

Comment on “A series of microRNA in the chromosome 14q32.2 maternally imprinted region related to progression of non-alcoholic fatty liver disease in a mouse model”

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Okamoto K, Koda M, Okamoto T, Onoyama T, Miyoshi K, Kishina M, Kato J, Tokunaga S, Sugihara TA, Hara Y, Hino K, Murawaki Y. A series of microRNA in the chromosome 14q32.2 maternally imprinted region related to progression of non-alcoholic fatty liver disease in a mouse model. *PLoS One* 2016;11:e0154676.

Non-alcoholic fatty liver disease (NAFLD) is a liver disease related to metabolic syndrome with rising socio-economic impact worldwide. NAFLD is defined by significant lipid deposition in hepatocytes that is unrelated to alcohol consumption. This high prevalence of liver disease occurs after a protracted inflammatory status caused by insulin resistance derived from high consumption of fructose-rich goods^[1] as shown by the multi-parallel hit theory.^[2,3]

NAFLD is currently classified in simple steatosis (SS) and non alcoholic steatohepatitis (NASH). NAFLD is a benign condition without histological signs of inflammation and could be reversed by change of life style, recovering from hyperinsulinism and the metabolic syndrome. However, a protracted inflammation and elevated serum transaminases determine a severe stage of disease, so called NASH, that affects the liver irreversibly leading to liver fibrosis, cirrhosis and cancer.^[4]

MicroRNAs (miRNAs) represent one of the key regulators of epigenetic modifications. They are normally expressed in clusters and their mature forms are able to combine together with proteins and form the RNA-inducing silencing complex (RISC).^[5] Once the RISC is formed, miRNAs bind the high

affinity mature mRNAs forming a double RNA sequence. The duplex impedes the translational machinery and stabilizes the mRNA or promote its degradation.

So the exact role exerted by miRNAs is based on the inhibition of gene products expression.^[6] This fine regulatory mechanism is responsible of several cellular processes and can be altered in several diseases including NAFLD.^[7-10]

Okamoto *et al.*^[11] present an outstanding study concerning a broad range analysis of miRNAs characterizing NAFLD mouse model and serum from patients affected by this disease.

They performed a microarray in order to identify the expression variation of miRNAs and their possible identification with NAFLD. The data obtained in the closest mouse model for NAFLD fatty liver shionogi ob/ob characterized by mice bearing a spontaneous obesity mutation of the leptin gene (Lepob, commonly known as ob) were processed for similarity with human expressed miRNAs.


Interestingly, analysis of similarity conservation of miRNAs between rodent and human confirmed the expression of the same miRNAs in patient affected by SS and NASH. These miRNAs were identified at the maternally imprinted region (mat) of the chromosome 14q32.2.

Seven miRNAs were identified as markers for NAFLD, especially for NASH, all belonging to the Dlk1-Dio3 mat cluster.

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Here, we highlight the importance that have these miRNAs as repressor of factors coordinating the cell fate by triggering pro-death mechanisms e.g. apoptosis and autophagy.

In particular, the authors reported that AMP-activated protein kinase (AMPK) is a target of the majority of the identified miRNAs. AMPK is responsible of metabolic processes as mentioned by the authors, thus conferring it also a key role during autophagy.^[12] In particular, AMPK is responsible of ULK1 (serine/threonine-protein kinase) phosphorylation with consequent mammalian target of rapamycin complex (mTORC) inhibition and autophagy activation during nutrient starvation.^[12] Autophagy represents a fine regulated mechanism to overcome cellular stress and promote cell death in case of protracted cellular stress. It has been shown that its modulation can be a promising target for cancer therapy in liver cancer.^[13] The expression of miRNAs repressing autophagy regulators like AMPK could highlight the variations occurring at epigenetic level conferring to cells an altered metabolism that irreversibly modifies the liver cells and tissue. These alterations could be responsible to trigger further pathological cellular features leading to cirrhosis and furthermore liver carcinogenesis.^[14,15] For this reason it will be interesting to further focus on the expression of the miRNAs localized at mat 14q32.2 in patients affected by cirrhosis and liver cancer, as it has been already shown for other miRNAs in liver cancer cells and thyroid cancer.^[16-18] The miRNAs discovered in this study can represent valid targets for the diagnosis of NAFLD and could be furthermore adopted as biomarkers for patients affected by cirrhosis and liver cancer.

Finally, inhibition of mTORC by the use of biguanides (metformin),^[19] a well known mTOR inhibitors currently used for the treatment of type 2 diabetes,^[20] could represent a therapeutic target for NASH^[21] in a translational setting defining mTORC as a major target of NASH related miRNA.

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Conflicts of interest

There are no conflicts of interest.

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