INHIBITION OF HBP BY TARGETING PGM3 ENZYME AS NEW ANTICANCER THERAPY

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Abstract: N-glycosylation (N-GlcNAC) and O-GlcNAcylation (o-GlcNAc) regulate several aspects of protein function and physiological processes. Cancer aberrant N- and O-glycosylation, frequently, results from an augmented flux through the Hexosamine Biosynthetic Pathway (HBP) and plays different roles in tumor progression. Among the different enzymes involved in this pathway, we focused on the N-Acetylglucosamine-phosphate Mutase (PGM3) that catalyses the conversion of N-Acetilglucosamine-6-phosphate (GlcNAc-6-P) into N-Acetylglucosamine-1-phosphate (GlcNAc-1-P). This enzyme has been chosen because it permits to control of both N- and O- Glycosylation and it is downstream to the HBP's savage pathway. The low specificity and toxicity of the existing HBP inhibitors prevented their use for cancer treatment, so we have developed a new PGM3 competitive inhibitor by modifying the chemical structure of GlcNAc, named FR054. Then, we decide to investigate the effect of HBP inhibition using FR054 in breast cancer and pancreatic cancer (PC) cell lines observing that FR054 induces a dramatic decrease in cell proliferation and survival and a strong reduction of cancer cell adhesion and migration in both type of tumors, while the in vivo analysis shows that FR054 is well tolerated and suppress tumor growth. The impaired survival of cancer cells upon FR054 treatment is associated with the activation of Unfolding Protein Response (UPR), accumulation of intracellular ROS, inhibition of EGFR signalling, and activation of an apoptotic process. In PC, transcriptional data also indicated an enrichment of terms associated with phospholipids remodelling and Ferroptosis. The analysis of some ferropototic genes indicated that UPR activation, upon FR054 treatment is able to induce an antioxidant and anti-ferropototic response. Given that, we tested the synergistic effect of FR054 in combination with Erastin, a SLC7A11 inhibitor able to induce Ferropotosis. Our results indicate that they have a synergistic effect as compared to untreated or single treated cells by increasing ferroptosis. Moreover, FR054 is also able to increase the sensitivity of PC cells to gemcitabine treatment, the main treatment for PC patients. In fact, FR054, inhibiting DNA repair protein O-GlcNAc, negatively regulates DNA damage repair and therefore, when combined with GEM, enhances apoptosis through the prevention of the GEM-induced intra-S-phase checkpoint activation. For all this reasons, inhibition of HBP may represent a novel anticancer therapy.