The Sigma-1 receptor– investigating mechanisms of cell death and potential as a prognostic biomarker in breast cancer

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Background: The Sigma-1 receptor (Sig1R) is a stress response protein that facilitates cytoprotective signalling by the unfolded protein response (UPR). Cancer cells are exceedingly dependent on the UPR for survival. Sig1R is sometimes overexpressed in cancer and Sig1R antagonists cause cell death in breast cancer (BCa) cells, however the signalling pathways triggered upstream of Sig1R antagonist-induced cell death have not been adequately investigated.

Methods: Sig1R gene (*SIGMAR1*) and protein expression was evaluated in several BCa patient cohorts. Sig1R expression and temporal UPR activation following treatment with a Sig1R antagonist, IPAG, were investigated in *in vitro* models using Western blotting (WB); Sig1R and UPR marker localizations were examined by immunofluorescence. The effect of exposure to IPAG on cell viability was examined by MTS assays.

Results: *SIGMAR1* was overexpressed in BCa, particularly in the oestrogen receptor-negative, Her2-negative patient populations. Its high expression correlated with earlier recurrence and poor disease-specific survival. Sig1R protein expression similarly associated with shorter survival. Sig1R was overexpressed in the triple-negative BCa cell line MDA-MB-468 but not in endocrine sensitive MCF7 cells. IPAG induced loss of viability in both these cell lines but not in non-cancerous mammary cells. IPAG caused differential temporal activation of the three arms of the UPR prior to cell death in three BCa cell lines. In tamoxifen-resistant LY2 cells, IPAG induced aggregation of Sig1R and co-localization with the stress marker BiP.

Conclusions: Our findings suggest that elevated Sig1R levels may predict the propensity of a breast tumour to relapse and that inhibiting Sig1R function hampers the stress coping mechanisms of BCa cells. Thus, Sig1R presents a potential target in BCa, particularly for therapeutically refractory subtypes.