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Knockdown of COUP-TFII enhances cell proliferation, movement, agression, and colony construction in human colorectal cancer HT-29 cells

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Abstract

Colorectal cancer (CRC) is one all told the foremost common malignant cancers worldwide Currently, tumor-node-metastasis (TNM) staging is that the foremost generally accepted system for risk stratification in colorectal cancer. Once patients are diagnosed with metastatic CRC, the prognosis would decrease strikingly. Thus, identifying the underlying mechanisms and biomarkers for CRC progression is urgently warranted to facilitate early diagnosis and treatment of CRC. Cancers share a typical phenotype of uncontrolled cell proliferation and must efficiently generate the energy and macromolecules required for cellular growth. Thus, cancer cells exhibit enhanced metabolic dependence that distinguishes them from normal cellular counterparts during which they display augmented nutrient acquisition strategies plus increased flux through downstream anabolic pathways. Metabolic reprogramming during tumorigenesis is a very important process in nearly all cancer cells .The Warburg effect is that the primary example of metabolic reprogramming that Otto Warburg discovered in 1920s. Cancer cells prefer glycolysis to mitochondrial process to return up with ATP (ATP), no matter the availability of oxygen. Many studies have confirmed that oncogenes and tumor suppressors, like hypoxia-inducible factor-1a, Myc, p53, PTEN, and Ras can reprogram energy metabolism in cancer cells. However, the mechanisms accounting for the activation of the Warburg effect and progression of CRC remains blurry. The Forkhead box (FOX) transcription factor family is defined by a highly conserved winged helix DNA-binding domain and participates during a mode of biological processes including cell cycle, proliferation, invasion, and metastasis. Also, variety of those transcription factors play fundamental roles in regulating Warburg effect. FOXE1, a significant member of FOX transcription factor family, has been proved in previous studies to be a transcriptional repressor. Recently, its expression was found to be significantly lower in cancer tissues than in paired normal tissues and silencing of FOXE1 contributed to poor prognosis for CRC patients. Although the prognostic value of FOXE1 has been suggested in CRC, it is necessary to understand the precise roles of FOXE1 within the event and progression of CRC. To date, the functions and downstream signaling cascades of FOXE1 in CRC remain unclear and no previous studies are conducted to explore the regulating effect of FOXE1 on aerobic glycolysis in CRC. during this study, whether and therefore the way FOXE1 modulated glycolysis in CRC cells. We demonstrated here that FOXE1 repressed Warburg effect by inhibiting the expression of the glycolytic enzyme hexokinase 2 (HK2), a key mediator of aerobic glycolysis, in CRC cells. FOXE1 bound on to the promoter region of HK2 and negatively regulated its transcription and thus prohibiting cell proliferation. These findings revealed a previously unrecognized mechanism of FOXE1 in human CRC by modulating the aerobic glycolysis and cell growth through regulation of HK2. Recently, many investigators have studied the role of the chicken ovalbumin upstream promoter-transcription factor II (COUP-TFII) in several cancers including prostate cancers. Our previous study demonstrated that COUP-TFII can be a decent prognosis consider patients with colorectal cancer. However, its underlying mechanisms are unknown. during this study, to analyze whether COUP-TFII affects cell proliferation, migration, invasion, and colony forming ability of human colorectal cancer cells (HT-29 cells), we established stable COUP-TFII-shRNA knocked down HT-29 cells (COUP-TFII shRNA-HT-29 cells). We confirmed COUP-TFII knockdown by western blot analysis and examined the effect of COUP-TFII knockdown on the cell proliferation, migration, invasion, and colony forming ability. Our results showed that cell proliferation, migration, invasion and colony forming ability was significantly

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inhibited in COUP-TFII-shRNA-HT-29 cells. to guage its underlying mechanisms, we examined the expression of several proteins related with cell proliferation, N-cadherin, and E-cadherin by western blot analysis. Expression of p-Rb, cyclin D1, and N-cadherin were increased, however, p53, PTEN, and E-cadherin were decreased in COUP-TFII-shRNA-HT-29 cells. Increased expression of p-Rb and cyclin D1 may contribute to enhanced cell proliferation in COUP-TFII-shRNA-HT-29 cells. Increased expression of N-cadherin and decreased expression of E-cadherin might contribute to increased cell migartion. These results suggest that COUP-TFII might act as a negative regulator in cell proliferation, migration, invasion, and colony formation in HT-29 cells. Further studies using different several colorectal cancer cells are needed to verify these findings. This study was supported by the essential Science Research Program through the National Reserach Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning