The human tweety homolog (TTYH) family (TTYH1-3), which comprises homologs of tweety in flightless Drosophila, encode large conductance chloride channels. TTYH family members are involved in embryonic development, and tumor progression. TTYH3 is a large conductance Ca2+-activated Cl- channel. Its activation is dependent on the intracellular Ca2+ concentration. Bioinformatics analysis has indicated that TTYH3 is overexpressed in gastric cancer and is related to poor prognosis. Here, we investigated the biological and molecular function, and clinical significance of TTYH3 in HCC.

Methods

The biological function of TTYH3 was investigated in vitro and in vivo through its overexpression and knockdown in HCC cell lines. The molecular mechanism by which TTYH3 regulates HCC cell invasion and metastasis was explored. The expression and clinical significance of TTYH3 were analyzed in HCC tissues. DNA methylation in TTYH3 was studied through microarray and pyrosequencing.

Results

TTYH3 promoted HCC cell proliferation and cellular motility. TTYH3 promoted tumor formation in the subcutaneous xenograft model and cell metastasis in the metastasis model. TTYH3 promotes calcium and chloride influx in HCC cells. TTYH3 promotes epithelial-mesenchymal transition through MK5 in HCC cells (Left); TTYH3 activates GSK3β/β-catenin signaling via MK5 (Right).

Conclusion

In conclusion, we identified that TTYH3 promotes HCC progression through MK5/GSK3β/β-catenin signaling by transporting Ca2+ and Cl- into the cytoplasm. The high expression of TTYH3 may be regulated by DNA methylation and positive feedback manner. Our study provides new insight into the role of chloride channels in regulating tumor metastasis.

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