PTGES (mPGES1), a potential oncogene, accelerates human cholangiocarcinogenesis and progression by the control of PTEN pathway

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Prostaglandin E synthase (PTGES), also called MGC10317, MGST-IV, MGST1-L1, MGST1L1, MPGES, mPGES-1, PGES, PIG12, PP102, PP1294, TP53I12, is a glutathione-dependent prostaglandin E synthase which catalyzes the formation of prostaglandin E2 (PGE2) from the endoperoxide prostaglandin H2 (PGH2). Our immunohistochemical detection showed mPGES-1 levels were elevated in most human cholangiocarcinoma tissues (CC) from 23 cases of CC patients. Overexpression of mPGES-1 accelerated the growth of CCLP1 cells to a significantly greater extent when compared with the control cells after 24 hours (P < 0.01), and mPGES-1 knockdown inhibited the growth of CCLP1 cells to a significantly greater extent when compared with the control cells after 48 hours (P < 0.01). mPGES-1 overexpression significantly accelerated transplanted tumor formation in SCID mice compared with that of control (P < 0.01) and mPGES-1 knockdown significantly inhibited the transplanted tumor formation compared with that of control (P < 0.01). G1 phase cells numbers were decreased (P < 0.01) and S phase cells numbers were increased (P < 0.05) in mPGES-1 overexpression CCLP1 stable cell lines, and G1 phase cells numbers were increased (P < 0.01) and S phase cells numbers were decreased (P < 0.01) in mPGES-1 knockdown CCLP1 stable cell lines. Transwell assay showed that the migration cells were higher in mPGES-1 overexpression CCLP1 stable cell lines (P < 0.01) and lower in mPGES-1 knockdown CCLP1 stable cell lines (P < 0.01). Western blot results showed that both PTEN and pPTEN (Ser380) expression were decreased in mPGES-1 overexpressed CCLP1 cells compared with control CCLP1 cells and increased in mPGES-1 knockdown CCLP1 cell line compared with control CCLP1 cells. Our results indicated that mPGES-1 inhibited PTEN expression and activated the EGFR-PI3K-mTOR pathway in CCLP1 cell lines. Mechanistically, mPGES-1 decreased EGR1 sumoylation and inhibited the binding of EGR1 to PTEN EGR1 Site DNA in CCLP1 cell lines. CHIP also showed that mPGES-1 inhibited the binding of the EGR1 to PTEN promoter in CCLP1 cell lines. In addition, we also found that mPGES1 increased the miR21 targeting 3’UTR of PTEN in CCLP1 cell line. Our conclusion is that mPGES1 accelerates human cholangiocarcinogenesis and progression via downregulation of PTEN expression.