Targeting the Hexosamine Biosynthetic Pathway with a novel PGM3 inhibitor, FR054, to suppress tumour growth and enhance chemotherapy sensitivity in cancer

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Aberrant variations in N-glycosylation and O-GlcNAcylation in cancer result from increased flux through the Hexosamine Biosynthetic Pathway (HBP), playing distinct roles in tumour progression. Among the various enzymes involved in this pathway, we focused on N-Acetylglucosamine-phosphate Mutase (PGM3), which regulates both N- and O-glycosylation and operates downstream in the HBP salvage pathway. Consequently, we developed a novel competitive PGM3 inhibitor, FR054, and investigated the effects of HBP inhibition in breast and pancreatic cancer (PC) cell lines. FR054 induces a significant decrease in cell proliferation and survival, along with a marked reduction in cancer cell adhesion and migration. It is well tolerated and suppresses tumour growth in in vivo models. The impaired survival of cancer cells upon FR054 treatment is associated with activation of the Unfolded Protein Response (UPR), accumulation of intracellular ROS, inhibition of EGFR signaling, and activation of apoptotic processes. In PC, transcriptional analysis reveals increased reliance on glutathione synthesis and activation of stress response pathways in FR054-treated PDAC cells. Therefore, we tested the synergistic effect of FR054 in combination with Erastin, an SLC7A11 inhibitor. FR054 also enhances the sensitivity of PC cells to gemcitabine treatment. By inhibiting the DNA repair protein O-GlcNAc, FR054 negatively regulates DNA damage repair and, when combined with gemcitabine, enhances apoptosis by preventing GEM-induced intra-S-phase checkpoint activation. For these reasons, inhibition of the HBP may represent a novel anticancer therapy.