

TGF β R1 inhibition drives hepatocellular carcinoma proliferation through induction of toll-like-receptor signalling

Info

PUBLIZIERT AM

2024-02-08

JOURNAL

International Journal of Experimental Pathology

LINK

<https://doi.org/10.1111/iep.12501>

Autoren

Fatma El Zahraa Ammar Mohamed Bedair Dewidar

Tao Lin Matthias P. Ebert Steven Dooley

Nadja M. Meindl-Beinker Seddik Hammad

Abstract

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 TGF β R1, 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 TGF β 1 cytokine or TGF β R1 kinase inhibitor (LY2157299) using PCNA and MTS assay. TGF β R1 expression is decreased in human and murine HCC and associated with downregulated pSMAD2, but increased IRAK1, TRAF6 and PCNA staining. TGF β R1 kinase inhibition abolished the cytostatic effects of TGF β 1 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 TGF β 1 on HUH-7. In another epithelial HCC cell line, that is, HepG2, TGF β R1 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 TGF β signalling. Disruption of this balance, by inhibition of the canonical pathway, induces HCC proliferation through TLR signalling.