Gas1: Epithelial-mesenchymal transition and Warburg effect inhibitor in colorectal carcinoma

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BACKGROUND: Growth arrest-specific 1(Gas1) plays a critical role in growth suppression. Our previous study indicated Gas1 was closely associated with survival in patients with colorectal cancer. However, the underlying molecular mechanism remains largely unclear.

HYPOTHESIS: Gas1 might play a critical role in the progression and metastasis of colorectal cancer.

METHODS:. Gas1 expression and pathological significance was evaluated by immunohistochemistry in a tissue microarray containing 203 cases of colon cancer patients. The role of Gas1 involved in proliferation, metastasis and Warburg effect was investigated both *in vitro* and *in vivo*. The underlying mechanism of FoxM1 transcriptional mediated Gas1 expression was studied using Luciferase assays and Chromatin immunoprecipitation assay.

RESULTS: Here we show that Gas1 decreases tumorigenicity and invasion by inhibiting epithelial-mesenchymal transition (EMT) and aerobic glycolysis. Further studies show that Gas1 expression down regulated the transcriptional level of key glycolytic enzymes LDHB, GLUT4, and HK2 in colon cancer cells. Growing cancer cells rely on aerobic glycolysis to generate energy is the hallmark of in vivo cancer imaging with 18-FDG PET/CT. In vivo study demonstrated that Gas1 expression associated with low SUVmax value and decreased expression levels of LDHB, GLUT4, and HK2. Mechanistically, Gas1 inhibit EMT and Warburg effect via AMPK/mTOR/ p70s6K signal pathway, and Gas1 itself is directly regulated by the transcription factor FOXM1.These findings provide mechanism of Gas1 in colorectal cancer and may aid the development of tumor biomarkers or antitumor therapeutics.