TGFβR1 inhibition drives hepatocellular carcinoma proliferation through induction of toll-like-receptor signalling

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Abstract

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Transforming growth factor (TGF)-β and toll-like receptors (TLRs) have been shown to independently modulate the proliferation of hepatocellular carcinoma (HCC). Since a direct cross-talk between these two signalling pathways in HCC has not been clearly described before, we aimed here to explore the possibility of such interaction. A human HCC tissue array (n = 20 vs. four control samples), human HCC samples (n = 10) and steatohepatitis-driven murine HCC samples (control, NASH and HCC; n = 6/group) were immunostained for TGFβR1, pSMAD2, TRAF6, IRAK1 and PCNA. The results were confirmed by immunoblotting. Effects of constant activation of the SMAD pathway by constitutive expression of ALK5 or knockdown of mediators of TLR signalling, IRAK1 and MyD88, on HCC proliferation, were investigated in the HCC cell line (HUH-7) after treatment with TGFβ1 cytokine or TGFβR1 kinase inhibitor (LY2157299) using PCNA and MTS assay. TGFβR1 expression is decreased in human and murine HCC and associated with downregulated pSMAD2, but increased IRAK1, TRAF6 and PCNA staining. TGFβR1 kinase inhibition abolished the cytostatic effects of TGFβ1 and led to the induction of IRAK1, pIRAK1 and elevated mRNA levels of TLR-9. Overexpression of ALK5 and knockdown of MyD88 or IRAK1 augmented the cytostatic effects of TGFβ1 on HUH-7. In another epithelial HCC cell line, that is, HepG2, TGFβR1 kinase inhibitor similarly elevated cellular proliferation. There is a balance between the canonical SMAD-driven tumour-suppressing arm and the non-canonical tumour-

promoting arm of TGFβ signalling. Disruption of this balance, by inhibition of the canonical pathway, induces HCC proliferation through TLR signalling.