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MiRNA146a IS A KEY COMPONENT OF IMMUNNOSUPRESSIVE ENVIRONMENT OF HEPATOCYTES CHRONICALLY INFECTED WITH HBV AND MELANOMA CELLS

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Interferon α (IFNα) is a pro-inflammatory cytokine with antiviral properties. Our project focuses on Toll-like receptors (TLR)7/9, which upon activation lead to a massive production of INFα.[1] Therefore, the process needs to be strictly regulated. One of the negative regulators of TLR7/9 signaling is a micro RNA (miRNA) miRNA146a.[2]

miRNAs are small non-coding RNAs, part of the RISC complexes, which regulate translation of target protein by silencing corresponding mRNA.[3] RISC complexes can be sorted to multivesicular bodies (MVBs), and then to extracellular vesicles (EVs). Once exported, the RISC complex stays functional and can affect different cells upon uptake of RISC complex-containing EVs.[4]

We focus on miRNA146a, which has immunosuppressive properties. It is the most abundant miRNA in hepatocytes. Furthermore, hepatocytes persistently producing HBV virus have significantly higher level of miRNA146a than HBV-negative hepatocytes. Moreover, increased levels of miRNA146a were detected in melanoma cells that correlated with immunosuppressive effects.[5]

We investigate whether miRNA146a is one of the key players in immunosuppression duringHBV infection and melanomas. We speculate that miRNA146a could be be packaged into EVs in the form of active RISC complex, and in turn, contribute to the immunosuppresive microenvironment.

We performed a series of experiments which show, that the miRNA146a intracellular and extracellular levels are increased in both HBV-producing cells and melanoma cells lines. Moreover, the supernatant from HBV-producing cells and melanoma cell lines reduces the IFNα secretion by Gen2.2 cells (model of plasmacytoid dendritic cells) upon TLR7/9 agonist treatment. Importantly, the inhibition of miRNA146a in HBV-producing cells restored the Gen2.2 cell response to TLR7/9 agonist, suggesting that miRNA146a could be an immunosupressive factor transfered from HBV-infected cells to immune cells via EVs.

We will further analyze the EVs composition by fractionation to determine the miRNA146a origin and the mechanism of transport. Regulation of the circulating levels of miRNA146a can be a new target in the clinical research as it can reimpose the immune response of the host.

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