







The HBP inhibitor FR054 synergizes with gemcitabine inducing in vitro and in vivo pancreatic cancer regression by enhancing DNA damage

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Abstract: Chemotherapy is the main treatment for pancreatic cancer (PC) patients. Presently, gemcitabine (GEM) monotherapy or in combination with other drugs is the most widely used scheme for PC. However, GEM therapy is poorly effective due to resistance development. GEM-resistance is linked to several mechanisms among which a relevant role is assigned to cancer metabolism. Of note, PC exhibits an increased flux through the Hexosamine Biosynthetic Pathway (HBP), involved in protein O-glycosylation (O-GlcNAc) and N-glycosylation. Importantly, our published results indicate that HBP is essential for PC cell survival and proliferation as well as for GEM resistance [1]. Despite the few studies correlating HBP flux and protein O-GlcNAc increase with chemosensitivity, recently it has been shown that protein O-GlcNAc regulates DNA damage response (DDR) factors and cell cycle progression, including DNA replication, mitosis, and cytokinesis. Here we show that inhibition of HBP, by using the specific inhibitor FR054, combined with GEM enhances cell death in several pancreatic cancer cells through the induction of a cell cycle arrest and an increase in DNA damage. In addition, combined treatment enhances cleaved poly[ADP-ribose]-polymerase and the number of annexin-V-positive cells, indicating the induction of apoptosis. In vivo, administration of GEM and FR054 was well tolerated and suppressed almost completely tumor growth either in xenograft or PDX mice. Mechanistically, the combined treatment elevated yH2A.X and cell cycle inhibitors and suppressed cyclin D1 expression. Interestingly, FR054 prevents the GEM-induced intra-S-phase checkpoint activation since a significant decrease of CHK1 and CHK2 phosphorylation was observed. Altogether these findings suggest a direct role of protein O-GlcNAc in S-phase checkpoint control. Given that the relationship between O-GlcNAc and the DNA damage response is still poorly understood. can suppose that O-GlcNAc, as previously shown for we phosphorylation, of DDR proteins is necessary for their function and that impingement of the activating role of O-GlcNAc in DDR proteins may overcome GEM resistance as well as resistance to other chemotherapeutic drugs providing a mechanistic link among metabolic reprogramming, genomic instability, and potential therapeutic response.