

Hexosamine biosynthetic pathway inhibition cooperates with gemcitabine inducing in vitro and in vivo pancreatic cancer regression by enhancing DNA damage

SpT-26-6

B. Zerbato^I, V. Brancato^I, C. Lattuada^I, M. La Chimia^{II}, D. Scumaci^{II}, **F. Chiaradonna^I**

^IUniversity of Milano Bicocca, Department of Biotechnology and Biosciences, Piazza della Scienza 2, 20126, Milano, Italy, ^{II}Magna Græcia University of Catanzaro, Department of Experimental and Clinical Medicine, Viale S. Venuta, 88100, Catanzaro, Italy

Pancreatic cancer (PC) is the seventh most common cause of death due to oncological diseases. Nearly 80% of patients are diagnosed at advanced stages and chemotherapy, based on gemcitabine (GEM) remains the main treatment. However, PC develops chemoresistance to GEM so an alternative therapeutic regimen should be investigated combining GEM with other drugs. PC shows metabolic alterations based on the increased glucose consumption to fuel glycolysis. This leads to an upregulation of the Hexosamine Biosynthetic Pathway (HBP) to produce, UDP-N-acetylglucosamine necessary for protein glycosylation, a nutrient- and stress-responsive post-translational modification.

Previous results establish that FR054, a small inhibitor of PGM3, a HBP enzyme, leads to growth arrest in PC cells in vitro, highlighting the role of HBP in promoting PC survival. In vivo, GEM and FR054 administration is well tolerated and suppresses almost completely tumor growth in xenograft and PDX mice. The activity of some metabolic pathways can influence the DNA Damage Repair (DDR) by regulating substrates availability required for the repair process and the function of its players. In this work we demonstrate that FR054 enhances GEM's efficacy. Indeed their combination, promote apoptosis through augmentation of the DNA damage and a significant change in the phosphorylation status of several proteins involved in DDR response. We demonstrate that Homologous Recombination is reduced. This is an important achievement since this DDR mechanism is correlated to chemoresistance. In addition, some proteins directly involved in DNA damage response are O-glycosylated, as shown by proteomics analysis. In conclusion, the study sheds light on the correlation between proteins glycosylation and DDR, suggesting a potential role of HBP in regulating cancer progression.

Supported by grants from MUR (# 2022ZBZFX3 PRIN-2022 Unione Europea - NextGenerationEU) to FC and DS, Fondo di Ateneo-Quota competitiva 2021, FAR 2022 to FC