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ZIP4, a Novel Determinant of Tumor Invasion in Hepatocellular Carcinoma, Contributes to Tumor Recurrence after Liver Transplantation

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Background and purpose: Recently, evidence that Zinc transporter ZRT/IRT-like protein 4 (ZIP4) is involved in invasiveness and apoptosis has emerged in pancreatic cancer and prostate cancer. Our aim was to assess the role of ZIP4 in invasiveness, migration and apoptosis of hepatocellular carcinoma (HCC). The prognostic value of ZIP4 in HCC after liver transplantation was evaluated. Methods: The role of ZIP4 in HCC was investigated by overexpressing ZIP4 in BEL7402 and HepG2 cells and inhibiting ZIP4 in HuH-7 and HepG2 cells, using overexpression and shRNA plasmids in vitro studies. Immunohistochemical analysis was used to evaluate ZIP4 expression in HCC tissues from 60 patients undergoing liver transplantation, 36 cirrhotic tissue samples, and 6 normal tissue samples. Prognostic significance was assessed using the Kaplan-Meier method and the log-rank test. Results: Specific suppression of ZIP4 reduced cell migration and invasiveness, whereas ZIP4 overexpression caused increases in cell migration and invasiveness. Furthermore, overexpression of ZIP4 resulted in increased expression of pro-metastatic genes (MMP-2, MMP-9) and decreased expression of pro-apoptotic genes (caspase-3, caspase-9, Bax). In contrast, suppression of ZIP4 resulted in an opposite effect. ZIP4 was more highly expressed in tumor tissues than non-tumor tissues ($P < 0.0001$). ZIP4 expression was significantly associated with tumor recurrence ($P = 0.002$), tumor node metastasis stage ($P = 0.044$), Child-Turcotte-Pugh score ($P = 0.042$), and tumor size ($P = 0.022$). Univariate analysis showed that ZIP4 expression was significantly associated with overall survival ($P = 0.020$) and tumor-free survival ($P = 0.049$). Multivariate analysis revealed that ZIP4 was an independent predictor of overall survival ($P = 0.037$) after liver transplantation. Conclusions: ZIP4 could promote migration, invasiveness, and suppress apoptosis in hepatocellular carcinoma, and represent a novel predictor of poor prognosis and therapeutic target for patients with HCC who undergo liver transplantation.

Key Word :
ZIP4, hepatocellular carcinoma, liver transplantation

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