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Resveratrol-Dependent Stimulation of Mitochondrial Fatty Acid Oxidation in Deficient Cells. Implication of miRNAs †

Virginie Aires [1,2], Dominique Delmas [1,2], Fatima Djouadi [3], Jean Bastin [3], Mustapha Cherkaoui [1] and Norbert Latruffe [1,*]

[1] Laboratory BioPeroxIL, University of Bourgogne-Franche Comté, 6 Blvd Gabriel, 21000 Dijon, France; virginie.aires02@u-bourgogne.fr (V.A.); ddelmas@u-bourgogne.fr (D.D.); malki@u-bourgogne.fr (M.C.)
[2] INSERM UMR 866, Blvd Jeanne d'Arc, 21490 Dijon, France
[3] INSERM U1124, Université Paris-Descartes, Rue des Saints-Pères, 75000 Paris, France; fatima.djaoui@inserm.fr (F.D.); jean.bastin@inserm.fr (J.B.)
* Correspondance: Norbert.Latruffe@u-bourgogne.fr
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1. Introduction

The mitochondrial-located enzyme Carnitine palmitoyltransferase-2 (CPT2) is involved in long-chain fatty acid transport into mitochondria and the subsequent shortening of these fatty acids by β-oxidation, to produce energy. Two phenotypes have been identified that associate with a reduced CPT2 activity in genetically deficient patients: showing either neonatal lethality or, in milder forms, myopathy. Resveratrol (RSV, trans-3,5,4′-trihydroxystilbene) is a phytophenol produced by grape plant in response to biotic or abiotic stresses that displays anti-oxidant properties. This polyphenol, is also present in grape juice, raisins and in red wine. It protects humans against various diseases (cardiovascular and inflammation-associated pathologies, like infection, cancer, neurodegenerescence, aging, etc.) through the modulation of several signaling pathways, including those mediated by α 3-beta 5 integrin receptor, transcription factors (AP-1, NFκB, PGC-1 α, and STAT-3) or the COX AMPK, and sirtuins enzymes. RSV can enhance residual CPT2 activities in human fibroblasts derived from CPT2-deficient patients and restores almost normal fatty acid oxidation rates via PGC-1 α /PPAR α [1,2].

2. Results

While we previously identified RSV-dependent miRNA modulation in THP-1 macrophages [3], here we report changes in miRNA expression linked to CPT2-deficiency. We also identified miRNAs whose expression changed following RSV treatment of control or CPT2-deficient fibroblasts isolated from patients [4]. We found that miR-378 was down-regulated by RSV in control fibroblasts. Interestingly, miR-378 putatively controls PPAR-α mRNAs expression and miR-21 was down-regulated by RSV in CPT2-deficient fibroblasts. In databases miR-21 has been reported to control NRF1 transcripts, that encodes a transcription factor implicated in the respiratory control.

3. Conclusions

It appears likely that changes in miRNA levels in CPT2-deficient cells might, at least in part, be involved in abnormal fatty acid oxidation. We confirm the emerging role of miRNAs in lipid metabolism as critical regulators of lipid synthesis, fatty acid ß-oxidation and lipoprotein metabolism. Changes in the expression of crucial miRNAs can impact gene regulatory network,

driving to metabolic syndrome and its related pathologies. Our findings suggest that RSV consumption might exert beneficiary effects in patients with CPT2 deficiency.

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