Targeting the Unfolded Protein Response for Breast and Pancreatic Cancer Therapy

Breast and pancreatic cancer remain difficult adversaries in the landscape of oncology, characterised by their aggressive behaviour, high metastatic potential, and limited treatment efficacy. These cancer cells are continuously challenged by limited oxygen, nutrient supply, and elevated protein synthesis that may cause induction of the Unfolding Protein Response (UPR), a complex signalling network activated by Endoplasmic Reticulum (ER) stress to restore cellular homeostasis. Accumulating evidence highlights the vital role of the UPR as a critical process that enables tumour cells to sustain malignancy. On the other hand, prolonged pharmacological activation of the UPR has been demonstrated to induce cell death in cancer. Considering this, we decided to use for our experiments, FR054, a competitive inhibitor of PGM3 enzyme. By inhibiting the Hexosamine Biosynthetic Pathway (HBP), FR054 causes a decrease in the N-glycosylation (N-GlcNAc) protein level and, consequently, an accumulation of misfolded proteins into the ER. This stress condition triggers a prolonged activation of UPR that induces ROS accumulation and subsequent cell death in breast cancer (BC) cells. Otherwise, as demonstrated by the non-complete restoration after N-Acetyl Cysteine (NAC) co-treatment, in pancreatic cancer (PC) cells this ROS-dependent cell death mechanism is somewhat inhibited. Our transcriptional data suggests a potential key player in this inhibition: the xCT/SLC7A11 antiporter. This antiporter indeeed is responsible for mediating the uptake of extracellular cystine in exchange for glutamate thereby participating in glutathione biosynthesis. To confirm this hypothesis, we observed how the inhibition of xCT/SLC7A11 by erastin, a recognized ferroptosis inducer, significantly enhanced the FR054 effect causing a noteworthy increase in cancer cell proliferation arrest and death. In conclusion, HBP inhibition triggers UPR in both breast and pancreatic cancer cells. Notably, pancreatic cancer cells exhibit a protective mechanism, offering a potential avenue for therapeutic exploitation through a synthetic lethality approach in cancer therapy.