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**Hepatic TM6SF2 activates antitumour immunity to suppress metabolic dysfunction-associate steatotic liver disease-related hepatocellular carcinoma**

**Zhang Y, Xie M, Wen J*, et al.* Hepatic TM6SF2 activates antitumour immunity to suppress metabolic dysfunction-associated steatotic liver disease-related hepatocellular carcinoma and boosts immunotherapy. *Gut*2025; 74: 640-652. doi: 10.1136/gutjnl-2024-333154**

Transmembrane 6 superfamily member 2 (TM6SF2) is implicated in metabolic dysfunction-associated steatotic liver disease-related hepatocellular carcinoma (MASLD-HCC). In this study, its role and potential to enhance immunotherapeutic effect in MASLD-HCC was explored.

Zhang *et al.,* first showed that TM6SF2 expression is downregulated (protein/RNA) in human MASLD-HCC tumours compared to adjacent normal tissues from biopsy samples. They then generated MASLD-HCC models using hepatocyte-specific *Tm6sf2* knockout (Tm6sf2∆hep) mice challenged by high fat, high cholesterol diet (HFHC), carcinogen injection or inoculation of tumour cells. Tm6sf2∆hep mice consistently had increased tumour formation and impaired antitumour immunity, with reduced CD8+ (cluster of differentiation 8) T-cell numbers. Conversely, *Tm6sf2* overexpression repleted CD8+ T-cells and concurrent administration of anti-CD8 antibodies, lead to tumour formation.

RNA-sequencing of tumours from the mice model, they found differentially expressed genes were enriched in immune-related pathways, specifically with cytokine-cytokine interaction. Looking at the cytokine profile, they showed that the supernatant of cultured *tm6sf2* knockout HKCI10 (Hong Kong Cancer Institute cell line 10 (a human hepatocellular cancer cell line) cells had increased IL-6 (interleukin-6) expression, which was reversed by *Tm6sf2* overexpression. CD8+ T-cells proliferation was suppressed when cultured with conditioned medium *tm6sf2* knockout HKCI10 cells; an effect reversed by Tocilizumab (IL-6 inhibitor).

On pulldown assays, IKKβ (Inhibitory kappa B kinase beta) was a binding partner of TM6SF2. Overexpression of *Tm6sf2* reduced NF-κB-IL-6 (Nuclear factor kappa-light-chain-enhancer of activated B interleukin-6) signalling, which was corroborated by their RNA sequencing data. Furthermore, inhibiting NF-κB restored antitumor immunity. Lastly, *Tm6sf2* overexpression was shown to boost the effect of anti-PD-1 (Programmed cell death protein 1) and Lenvatinib (a multi-kinase inhibitor) therapy in MASLD-HCC mice.

Zhang *et al.,* conclude that TM6SF2 suppresses MASLD-HCC by enhancing cytotoxic CD8+ T cell activity via NF-κB-IL-6 axis. Adjunctive targeting of TM6SF2 could be useful for MASLD-HCC therapy.