PDGFD up-regulation due to reversible promoter demethylation contributes to gemcitabine resistance via STAT3 activation

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Abstract

Background and Purpose. Drug resistance is a major problem in cancer treatment with traditional or targeted therapeutics. Gemcitabine, a traditional chemotherapeutics, is approved for several human cancers and the first line treatment for locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC). However, gemcitabine resistance is frequently observed and a major problem in successful treatments of these cancers and the mechanism of gemcitabine resistance remains largely unknown. In this study, we aim to seek new and understand the molecule mechanisms of gemcitabine resistance in PDAC. Experimental Approach. Using whole genome Reduced Representation Bisulfite Sequencing analysis, we investigated a gemcitabine resistant PDAC cell line M3K compared with its parental MiaPaCa-2 cells and the resistance revertant cell line Rev followed by detailed analyses of PDGFD in gemcitabine resistance using MTT survival assay, bisulfite sequencing, Western blot, siRNA knockdown and over-expression. Key Results. We found that 65 genes had reversible methylation changes in their promoters in gemcitabine resistant PDAC cells. One of these genes, PDGFD, was further studied in detail for the reversible methylation change in its promoter and shown to reversibly up-regulate in expression, contribute to gemcitabine resistance in vitro and in vivo via activating STAT3 signaling in both autocrine and paracrine manners. Its expression also positively associates with poor outcome of PDAC patients. Conclusion and Implications. Reversible epigenetic regulation may play an important role in gemcitabine resistance and targeting PDGFD signaling may alleviate gemcitabine resistance for PDAC treatment.

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