Regulation of the transition from metabolic dysfunction and non-alcoholic steatohepatitis to hepatocellular carcinoma

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Diverse functions of normal or cancerous cells including proliferation, migration and invasion critically and greatly depend on extracellular environment during their survival and metastasis. The environment consists of extracellular matrix proteins, neighboring cells, and soluble factors, including of cytokines, chemokines, and growth factors. Driving factor(s) mechanistic for the chronic and multiphase liver malignancy remains unclarified. We thus investigated roles of transmembrane 4 L six family member 5 (TM4SF5) in the aggravation of liver malignancy, using cognately genetic or chemical-induced models of *in vitro* hepatocytes and *in vivo* animals. TM4SF5 is a transmembrane glycoprotein highly expressed in many types of cancers including hepatic cancer and shown to cause epithelial-mesenchymal transition. TM4SF5 in hepatocytes is induced by diverse cytokines/chemokines, which are involved in development of NASH and liver fibrosis. We have recently found that TM4SF5 expression in hepatocytes can cause or promote nonalcoholic fatty liver disease (NAFLD) including steatohepatitis associated with fibrosis presumably following abnormal metabolic-inflammatory dysfunctions. The relevance of TM4SF5 in the bidirectional communications among hepatocytes, immune cells and environmental factors can also be importantly involved in the pathological development toward hepatocellular carcinoma. Meanwhile, NASH is emerging as the most rapidly rising cause for developing HCC and NASH-related HCC at an advanced stage showed limit for the curative ablation, resection, liver transplantation, or immunotherapy. Thus, new biomarkers for the transition from NASH to HCC would be essential for the curative options. Therefore, in this study, therapeutic reagents specifically inhibitory against TM4SF5 including small compound or antibody appears to inhibit the TM4SF5-mediated NAFLD toward HCC.

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