Title	Overexpression of Hexokinase 2 (HK2) in ovarian cancer contributes to cell migration, invasion and cancer stem-like cells regulation and correlates with poor patient survival
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144 OVEREXPRESSION OF HEXOKINASE 2 (HK2) IN OVARIAN CANCER CONTRIBUTES TO CELL MIGRATION, INVASION AND CANCER STEM-LIKE CELLS REGULATION AND CORRELATES WITH POOR PATIENT SURVIVAL

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INTRODUCTION: Altered glucose metabolism is a new hallmark for cancer. High lactate production and low glucose oxidation, regardless of the oxygen availability, known as the Warburg effect (aerobic glycolysis), are commonly found in cancers. Hexokinase 2 (HK2) converts glucose to glucose-6- phosphate, the first committed step in glycolysis. HK2 regulates glycolysis and tumorigenesis in different human cancers, yet the mechanisms remain poorly defined. In this study, we investigate the clinical significance, effects and mechanisms of HK2 on cell migration, invasion and cancer stem-like cells (CSCs) regulation in ovarian cancer.

MATERIAL AND METHOD: Expression of HK2 was examined in 93 clinical samples including 19 benign/borderline tumors, 46 primary tumors and 28 matched metastatic foci by immunohistochemistry and correlated with clinicopathological parameters. Effects of HK2 on lactate production, migration, invasion and CSCs regulation in A2780CP cells were determined by lactate assay, migration and invasion assays and sphere formation assay, respectively. The downstream target of HK2 was evaluated by qPCR and immunoblotting. The mechanism governing HK2 deregulation was determined by immunoblotting after treatment of SKOV-3 cells with interleukin-6 (IL-6).

RESULTS AND DISCUSSION: We found up-regulation of HK2 in ovarian cancer patients with significantly higher HK2 found in metastatic foci. High HK2 immunoreactivity was significantly associated with advanced stage (Stage 4), serous/clear cell histological subtypes and shorter disease-free survival (all $p<0.05$). HK2 was also overexpressed in ovarian cancer cell lines. Knockdown of HK2 in ovarian cancer cells decreased lactate production, inhibited cell migration and invasion, along with reduced ERK1/2 activation and (matrix metalloproteinase 9) MMP-9 mRNA expression. Inversely, ectopic expression of HK2 promoted ovarian cancer cell migration, invasion, anchorage-independent growth and sphere formation, which was accompanied by induced ERK1/2 activation and stem cell related gene NANOG protein expression. Moreover, HK2 expression can be up-regulated by IL-6.

CONCLUSION: Our findings suggested that HK2 was associated with ovarian cancer metastasis and CSCs regulation. A possible crosstalk between IL-6 (tumor microenvironment), HK2 (altered glucose metabolism) and ovarian cancer metastasis/ CSCs regulation was revealed. HK2 could be a potential prognostic marker and therapeutic target for ovarian cancer.