PIOGLITAZONE IMPROVES MITOCHONDRIAL ORGANIZATION AND BIOENERGETICS IN DOWN SYNDROME CELLS


(1) Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Napoli (Italy)
(2) Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara (Italy)
(3) Institute of Experimental Endocrinology and Oncology, National Research Council, Napoli (Italy)
(4) Department of Biology, University of Naples Federico II, Napoli (Italy)
(5) Department of Neuroscience, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Napoli (Italy)
(6) Department of Biomedicine, University of Basel, Basel (Switzerland)

Mitochondrial dysfunction plays a primary role in neurodevelopmental anomalies and neurodegeneration of Down Syndrome (DS) subjects. For this reason, targeting mitochondrial key genes, such as PGC-1α/PPARGC1A, is emerging as a good therapeutic approach to attenuate cognitive disability in DS.

After demonstrating the efficacy of the biguanide metformin (a PGC-1α activator) in a cell model of DS, we extended the study to other molecules that regulate the PGC-1α pathway acting on PPAR genes. We, therefore, treated trisomic fetal fibroblasts with different doses of pioglitazone (PGZ) and evaluated the effects on mitochondrial dynamics and function. Treatment with PGZ significantly increased mRNA and protein levels of PGC-1α. Mitochondrial network was fully restored by PGZ administration affecting the fission-fusion mitochondrial machinery. Specifically optic atrophy 1 (OPA1) and mitofusin 1 (MFN1) were upregulated while dynamin-related protein 1 (DRP1) was downregulated.

This effects, together with a significant increase of basal ATP content and Oxygen consumption rate, and a significant decrease of ROS production, provide strong evidences of an overall improvement of mitochondria bioenergetics in trisomic cells.

In conclusion, we demonstrate that PGZ is able to improve mitochondrial phenotype even at low concentrations (0.5 μM). We also speculate that combination of drugs that target mitochondrial function might be advantageous, offering potentially higher efficacy and lower individual drug dosage.