Potentiation of AlPcS₂ mediated photodynamic therapy by energy metabolism inhibitors in human tumour cell lines

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Introduction

Cancer cells often exhibit increased rates of glycolysis and reduced rates of oxidative phosphorylation [1], suggesting that inhibition of the glycolytic pathway could be used to selectively target tumour cells. Indeed, energy metabolism inhibitors have been shown to potentiate the cytotoxic effects of chemotherapy and radiotherapy [2, 3]. However, this metabolic switch does not occur in all tumour types [4], leading to some discrepancy regarding the correlation between the degree of malignancy and the rate of ATP synthesis from glycolysis or oxidative phosphorylation [5]. We used tumour cell types with differing metabolic profiles to determine whether energy metabolism inhibitors could potentiate the cytotoxicity of Photodynamic therapy (PDT). We compared 2-Deoxyglucose (2-DG), an inhibitor of glycolysis [6], and oligomycin, an inhibitor of mitochondrial ATP-synthase [7], on the PDT toxicity of disulfonated aluminium phthalocyanine (AlPcS₂) in MCF-7 and MDA-MB-435 tumour cell cultures. MDA-MB-435 have been shown to have higher rates of glycolysis compared to MCF-7 cells [8].

Methods

Cells grown in 24-well plates were incubated with 5 µg/ml AlPcS₂ with or without energy metabolism inhibitors for 30 minutes, then washed three times with PBS and fresh media was added. For dark toxicity, the cells were not exposed to light, whilst for phototoxicity the cells were irradiated under visible light (500 W halogen lamp) for 15 minutes at room temperature. After 24 hrs incubation, dark toxicity and phototoxicity were studied by propidium iodide exclusion assay using flow cytometry on a Becton Dickinson FACSCalibur temperature. After 24 hrs incubation, dark toxicity and phototoxicity were studied by propidium iodide exclusion assay using flow cytometry on a Becton Dickinson FACSCalibur.

Results

1. AlPcS₂ uptake

   - Energy metabolism inhibitors do not alter the uptake of AlPcS₂, although MDA-MB-435 cells show a generally higher uptake than MCF7 cells

2. Dark toxicity

   - Dark toxicity was minimal in both cell lines and there was no significant difference in cell survival in the two cell lines across the different treatment conditions

3. Phototoxicity

   - In both cell lines, AlPcS₂ phototoxicity increased by over 30 % in the presence of either 30mM 2-DG or 0.01µM oligomycin compared to AlPcS₂ alone.

Conclusions

- Energy metabolism inhibitors significantly potentiate the effect of PDT, compared to AlPcS₂ alone, after 24 hrs incubation (30mM 2-DG: P<0.01 in MCF-7 and P<0.001 in MDA-MB-435. 0.01µM oligomycin: P<0.001 in both cell lines).
- In MCF-7 cells, there was no significant difference between the potentiating effect of 2-Deoxyglucose or Oligomycin. This is in keeping with the known energy metabolic profile of these cells.
- In MDA-MB-435 cells there was a significant difference between the potentiating effect of 20mM and 30mM 2-DG compared to 0.05 µM oligomycin, suggesting that these cells are more sensitive to 2-DG than Oligomycin. This is in keeping with the known preferential reliance of MDA-MB-435 cells on glycolysis.
- Our preliminary findings support the use of a combination of photosensitizers and energy metabolism inhibitors to improve the efficiency of PDT. Furthermore, we demonstrate that matching the choice of inhibitors to the tumour metabolic profile maximised the therapeutic effect.

References


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