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**D2-Troglitazone alters energetic metabolism in triple-negative breast cancer cells:
a mechanism to sensitize cancer cells to chemotherapy?**

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Background: Resistance to conventional therapies and absence of targeted therapy for triple-negative mammary tumors are strong arguments for the search for new therapeutic agents [1]. A promising strategy is to develop drugs targeting energetic metabolism [2]. Indeed, energetic metabolism is often modified in cancer cells and drugs targeting it can sensitize cancer cells to chemotherapy. Thiazolidinediones display antiproliferative effects *in vitro* and *in vivo* which could be the result of mechanisms altering cell metabolism [3]. Our objectives are 1) to characterize the modifications of breast cancer cell metabolism after Delta-2-Troglitazone (D2T) exposure, 2) to define whether D2T could potentiate the action of conventional chemotherapeutic agents.

Methods: The triple-negative breast cancer cell line MDA-MB231 was exposed to D2T, 2-deoxyglucose (2-DG, inhibitor of glucose metabolism) and metformin (inhibitor of mitochondrial respiration) for different time periods. Cell numbers were assessed by crystal violet staining. NAD⁺ (nicotinamide adenine dinucleotide) and NADH concentrations were determined by chemiluminescence (Promega kit). Lactate and glucose concentrations in cell culture medium were measured with an YSI 2950 Biochemistry Analyzer. Mitochondrial oxidation rate was assessed by oxygraphy with a Clark electrode. An ATPase inhibitor (Oligomycin 10 µg/ml) and an uncoupling agent (Carbonyl Cyanide m-ChloroPhenylhydroxone (CCCP) 500 nM) were used to quantify mitochondrial efficiency and mitochondrial uncoupling, respectively.

Results: 48h cell treatment with D2T (75 µM) inhibited cell proliferation and induced a cell cycle blockage. At the metabolic level, NAD⁺/NADH ratio was increased after a 24h

treatment with D2T or 2-DG. This result suggested that glycolysis and/or mitochondrial respiration could be altered. Oxygen consumption was diminished after a 6h exposure to D2T and metformin. Moreover, D2T decreased mitochondrial efficiency and reduced mitochondrial sensitivity to CCCP, suggesting a mitochondrial decoupling. At the glycolytic level, lactate production and glucose consumption were increased in D2T-treated cells. Conversely, 2-DG induced a diminution of lactate production. Besides, in contrast to 2-DG, the D2T-induced decrease in cell numbers still occurred in the presence of an excess of glucose (10 mg/mL) in the culture medium. Finally, D2T at a lower dose (15 μ M) potentiated the effects of 2-DG and doxorubicin on cell viability.

Conclusion: Our results show that D2T induces metabolic changes in triple-negative breast cancer cells MDA-MB231. In contrast to 2-DG, D2T targets mitochondrial activity leading to the stimulation of glycolysis. The mitochondrial targets of D2T have yet to be identified. Synergism between D2T and 2-DG on cell viability confirms that D2T and 2-DG exhibit divergent, but complementary, mechanisms of action. Besides, a low dose of D2T (15 μ M) potentiates the action of doxorubicin on cell viability. The impact of the D2T/doxorubicin combination on proliferation and apoptosis has to be characterized. Overall, the link between the metabolic alteration observed with D2T and its antiproliferative effect has now to be demonstrated.

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