AB108. P082. Role of epigenetic modifying enzymes in the chemoresistance of pancreatic cancer

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Abstract: Gemcitabine (GEM) is a chemotherapeutic drug and the standard treatment option for pancreatic cancer patients. Although some patients respond well in the treatment firstly, development of resistance is commonly observed in clinic. To dissect the mechanism underlying GEM resistance, we screened for the epigenetic modifying enzymes that are increased in GEM-resistant pancreatic cancer cells and identified 21 upregulated enzymes in resistant cells. We first addressed the functional role of a H3K9 methyltransferase EHMT2 and found that ectopic expression of EHMT2 in pancreatic cancer cells increased GEM resistance while inactivation of EHMT2 in resistant cancer cells reduced it. Mechanistically, we showed that interleukin-8 (IL-8) is one of the downstream effectors of EHMT2 to increase GEM resistance. EHMT2-overexpressing cancer cells exhibited autocrine IL-8/CXCR1/2 stimulation to prevent GEM cytotoxicity which could be attenuated by anti-IL-8 antibody or chemical inhibitor. IL-8 released by cancer cells also activated pancreatic stellate cell (PSC) to increase GEM resistance. Combination of EHMT2 inhibitor and GEM significantly decreased tumor growth, metastasis, IL-8 expression and PSC activation in animals. Expanding from our previous study, we also found the upregulation of protein arginine methyltransferase 3 (PRMT3) in GEM-resistant pancreatic cancer cells. By using proteomics approach, we identified a number of PRMT3-interacting proteins. One candidate gene possibly involves in the chemoresistance is the transporter ATP binding cassette subfamily G member 2 (ABCG2). In this study, we will introduce how PRMT3 modulates the expression of ABCG2 via a novel post-transcriptional mechanism. Our results suggest that PRMT3 could be a potential target to overcome GEM resistance.

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