBase.

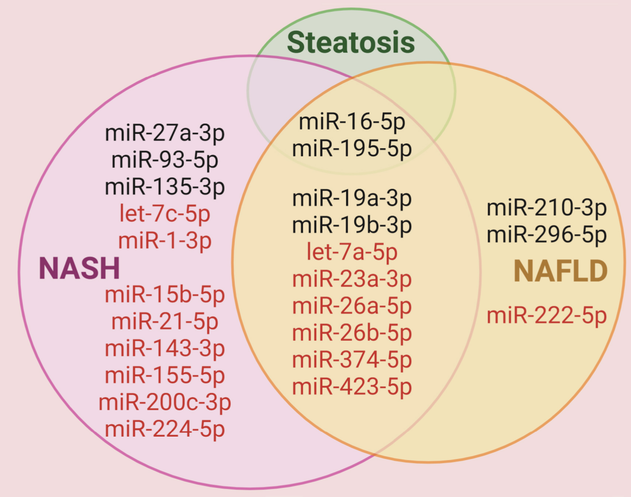


Figure 1. *Venn diagram of the distribution of 24 DEMs in the study groups, black - downregulated, red - upregulated DEMs*

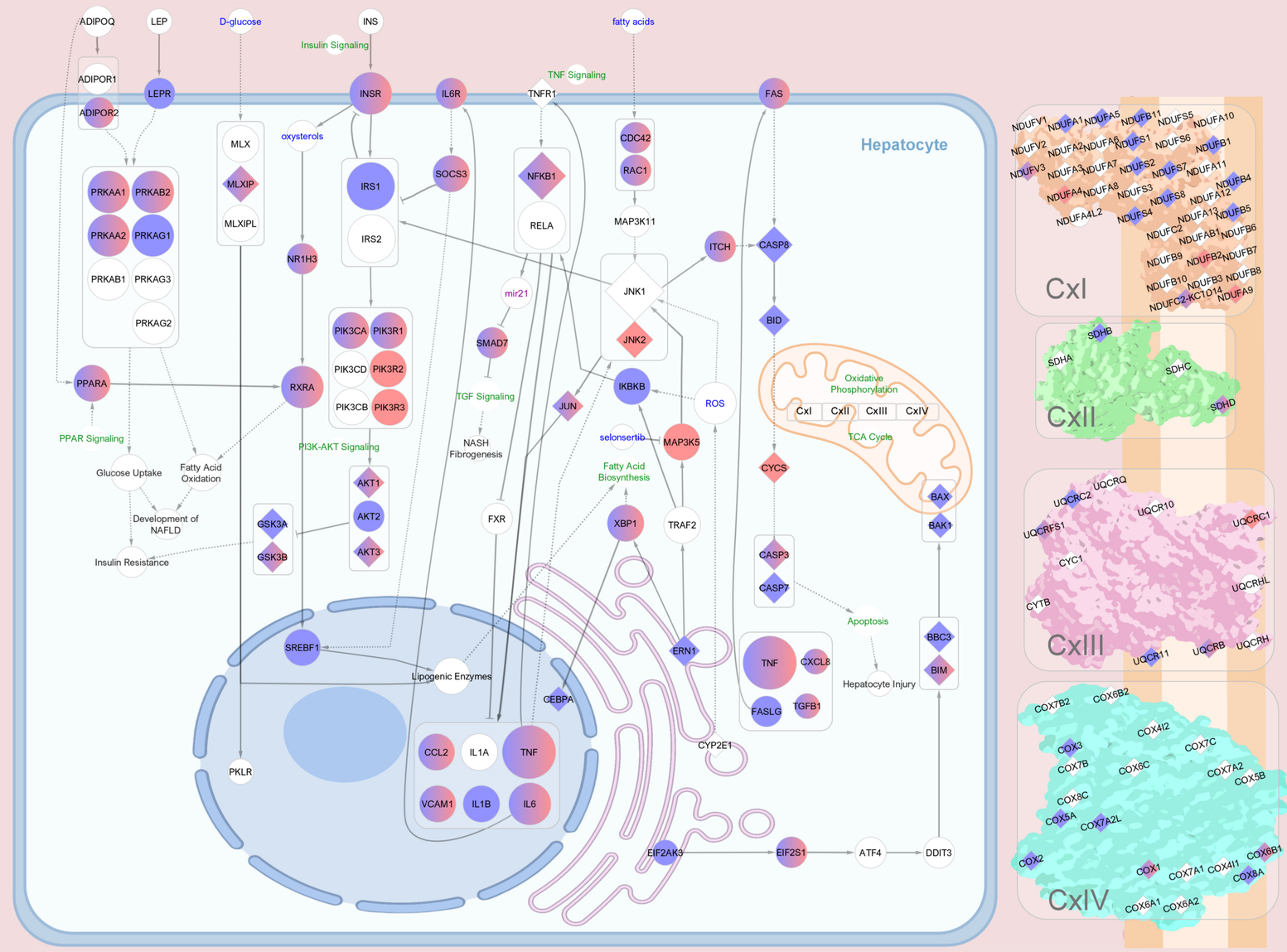


Figure 2. *Modified map of NAFLD pathogenesis showing putative miRNA-dependent regulation of mitochondrial genes. Pink - genes targeted by downregulated miRNAs (these proteins are presumably increased); blue - genes targeted by upregulated miRNAs (these proteins are presumably decreased); gradient fill - genes targeted by both up- and downregulated miRNAs. Diamond-shaped genes are mitochondrial genes; circular genes are other, non-mitochondrial genes. The pathway was imported from WikiPathways. The figure was created in Cytoscape.*

REFERENCES

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CONCLUSION

The presented study is an example of how data from microRNA screening can be used to find new potential contributors to pathology. We found 24 serum microRNAs differentially expressed at different stages of NAFLD (Fig. 1). Using a database of experimentally confirmed miRNA targets, we identified target genes for miRNAs that are deregulated in NAFLD. We then visualized the obtained data by plotting the sum of microRNA effects on a map of NAFLD pathogenesis (Fig. 2). We found that 49 mitochondrial proteins were under the influence of miRNAs deregulated in NAFLD. Presumably, genes responsible for ATP production are repressed by increased microRNAs (let-7c-5p, miR-155-5p, miR-423-5p, miR-15b-5p, miR-143-3p, and miR-26a-5p). Let-7c-5p and miR-423-5p can suppress hepatocyte apoptosis by targeting BAK1 and BAX genes, which activate the intrinsic pathway of apoptosis in NAFLD. Reduction of IKB and JUN activity by miR-423-5p may lead to inhibition of the NF-kB pathway and inactivation of proapoptotic factors. The work is predictive, and the proposed assumptions need to be experimentally proven.

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