THE HBP INHIBITOR FR054 SYNERGIZES WITH GEMCITABINE INDUCING IN VITRO AND IN VIVO PANCREATIC CANCER REGRESSION BY ENHANCING DNA DAMAGE

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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 related to several mechanisms among which a relevant role is assigned to cancer metabolism. Noteworthy, PC exhibits an increased flux through the Hexosamine Biosynthetic Pathway (HBP), involved in protein O- and N-glycosylation (O-GlcNAc, N-gly). Notably, our previously results establish that FR054, a small molecule able to target PGM3 a key HBP's enzyme, fight PC enforcing the notion that HBP is crucial for PC cell survival and GEM resistance. Recently it has been shown that protein O-GlcNAc may regulate DNA damage response (DDR) factors. Here we show that inhibition of HBP, by using the inhibitor FR054, combined with GEM enhances apoptosis in several PC cells through the induction of DNA damage. In vivo, administration of GEM and FR054 is well tolerated and suppresses almost completely tumor growth either in xenograft or PDX mice. Mechanistically, the combined treatment elevates γH2AX and changes cyclins expression levels. Interestingly, FR054 prevents the GEM-induced intra-S-phase checkpoint activation since a significant decrease of the phosphorylation status of several DNA damage sensitive proteins is observed. Altogether these findings suggest a direct role of protein glycosylation in S-phase checkpoint control. Given that the relationship between glycosylation and the DNA damage response is still poorly understood, we can suppose that glycosylation of DDR proteins is necessary for their function and that impingement of this post translational mechanism may overcome GEM resistance as well as resistance to other chemotherapeutic drugs.

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