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# Interferon-Induced Transmembrane Protein-3 rs12252-CC Associated with the Progress of Hepatocellular Carcinoma by Up-Regulating the Expression of Interferon-Induced Transmembrane Protein 3

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**Abstract :** Background and Aims: Interferon-induced transmembrane protein 3 (IFITM3) is a component of ISG (Interferon-Stimulated Gene) family. IFITM3 has been recognized as a key signal molecule regulating cell growth in some tumors. However, the function of IFITM3 rs12252-CC genotype in the hepatocellular carcinoma (HCC) remains unknown to author's best knowledge. A cohort study was employed to clarify the relationship between IFITM3 rs12252-CC genotype and HCC progression, and cellular experiments were used to investigate the correlation of function of IFITM3 and the progress of HCC. Methods: 336 candidates were enrolled in study, including 156 with HBV related HCC and 180 with chronic Hepatitis B infections or liver cirrhosis. Polymerase chain reaction (PCR) was employed to determine the gene polymorphism of IFITM3. The functions of IFITM3 were detected in PLC/PRF/5 cell with different treated:LV-IFITM3 transfected with lentivirus to knockdown the expression of IFITM3 and LV-NC transfected with empty lentivirus as negative control. The IFITM3 expression, proliferation and migration were detected by Quantitative reverse transcription polymerase chain reaction (qRT-PCR), QuantiGene Plex 2.0 assay, western blotting, immunohistochemistry, Cell Counting Kit(CCK)-8 and wound healing respectively. Six samples (three infected with empty lentiviral as control; three infected with LV-IFITM3 vector lentiviral as experimental group ) of PLC/PRF/5 were sequenced at BGI (Beijing Genomics Institute, Shenzhen,China) using RNA-seq technology to identify the IFITM3-related signaling pathways and chose PI3K/AKT pathway as related signaling to verify. Results: The patients with HCC had a significantly higher proportion of IFITM3 rs12252-CC compared with the patients with chronic HBV infection or liver cirrhosis. The distribution of CC genotype in HCC patients with low differentiation was significantly higher than that in those with high differentiation. Patients with CC genotype found with bigger tumor size, higher percentage of vascular thrombosis, higher distribution of low differentiation and higher 5-year relapse rate than those with CT/TT genotypes. The expression of IFITM3 was higher in HCC tissues than adjacent normal tissues, and the level of IFITM3 was higher in HCC tissues with low differentiation and metastatic than high/medium differentiation and without metastatic. Higher RNA level of IFITM3 was found in CC genotype than TT genotype. In PLC/PRF/5 cell with knockdown, the ability of cell proliferation and migration was inhibited. Analysis RNA sequencing and verification of RT-PCR found out the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin(PI3K/AKT/mTOR) pathway was associated with knockdown IFITM3.With the inhibition of IFITM3, the expression of PI3K/AKT/mTOR signaling pathway was blocked and the expression of vimentin was decreased. Conclusions: IFITM3 rs12252-CC with the higher expression plays a vital role in the progress of HCC by regulating HCC cell proliferation and migration. These effects are associated with PI3K/AKT/mTOR signaling pathway.

**Keywords :** IFITM3, interferon-induced transmembrane protein 3, HCC, hepatocellular carcinoma, PI3K/ AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin
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