

Commentary

Transforming growth factor beta signaling in hepatocellular carcinoma: as a victim or culprit?

Varun Kumar Sharma¹, Charu Tyagi², Yugandhar P. Reddy³,
Jayanand Manjhi¹, Lomas Kumar Tomar^{1*}

¹Department of Biotechnology and Microbiology, School of Sciences, Noida International University-NIU, Gautam Budh Nagar 201308, Uttar Pradesh, India

²Department of Biotechnology, VSPG(PG) College, CCS University, Meerut 250004, Uttar Pradesh, India

³Department of Zoology, The Adoni Arts and Science College, Adoni, Kurnool, Andhra Pradesh, India

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*Correspondence:

Dr. Lomas Kumar Tomar,

E-mail: lomas.iitd@gmail.com

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ABSTRACT

The transforming growth factor- β (TGF β) signalling pathway control various cellular function and play a pivotal role in tumour suppression. In contrary, overexpression of TGF β is linked to promote the cancer development. TGF β facilitate cell-growth and cell-differentiation process which support tumour propagation. In case of hepatocellular carcinoma (HCC), TGF β signalling pathway is the master regulator of HCCs pathogenesis and functionally involved in the regulation of HCCs phenotype via modulating the downstream signalling pathways. In this article, we have highlighted the contradictory behaviour of TGF β in hepatocellular carcinoma. Observations suggest that the TGF β signalling pathway is positively correlated to the expression of genes linked with various hepatic pathological conditions, including fibrosis, cirrhosis, inflammation and cancer. TGF β pathway play dual role as pro and anti-tumoural activities in cancer cells depending on their context.

Keywords: Hepatocellular carcinoma, Signaling pathway, Transforming growth factor- β

The transforming growth factor- β (TGF β) signaling pathway consist pleiotropic functions across diverse context and tissues, and control various cellular function, including cell growth, differentiation, apoptosis, angiogenesis, immune response and others. In normal scenario, functionally active TGF β control cancer growth and exert tumor suppressive behavior. However, aberrant expression could promote the uncontrolled cell growth leads to the cancer development. TGF β facilitated cell growth, differentiation, motility and invasion could be abused in cancerous cells. Therefore, the output of a TGF β mediated response is extremely valuable during the development in normal tissues as well as transformed cells.¹⁻³ The TGF- β signals regulates via protein kinase

receptors and SMAD mediators and regulate a large number of biological processes. A wide range of biomolecules have been identified which could directly or indirectly modulate the TGF β signaling pathways. Interestingly, the TGF β pathway shows as dual role as pro- and anti-tumoral activities in cancer cells depending on their context. For instance, TGF β promote tumorigenic in mammary gland tumorigenesis in mouse model. However, in case of colorectal cancer, pancreatic cancer and hepatocellular carcinomas, TGF β has been identified to inhibit cancer development and shows as tumor suppressive in nature.^{1,3-5}

Hepatocellular carcinoma (HCC) is a heterogeneous cancer stage associated with remarkably poor prognostic outcome. HCC is a second deadliest cancer type which could be influenced by various risk factors including, infection of HBV or HCV, alcohol consumption and others. With poor prognostic outcome and drug resistance behavior of HCCs, patients could go under therapy using liver transplantation, surgical resection, and radiofrequency ablation. Recent research work published by Chen J. and his colleagues have demonstrated the critical role of TGF β pathway in HCCs.⁵ In case of Beckwith-Wiedemann syndrome (BWS; also known as an overgrowth syndrome), it has been observed that combinational loss of SMAD adopters Sptbn1 and Smad3 (Sptbn1^{+/-}/Smad3^{+/-}) of TGF β signaling induce higher risk of tumorigenesis and increases the risk to develop hepatocellular carcinoma (HCC) by 40%.⁵ It has been identified that BWS individuals have more risk to develop different tumor type in same organ or at same sites in body. For instance, in one of the patients, it has been observed that co-occurrence of a mesenchymal hematoma, capillary hemangioma hepatoblastoma, and cholangio carcinoma within the liver.^{5,6} Additionally, TGF β signaling pathway deficient Sptbn1^{+/-}/Smad3^{+/-} mouse model demonstrated tumor suppressive role of TGF β signaling pathway in HCC.^{5,6} Additionally, microRNAs signature is also identified in various signaling pathways and linked to wide varieties of pathological conditions, including autoimmunity and cancer.^{7,8} In HCCs, It has reported miR-122 is a biomarker for the progression of HCCs.⁷

Authors have analyzed a large number of open access and newly identified HCCs cases. Observations suggest that TGF β signaling is not only a key player hepatocyte proliferation and extracellular matrix deposition in the liver, but also play an important role in the genomic stability in the context of genotoxic injury. Previous observation based on The Cancer Genome Atlas (TCGA) Research Network, authors provided deep and comprehensive functional analysis of TGF β signaling pathway in patients with HCCs.^{9,10} Based on genomic and transcriptomic profiling, they identified frequent aberrations of TGF β signaling in liver samples obtained from patients with HCCs compared to healthy controls. Observations suggest that the expression of 18 genes were dysregulated in HCCs which includes SMAD-3, -4, -5, -7, DLG1, CTCF, EP300, CREBBP, SPTBN1, BMPR1A, RUXN2, TGFB-1, -2, -3, ACVR2A, TGFB-1, -2 and BMPR2.⁵ Hierarchical clustering based study revealed four distinct clusters of TGF β pathways. Each cluster consists of specific characteristics; Cluster A represents highly activated TGF- β pathway with elevated expression of selected genes, Cluster B also expressed induced expression of selected gene but shows lower level compared to Cluster A, Cluster C indicates few upregulated expressions of selected gene and represent nearly as normal sample, and Cluster D designates downregulation of selected genes expression and shows suppressed TGF β pathways. Authors considered Cluster

A and B as activated cluster, Cluster B as normal and Cluster D as inactivated cluster.⁵ Additionally, the key observations from this article is to understand the connections between the TGF β pathway, pro-inflammatory and DNA repair pathways and help to demonstrate the clinico-functional importance of TGF β in inflammation, genome integrity and cancer development.^{5,9}

Authors observed that the TGF β signaling pathways is linked with regulation various oncogenes in HCCs. These oncogenes such as KRAS, MDM2, MTOR, IGF2, and VEGFA expression were induced in activated cluster and indicate tumor promoting behavior of TGF β pathways via promoting inflammation or/and epithelial-mesenchymal transition.⁵ Over-expression of MDM2 (known as negative regulator of p53, a tumor suppressor protein) in activated cluster support tumor progressive nature of TGF β signaling. Additionally, Forced suppression of TGF β signaling via modulating the expression of SMAD-2, -3, -4 and -7 also support HCCs progression. Furthermore, Authors demonstrated the positive correlation between TGF β signaling and the expression of genes linked with various hepatic pathological conditions, including fibrosis, cirrhosis, inflammation, and cancer.^{5,6,9} Observations suggest that expression of gene profile associated with collagen synthesis, growth factors, cytokines and matrix metalloproteases are positively and the gene linked to DNA recombination, genomic stability, and aging are inversely correlated with TGF β signaling. Experiment based on mouse model identified that SIRT1 expression is directly associated with TGF β signaling. They observed that SIRT1 protein expression is reduced (but not in RNA level) in disrupted TGF β signaling (Sptbn1^{+/-}/Smad3^{+/-}) experimental model, suggests a posttranscriptional regulation of Sirt1 by TGF β . Interestingly, SIRT3-6mRNA expression is also reduced in cells with defective TGF β signaling. Observations based on cBioPortal cancer genomics data analysis revealed that suppressed expression of SIRT1, SIRT2, SIRT3, or SIRT6 combine with loss of SPTBN1 reduces the survival rate of the patients with HCCs. Additionally, Sirtulin deficient mice model have shown prevalence of cancer progression.⁵

In TCGA analysis, authors observed a strong correlation between mutation in TGF β pathway and DNA repairing pathways associated genes such as, ATR, FANCD2, FANCM, FAN1, RAD51, and TP53BP1, at genomic level. Observation also revealed that inactivated cluster of TGF β signaling is linked with loss of tumor suppressor genes, including ATM, BRAC1 and FANCF.⁵ They observed higher incidence (38%) of somatic mutations in at least one of the thirty two TGF β signaling pathway genes. SPTBN1 mutation is identified in almost 6% of patients with HCCs. Mutated gene such as ATR, FANCD2 and TP53BP1 which play active role in DNA repair pathway were significantly linked with mutations of the TGF β signaling genes.⁵

In conclusion, this study determined that the impaired TGF β signaling pathway via somatic mutation at least one of the thirty-two TGF β pathway genes facilitates the regulation of a set of gene associated to the various pathways including DNA damage repair, genomic instability, inflammation, tumor progression and cancer development in liver, leads to HCCs.^{5-7,9} These observations suggest that TGF β signaling pathway is the master regulator of HCC pathogenesis and functionally involved in the regulation of HCCs phenotype via modulating the downstream signaling pathways. As defectiveness of TGF β pathway via somatic mutation has shown to rescue the tumorigenic behavior in HCCs.⁵ It would be worth exploring whether these dysregulation at genomic and transcriptomic level are associated with TGF β pathway in HCCs.

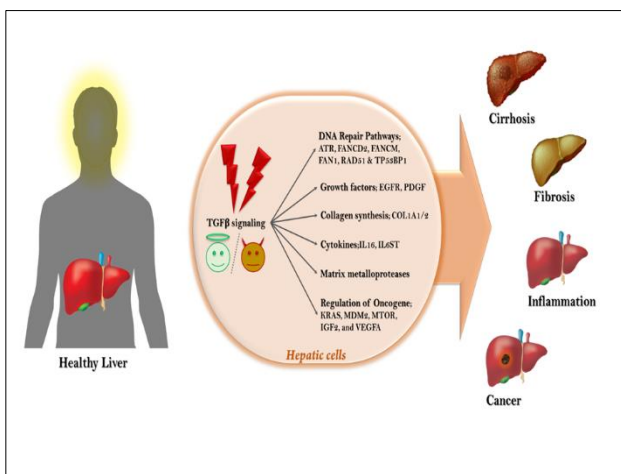


Figure 1: Impaired TGF β pathway regulation in hepatocellular carcinoma.

TGF β pathway is a key modulator in a large set of cellular process and functionally active TGF β pathway suppresses tumor progression. Interestingly, Impaired TGF β pathway either functionally inactive or mutation in at least 1 of the 32 TGF β pathway genes facilitates the regulation of a diverse range of signaling pathways (DNA damage repair and genomic instability) and other important cellular factors, such as collagen synthesis, matrix metalloproteases, oncogene, growth factor and others. Overall, these acquired physiological outcome of impaired TGF β signaling pathway facilitates the development of fibrosis, cirrhosis, inflammation, tumor progression and cancer development in liver, leads to HCCs.

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