An Evaluation of the Combination of Metformin and Y15 for the Treatment of Platinum-Resistant Ovarian Cancer

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Background

Ovarian cancer is the fifth leading cause of cancer mortality among women. This high mortality rate is linked to the development of resistance to first-line chemotherapy with platinum compounds which has been attributed in part to increased activity of focal adhesion kinase (FAK). The anti-diabetic drug Metformin was previously shown to inhibit the proliferation and migration of ovarian cancer cells and thus, the combination of a FAK inhibitor, Y15, and Metformin may be a promising treatment for platinum-resistant ovarian cancer (PROC). The objective of this study was to evaluate the combination of Y15 and Metformin on PROC cell viability and the mechanism of cell death.

Methods

An MTT assay was used to analyze cell viability in PROC OVCAR3 cells after 48 h of treatment by measuring the absorbance at 570 nm with a microplate reader. Western blot was used to determine the protein levels of the apoptosis marker cleaved PARP and caspase 3 and the autophagy marker LC3B-II.

Results

The exposure of OVCAR3 platinum-resistant ovarian cancer cells to Metformin (4.5 mM) + Y15 (5.5 μM) resulted in a significantly enhanced cytotoxicity (32.6 ± 1.8%) compared to single drug treatment with either Metformin (4.5 mM) (65.0 ± 4.2%) or Y15 (5.5 μM) (66.0 ± 4.8%). A combination of Metformin (7.8 mM) + Y15 (5.5 μM) resulted in a significantly enhanced cytotoxicity (22.8 ± 1.5%) compared to single drug treatment with either Metformin (7.8 mM) (50.7 ± 3.7%) or Y15 (5.5 μM) (66.0 ± 4.8%). Cells treated with the combination of Metformin and Y15 for 24, 48, and 72-hours showed an increase in cleaved PARP compared to the control, Metformin alone and Y15 alone. For Metformin alone, there was an increase in cleaved PARP compared to the control at all timepoints and increased from 24 hours to 72 hours. For Y15 alone, the amount of cleaved PARP was also higher compared to the control at all time points, however, decreased over time from 24 to 72 hours. Cells treated with the combination of Metformin and Y15 for 72-hours showed an increase in caspase 3 compared to control, Metformin alone and Y15 alone. Cells treated with Metformin, Y15, and a combination of Metformin and Y15 showed no conversion of LC3B-I to LC3B-II, which occurs during autophagy.

Conclusion

Thus, it is concluded that the mechanism of cell death for both Metformin and Y15 is through apoptosis and not autophagy and apoptosis is enhanced with the combination of the drugs. The delivery of Metformin and Y15 can result in an additive effect on cell viability through apoptosis and can be further explored as a promising approach for the treatment of PROC.