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Effect of metformin on glucose-starved and 2-deoxyglucose exposed triple negative MDA-MB 231 breast cancer cells

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Introduction: Metformin exhibits anti-cancer properties and we have reported that treatment with metformin (2mM) in glucose-starved or 2-deoxyglucose (2DG;5mM) exposed tumour endothelial cells reversed pro-survival autophagy, inhibited the mTOR pathway and reduced cell viability [1]. Triple-negative breast cancers (TNBC) lack estrogen and progesterone receptors as well as HER2 and do not benefit from hormonal or HER2 targeted therapies [2, 3]. Although chemotherapy is the primary established systemic treatment for patients with TNBC, the lack of targeted therapies, its aggressiveness, early recurrence, rapid metastasis and poor prognosis [2, 3] calls for alternative therapeutic approaches. It was reported that the anti-proliferative effect of metformin in triple-negative MDA-MB-231 breast cancer cells is highly dependent on glucose concentration [4]. Thus, we investigated the effects of metformin in glucose-starved and 2DG exposed MDA-MB 231 TNBC cells.

Method: MDA-MB 231 cells were glucose-starved/treated with 2DG (10mM) for 48h in the absence/presence of metformin (2mM). Western blot analysis (n=3-4; to assess the status of the mTOR and autophagy pathway), cell proliferation (MTT assay; n=5), migration (Radius Cell Migration Assay; n=4) and viability (propidium iodide assay; n=5) were performed. Statistical significance was determined by one-way analysis of variance (ANOVA).

Results: Cell proliferation rate significantly decreased in 1) glucose-starved cells treated with metformin (by 95%) when compared to non-treated glucose-starved cells (by 88%) and 2) 2DG exposed cells treated with metformin (by 46%) when compared to cells that were treated with either metformin (by 20%) or 2DG (by 28%) alone. Cell viability significantly ($P<0.05$) decreased in glucose-starved cells treated with metformin (by 34%) when compared to non-treated glucose-starved cells (by 18%). We observed a marked reduction in cell migration in 2DG exposed cells treated with metformin. Western blot analysis revealed that treatment with metformin significantly decreased (fold change) the levels of LC3A-II (2.4&1.8) and LC3B-II (2.3&1.6), pmTOR(S2448;1.6&1.4) and downstream p4E-BP1(T36/47;1.5&1.3), pS6(S235/236;4.7&2.8) and pS6(S240/244;3.2&1.8) in glucose-starved and 2DG-exposed cells treated with metformin.

Conclusion: Results show that using metformin in glucose-starved and 2DG exposed TNBC cells could prove to be a potential anti-cancer therapy as an adjunct in the treatment of triple-negative breast cancers.

References:

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