miRNA-218 TARGETS LIPIN-1 AND GLUT-4 GENES IN LOPINAVIR/RITONAVIR TREATED 3T3-L1 CELLS

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Lipodystrophy syndrome (LS), a metabolic condition characterized by adipose tissue redistribution, is a commonly adverse event reported in human immunodeficiency virus (HIV)-infected patients treated with combination antiretroviral therapy (cART). LS is often associated with metabolic disturbances and insulin resistance, leading to an increased cardiovascular and diabetic diseases risk.

Lipin-1 has is involved in the development of LS by interacting with the nuclear peroxisome proliferator-activated receptor γ2 (PPARγ2), which regulates the expression of specific genes required for adipocytes maturation and maintenance, like GLUT-4.

Moreover, previous studies revealed that miRNA-218 is more expressed in HIV+ patients compared with HIV- subjects.

Starting from these observations, the aims of this study were 1) to verify whether lipin-1 mRNA expression is regulated by miRNA-218 and 2) to investigate the possible functional link between miRNA-218 and GLUT-4 mRNA expression in 3T3-L1 cells.

Differentiated 3T3-L1 adipocytes were treated with the lopinavir/ritonavir (LPV/r) combination at different concentrations (12μM:3μM and 16μM:4μM). Cell viability, lipid accumulation, lipin-1 and GLUT-4 mRNA, and miRNA-218 levels have been determined. Transfection of antimiR-218 or miRNA-218 mimic has been used to investigate the role of miRNA-218 in lipogenesis.

LPV/r treatment did not affect the viability of differentiated 3T3-L1 cells. Interestingly, it caused a significant decrease of intracellular lipid accumulation, a reduction of GLUT-4 and lipin-1 mRNA levels, and an overexpression of miRNA-218 levels.

The transfection of antimiR-218 in 3T3-L1 cells during LPV/r treatment significantly restored lipin-1 mRNA levels. On the contrary, the overexpression of miRNA-218, by specific miRNA-218 mimic transfection, reduced the cellular lipid fraction and lipin-1mRNA levels.

In conclusion, we have demonstrated that in differentiated 3T3-L1 cells the treatment with LPV/r alters lipid accumulation by increasing miRNA-218 levels that, in turn, targets lipin-1 mRNA. Moreover, the increase of miRNA-218 levels correlates negatively with GLUT-4 mRNA levels, suggesting a role for miRNA-218 in insulin resistance correlated to cART. These results could explain the role of LPV/r in development of LS.