TM4SF5 drives aggravation from nonalcoholic fatty to fibrotic and cancerous liver

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Chronic liver injury can lead to inflammation, fibrosis, cirrhosis, and tumorigenesis. Since TM4SF5, a tetraspan (in) with four transmembrane domains is shown to be involved in liver fibrosis, it is reasonable to consider that TM4SF5 can play roles in important roles development of liver diseases. In CCl_4-administrated animal livers, the pattern of TM4SF5 expression along the fibrotic septa was in parallel to those of TGFβ1, α-SMA, and collagen I deposition. TM4SF5 is induced by signaling activities of TGFβ1- and EGFR-mediated signaling pathways. Therefore, in this current study, we further explored how TM4SF5 is involved in development of liver fibrosis and HCC, using *in vitro* cell and *in vivo* animal systems in addition to human tissues. Primary hepatocytes isolated from mice treated with CCl4 for four or 16 weeks, to mimic fibrotic and cirrhotic livers, respectively, showed enhanced TM4SF5, α-SMA, collagen I, and laminins expression, in addition to increased c-Src and STAT3 activities. Suppression or inhibition of TM4SF5, c-Src, or STAT3 could result in blocking of collagen I and laminin expression. Furthermore, when CCl_4 administration was performed together with IP or intratumoral treatment of anti-TM4SF5 antibody, the mice showed reduced development of CCl_4-mediated fibrosis phenotypes in livers and tumor formation by xenografts, in addition to reduced STAT3 signaling activity and ECM deposition. These observations suggest that TM4SF5 may be involved in the development of fibrosis and tumorigenesis, via its roles in ECM induction through c-Src and STAT signaling pathways.

Speaker Biography

Jung Weon Lee has completed his PhD from University of North Carolina at Chapel Hill, NC, USA and Post-doctoral studies from MSKCC at NY. These days, his research group mostly focuses on the roles of a tetraspanin, TM4SF5, in NASH, fibrosis, tumorigenesis and metastasis, and on the anti-TM4SF5 reagents to block TM4SF5-mediated liver diseases, in either 2D or extracellular matrix-surrounded 3D culture conditions via biochemical, cell biological and molecular biological approaches in addition to animal models, and clinical samples for the fibrotic and tumor models or patients (Lab homepage: http://www.snupharm.ac.kr/jwl/). He has published more than 100 papers in reputed journals.

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