

152 PYRUVATE DEHYDROGENASE KINASE 1 (PDHK1) REGULATES OVARIAN CANCER CELL MIGRATION, INVASION, AND CHEMORESISTANCE AND CONTRIBUTES TO POOR PROGNOSIS IN PATIENTS

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INTRODUCTION: Pyruvate dehydrogenase kinase 1 (PDHK1) is a gate-keeping enzyme which negatively phosphorylate pyruvate dehydrogenase (PDH), leading to the conversion of pyruvate to lactate in the cytoplasm instead of further oxidation in the mitochondria, a phenomenon known as the Warburg effect. In this study, we sought to characterize the clinical and functional significance of PDHK1 in ovarian cancer.

MATERIAL AND METHOD: The expression of PDHK1 was assessed in 103 clinical samples and 9 cell lines by immunohistochemistry, qPCR and immunoblotting, and correlated with clinical outcomes. Effects of PDHK1 and DCA, a PDHK inhibitor, on lactate production, migration, invasion and apoptosis in ovarian cancer cells following cisplatin exposure were evaluated by lactate assay, migration and invasion assays, and cytometry with Annexin V/PI staining respectively. The downstream target was determined by qPCR and immunoblotting. The mechanisms governing PDHK1 deregulation was determined by selective blockage of omental cytokine interleukin-8 (IL-8) and its receptor (IL-8RA) with anti-IL-8 antibody and anti-IL-8RA antibody respectively.

RESULTS AND DISCUSSION: The mRNA and protein expression of PDHK1 was found to be significantly increased in ovarian cancer clinical samples and cell lines. Significantly higher PDHK1 was found in metastatic foci than their corresponding primary carcinomas. Furthermore, high PDHK1 expression was significantly correlated with shorter overall and disease-free survival. Knockdown of PDHK1 in A2780CP, an ovarian cancer cell line, led to reduced lactate level, cell migration and invasion, along with decreased expression of urokinase type plasminogen activator (uPA), gene related to migration and invasion. Moreover, PDHK inhibitor DCA was found to reduce cell migration and invasion, and enhance the chemosensitivity of A2780 treated with cisplatin. Furthermore, we found blockage of IL-8 and IL-8RA could decrease PDHK1 protein expression in SKOV-3 cells, suggesting PDHK1 could be regulated by IL-8 through IL-8RA.

CONCLUSION: Our data suggested that PDHK1 was associated with ovarian cancer progression, metastasis and chemoresistance. PDHK1 could be a novel prognostic marker and potential therapeutic molecular target in ovarian cancer.