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Review Article

Novel oncogenes and tumor suppressor genes in hepatocellular carcinoma[☆]Fang Wang^a, Peter Breslin S J^b, Wei Qiu^{a,*}^a Department of Surgery and Cancer Biology, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA^b Department of Molecular/Cellular Physiology, Cancer Biology, Cardinal Bernardin Cancer Center, Loyola University Medical Center, and Biology, Loyola University Chicago, Chicago, IL, USA

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ABSTRACT

Hepatocellular carcinoma (HCC) is a very deadly disease. HCC initiation and progression involve multiple genetic events, including the activation of proto-oncogenes and disruption of the function of specific tumor suppressor genes. Activation of oncogenes stimulates cell growth and survival, while loss-of-function mutations of tumor suppressor genes result in unrestrained cell growth. In this review, we summarize the new findings that identified novel proto-oncogenes and tumor suppressors in HCC over the past five years. These findings may inspire the development of novel therapeutic strategies to improve the outcome of HCC patients.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest cancers worldwide.¹ There are many risk factors for HCC, such as infections with hepatitis B virus or hepatitis C virus, chronic alcohol use, aflatoxin, autoimmune hepatitis, obesity, and diabetes.² Current therapies provide limited clinical benefit for these patients.² A better understanding of the molecular mechanisms of HCC development is critical for developing new effective therapeutic strategies for treating it.³ HCC initiation and progression involve multiple genetic events, such as the activation of proto-oncogenes and disruption of the functions of specific tumor suppressor genes. Oncoproteins encoded by oncogenes stimulate or enhance the division and viability of cells.⁴ In contrast, tumor suppressor genes can directly or indirectly prevent cell proliferation or result in cell death. Tumor protein p53 (*P53*), phosphatase and tensin homolog (*PTEN*), axin 1 (*AXIN 1*), and retinoblastoma transcriptional corepressor 1 (*RB1*) are well-known tumor suppressor genes in HCC. For example, *P53* is mutated or silenced in 30–60% of HCC, while *PTEN* is lost in over 40% of HCC.^{5,6} In 2015, Kanda *et al.*⁷ summarized the

functions of putative oncogenes and tumor suppressors in HCC. Also, in a recent special issue of *Liver Research*, several diagnosis markers, such as Golgi protein 73, Glypican-3, Galectin-1 and Galectin-3, Yes-associated protein-1 for HCC were discussed.^{8–10} However, these biomarkers do not necessarily functionally contribute to HCC initiation and progression. This review provides an updated overview of recently published articles from the past five years addressing HCC-related oncogenes (30 genes) and tumor suppressor genes (12 genes), which functionally contribute to HCC initiation and progression. These genes are introduced because the studies on functions of these genes in HCC have potentially significant influences on the discovery, pathogenesis, or treatment of liver cancer. These findings may stimulate the development of novel therapeutic strategies for the treatment of HCC.

2. Novel oncogenes in HCC

2.1. *Abelson murine leukemia viral oncogene homolog 1 (ABL1)*

ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*) was first discovered as an oncogene in human leukemia more than 30 years ago. *ABL* inhibitors have been very successfully used for the treatment of breakpoint cluster region (BCR)-*ABL1*-positive leukemia. Recently, activation of *ABL1* has been detected in many solid tumors.¹¹ However, for a long time, the role of *ABL1* in the

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development of HCC was not known. Recently, we found that *ABL1* is overexpressed and activated in human HCC tissues, and its overexpression correlates with poor survival in HCC patients.^{12,13} Functional inhibition of *ABL1* impairs HCC growth and extends the overall survival of mice with HCC.¹³ Mechanistically, we found that inhibition of *ABL1* decreases the expression of *c-MYC* and notch receptor 1 (*NOTCH1*) and suppresses HCC cell growth.¹³ We also found a strong correlation between *ABL1*, *c-MYC*, and *NOTCH1* in human HCC specimens.¹³ Significantly, *ABL1* inhibitors suppressed HCC growth in xenograft and oncogene-driven HCC models.¹³ Overall, these results suggest that *ABL1* plays a crucial role in promoting HCC development.

2.2. Annexin A protein family

Annexins are Ca^{2+} -regulated phospholipid-binding proteins that play vital roles in cell proliferation, exocytosis, and cell death.¹⁴ Twelve annexin proteins (A1–12) have been identified in humans.^{15,16} Several Annexin proteins have been shown to function as putative oncoproteins in HCC development. Annexin A3 (*ANXA3*) expression is substantially elevated in HCC tissues in comparison to adjacent normal tissues.^{17,18} *ANXA3* expression is positively correlated with the number, size, stage of the tumor, and poor prognosis.¹⁷ *ANXA3* overexpression promotes cell growth and metastasis in HCC cell lines.¹⁷ In contrast, the knockdown of *ANXA3* inhibits these processes. Its blockade with an anti-*ANXA3* antibody results in a significant reduction in tumor growth.¹⁹ Additionally, overexpression of *ANXA3* in HCC cells enhances resistance to treatment with sorafenib and regorafenib.²⁰ Mechanistically, upregulated *ANXA3* suppresses protein kinase C delta (*PKCδ*)/p38-associated apoptosis and activates autophagy in sorafenib-resistant HCC cells.²⁰ Significantly, anti-*ANXA3* monoclonal antibody therapy enhances the efficiency of sorafenib/regorafenib in suppressing HCC tumor growth *in vivo*.²⁰

ANXA4, another member of the Annexin A family, is another putative proto-oncogene in HCC. Serum *ANXA4* levels are substantially greater in HCC patients than patients with cirrhosis of the liver and healthy controls.²¹ Overexpression of *ANXA4* promotes HCC cell proliferation, and the downregulated expression of *ANXA4* inhibits HCC cell growth and tumorigenesis.²² Similarly, high expression of *ANXA2* promotes the progression of HCC and predicts poor prognosis.²³ Mechanistically, *ANXA2* enhances HCC progression via the remodeling of cell motility-associated structures and interaction with engulfment and cell motility protein 1.^{24,25}

2.3. Focal adhesion kinase (FAK)

FAK, a non-receptor tyrosine kinase, promotes tumor growth and progression by kinase-dependent and -independent pathways.²⁶ Although FAK functions in other types of cancer have been intensively studied, and it was known that FAK is overexpressed in HCC specimens,^{27,28} FAK's precise role in HCC remained elusive in the past. Our lab generated hepatocyte-specific *FAK*-knockout mice.²⁹ We found that loss of FAK dramatically stifles cellular-mesenchymal epithelial transition factor (*c-MET*)/ β -catenin-induced tumor growth and prolongs animals' survival in this model. Mechanistically, we found that *c-MET* activates *FAK*, which is critical for the activation of protein kinase B (*AKT*) and extracellular signal-regulated kinase (*ERK*) in HCC cells.²⁹ β -catenin does not directly activate *FAK*; instead, it enhances the activation of *FAK* by *c-MET*.²⁹ Further, we demonstrated that *FAK* promotes *c-MET*/ β -catenin-induced HCC via its kinase activity.³⁰ Consistently, the *FAK* kinase inhibitor PF-562271 suppresses the progression of HCC in mouse models.³⁰ *FAK* can also regulate enhancer of zeste homolog

2 (*EZH2*), which modulates transcription of *p53*, *E2F2/3*, and *NOTHC2* to promote HCC cell growth.³¹

Our lab recently discovered that *FAK* overexpression alone is insufficient to induce HCC; instead, *FAK* cooperates with β -catenin to induce HCC.³² Consistent with this, one-third of human HCC samples with *FAK* amplification are coincidental with β -catenin mutations.³² Mechanistically, increased expression of *FAK* increases androgen receptor (*AR*) expression by enhancing the binding of β -catenin to *AR*'s promoter. Importantly, inhibition of *AR* suppresses *FAK*/ β -catenin-induced HCC development.³²

2.4. Human forkhead box (FOX) family

FOX proteins are transcription factors that play a significant role in cell proliferation, differentiation, embryogenesis, and senescence.^{33,34} The expression of *FOXK1* is upregulated in human HCC tissues, and its high expression correlates with poor outcomes and regulates the stemness of HCC cells.^{35,36} *FOXK1* knockdown impairs the proliferation, migration, and invasion of HCC cells and reduces the growth of tumors in xenograft mouse models, which might be explained by the downregulation of β -catenin and its downstream targets *c-Myc* and cyclin D1.³⁵ Recently, long non-coding RNA (*lncRNA*) *TMPO* antisense RNA 1 (*TMPO-AS1*), has been shown to *FOXK1*-mediated *AKT*/*mTOR* signaling pathway and contribute to HCC progression by sponging *miR-329-3p*.³⁷

FOXR2, another FOX protein, is upregulated in HCC specimens compared to neighboring non-cancerous tissues.³⁸ *FOXR2* overexpression promotes HCC cell and tumor growth, while silencing of *FOXR2* inhibits HCC cell growth.³⁸ *FOXR2* promotes HCC malignancy by regulating its potential downstream targets such as β -catenin, S-phase kinase associated protein 2 (*Skp2*), *c-Myc*, and *Gli-1*.³⁸

FOXA3, another FOX protein, in the combination of hepatocyte nuclear factor (*HNF*) 1A and *HNF4A*, reprograms HCC cells to hepatocyte-like cells. These cells lose the malignant phenotypes of cancer cells and retrieve hepatocyte-specific characteristics. Consistently, intratumoral injection of these three factors suppresses tumor growth in patient-derived tumor xenografts *in vivo*. Mechanistically, exogenous expression of *FOXA3*, *HNF1A*, and *HNF4A* in HCC cells restored the endogenous expression of numerous hepatocyte nuclear factors, which promoted the conversion.³⁹

2.5. Kinesin superfamily protein (KIF)

KIFs are motor proteins that transport membranous organelles and protein complexes.^{40,41} *KIF15*, a KIF family member, shows high expression in tumor samples from HCC patients.⁴² Higher expression of *KIF15* predicts poor prognosis in HCC patients.⁴³ *KIF15* overexpression enhances HCC cell growth.^{42,44} Mechanistically, *KIF15* interacts with phosphoglycerate dehydrogenase (*PHGDH*), which inhibits proteasomal degradation of the latter and leads to the imbalance of reactive oxygen species (*ROS*), thereby promoting HCC malignancy.⁴⁴

KIF2C expression is also substantially higher in tumor tissues than in adjacent normal tissues.⁴² Overexpression of *KIF2C* predicts poor prognosis, promotes HCC cell proliferation, and impedes apoptosis.⁴⁵ *KIF2C* interacts with various cell cycle-related proteins and upregulates proliferating cell nuclear antigen (*PCNA*) and *CDC20* expression.⁴⁶

A higher expression level of *KIF1C* correlates with a poor prognosis for HCC patients and promotes HCC cell proliferation.^{47,48} Mechanistically, the silencing of *KIF1C* decreases the expression of the apoptosis-related protein B-cell lymphoma-2 (*Bcl-2*) and increases the levels of *p53* and *Bcl-2*-associated X protein. Moreover,

KIFC1 knockdown decreases phosphoinositide 3-kinase (PI3K)/AKT signaling in HCC cells.⁴⁸ KIFC1 is downregulated by miR-532-3p but is activated by TCF-4 in HCC.^{49,50}

2.6. Non-structural maintenance of chromosomes (SMC) condensin I complex (NCAP) family

SMC and non-SMC proteins build NCAP and control chromosome condensation and segregation during cell division, thus playing key roles in cell proliferation.^{51,52} Genome-wide CRISPR-knockout screening identifies non-structural maintenance of chromosomes condensin I complex subunit G (NCAPG) as an essential oncogene for HCC tumor growth.⁵³ NCAPG silencing in HCC cells leads to abnormal mitosis, mitochondrial fragmentation, and apoptosis.^{53,54} Mechanistically, NCAPG promotes HCC proliferation via the PI3K/AKT signaling pathway, further supported by the observation that LY294002, a PI3K inhibitor, could abolish the role of NCAPG in promoting HCC cell growth.

NCAPG2, a member of the NCAP family, is often highly expressed and is positively correlated with poor prognosis in HCC patients.^{53,55} Overexpression of NCAPG2 promotes HCC cell growth and metastasis by activating the PI3K/AKT, nuclear factor-kappaB (NF-κB), and signal transducers and activators of transcription-3 (STAT3) signaling pathways.^{55,56} Both miR-188-3p and miR-181c suppress HCC growth and metastasis through modulation of NCAPG2.^{55,57} Excessive expression of non-structural maintenance of chromosomes condensin I complex subunit H (NCAPH), another NCAP family member, predicts poor prognosis in HCC patients.^{58,59} Similar to NCAPG2, NCAPH also promotes HCC tumor growth and metastasis.⁵⁹ However, the action mechanisms of NCAPH remain unknown and to be determined.

2.7. Never-in-mitosis A (NIMA)-related kinase (NEK) family

NEKs play essential roles in the mitosis entry of cells.⁶⁰ A number of family members, including NEK2, NEK6, NEK7, and NEK9, play roles in establishing the microtubule-based mitotic spindle, while some other members, such as NEK1, NEK10, and NEK11, play roles during DNA damage.⁶¹ NEK2 is highly expressed in HCC tissues, which correlates with a poor prognosis for the disease.^{62–65} Increased NEK2 promotes HCC progression by enhancing PP1/AKT activation, WNT signaling, and epithelial-mesenchymal transition (EMT).^{66,67} Besides, NEK2 augments sorafenib resistance by regulating the ubiquitination and localization of β-catenin in HCC.⁶⁸

NEK7 is also significantly overexpressed in HCC, and its excessive expression is positively associated with numbers, size grades, and stages of HCC tumors.⁶⁹ The silencing of NEK7 using lentivirus-mediated Nek7 interference approach suppresses HCC growth *in vitro* and a xenograft mouse model.⁶⁹ Mechanistically, inhibition of NEK7 suppresses HCC growth by decreasing the expression of cyclin B1 both *in vitro* and *in vivo*.⁶⁹

2.8. Protein arginine methyltransferase (PRMT) family

PRMTs methylate numerous nuclear and cytoplasmic substrates and play critical roles in apoptosis, cell proliferation, and RNA processing.⁷⁰ Excessive expression of PRMT1 is correlated with poor survival for HCC patients.⁷¹ Overexpression of PRMT1 promotes HCC growth and metastasis by activating the STAT3 signaling pathway.⁷² PRMT1 regulates the production of IL-6 in macrophages, thereby promoting alcohol-induced HCC progression.⁷³ Moreover, miR-503 suppresses HCC metastasis by targeting PRMT1.⁷⁴

Similar to PRMT1, higher PRMT2 expression in HCC specimens associates with shorter survival in HCC patients.⁷⁵ PRMT2 knockdown inhibits cell growth and survival by regulating H3R8 asymmetric methylation (H3R8me2a), which promotes *Bcl2* gene expression.⁷⁵ Elevated levels of PRMT5 in HCC tissues predict poor prognosis.⁷⁶ The inhibition of PRMT5 expression dramatically inhibits the severity of HCC by increasing the expression of HNF4α.⁷⁷ A novel PRMT5 inhibitor, DW14800, suppresses HCC tumor growth in cell cultures and xenograft mouse models.⁷⁷

2.9. Sirtuin (SIRT) family

SIRT family of proteins acts predominantly as nicotinamide-adenine dinucleotide (NAD)-dependent deacetylases.⁷⁸ Sirtuin family members play diverse roles in different kinds of cancer.⁷⁹ SIRT1 plays a vital role in cancer development, including HCC.^{78,80,81} Recently, SIRT1 was shown to facilitate HCC metastasis through facilitating peroxisome proliferator-activated receptor-gamma co-activator-1alpha (PGC-1α)-mediated mitochondrial biogenesis.⁸² In addition, SIRT1 overexpression promotes HCC growth through enhancing YAP- and mitogen-activated protein kinase kinase 3 (MKK3)-dependent p38 phosphorylation.⁸³

Increased SIRT5 expression is associated with poor prognosis in HCC patients.⁸⁴ Mechanistic studies revealed that SIRT5 promotes HCC growth and metastasis through decreasing the expression of E2F1.⁸⁴ Additionally, SIRT5 knockdown increases HCC cellular apoptosis by regulating the mitochondrial pathway.⁸⁵ However, a recent study reported that SIRT5 suppresses HCC development by suppressing peroxisomal acyl-CoA oxidase 1 (ACOX1) and oxidative stress.⁸⁶ These conflicting results suggest that SIRT5 has multiple functions and the full range of its biological features needs to be further investigated.

SIRT7 expression is often increased in HCC specimens, and its higher expression predicts poor prognosis.^{87,88} SIRT7 promotes HCC development by deacetylation of USP39.⁸⁹ In addition, SIRT7 promotes HCC growth and cell survival by deacetylating and inhibiting p53.⁸⁷ A recent study further showed that disruption of SIRT7 increases checkpoint inhibition efficacy via myocyte enhancer factor 2D (MEF2D)-mediated regulation of programmed cell death 1 ligand 1 in treating HCC.⁹⁰

2.10. Tripartite motif (TRIM) family

TRIM family proteins are RING-type E3 ubiquitin ligases involved in many diseases, including cancer and autoimmune disease.⁹¹ TRIM31 expression is significantly upregulated in HCC tissues, and its overexpression is significantly associated with advanced disease status.⁹² TRIM31 promotes the malignancy of HCC cells by directly associating with the tuberous sclerosis complex (TSC) 1 and TSC2, and promoting the E3 ligase-mediated K48-linked ubiquitination and degradation of this complex.⁹² In addition, TRIM31 promotes resistance anoikis of HCC cells by degrading p53 and activating the adenosine monophosphate-activated protein kinase (AMPK) pathway.⁹³

TRIM32 expression is also elevated in HCC specimens, and its expression is associated with tumor grades and sizes as well as HBsAg in HCC patients.⁹⁴ TRIM32 accelerates the G1–S phase transition, promotes cellular proliferative rates, and induces HCC patients' resistance to oxaliplatin.⁹⁴ TRIM44 also functions as an oncogene in HCC. Excessive expression of TRIM44 in HCC is associated with shorter overall survival.⁹⁵ TRIM44 overexpression promotes cell growth and metastasis, and enhances resistance to doxorubicin via accelerating the activation of NF-κB in HCC cells.⁹⁵

2.11. Ubiquitin-specific proteases (USPs) family

USPs are a family of unique hydrolases that precisely remove polypeptides covalently linked via peptide or isopeptide bonds to the C-terminal glycine of ubiquitin.⁹⁶ Several USP family members play essential roles in cancer.⁹⁷ USP5, a USP family member, is significantly elevated in HCC specimens.⁹⁸ USP5 promotes tumorigenesis in HCC through the inactivation of p14^{ARF}-p53 signaling.⁹⁸ Additionally, USP5 stabilizes SLUG and promotes EMT in HCC cells.⁹⁹

USP7 expression is also significantly upregulated in HCC tumors and is correlated with its progression.¹⁰⁰ Disruption of the USP7 function induces HCC cell death and inhibits cell proliferation and migration, which might be due to BCL2 associated X (BAX) activation.¹⁰⁰ A recent study indicated that USP7 stabilizes the Hippo pathway by deubiquitinating the transcriptional coactivator Yorkie, promoting HCC growth.¹⁰¹ Further, USP7 participates in lipogenesis-associated HCC progression by promoting stabilization and transcription of zinc-finger protein 638.¹⁰²

USP11 is upregulated in HCC and is correlated with shorter survival in HCC patients.^{103,104} USP11 promotes HCC cell survival, invasion, and metastatic potency *in vitro* and *in vivo*.^{103,104} Mechanistically, USP11 interacts with nuclear factor 90 (NF90) and promotes its deubiquitination, thereby stabilizing it in HCC cells.¹⁰³ Consistent with this, USP11 expression positively correlates with NF90 expression in human HCC tissues.¹⁰³ Similar to USP11, elevated USP13 in HCC patients is associated with a poor prognosis.¹⁰⁵ The knockdown of USP13 by short hairpin RNAs (shRNAs) markedly decreases cell growth in HCC by reducing *c-Myc* expression.¹⁰⁵

USP14 also functions as an oncogene in HCC. USP14 expression is increased in HCC specimens compared to adjacent normal liver tissues.¹⁰⁶ The knockdown of USP14 in HCC cells impairs cell growth and results in cell death.¹⁰⁶ Mechanistically, USP14 deubiquitinates and activates PI3K/AKT in HCC cells.¹⁰⁷ USP14 is a direct target of miR-4782-3p, and decreased expression of miR-4782 might contribute to increased expression of USP14 in HCC tissues.¹⁰⁸

3. Novel tumor suppressor genes in HCC

3.1. Suppressors related to the MEK/ERK pathway

The mitogen-activated protein kinase (MEK)/ERK pathway plays critical roles in tumor growth and progression in numerous types of cancer, including HCC.¹⁰⁹ Some suppressors which regulate the MEK/ERK signaling pathway have been identified as regulators of HCC development. Hippocalcin-like 1 (HPCAL1), a calcium sensor protein, was recently identified as a novel HCC suppressor. HPCAL1 expression decreases in tissues and plasma of HCC patients, which is correlated with a worse prognosis for these patients.¹¹⁰ HPCAL1 overexpression inhibits HCC cell growth while HPCAL1 silencing promotes cell proliferation by stabilizing p21 in an ERK-dependent manner.¹¹⁰

Mitogen-activated protein kinase phosphatases-4 (MKP-4) was identified as a binding partner with ERK1/2.¹¹¹ Decreased expression of MKP-4 predicted a better prognosis in HCC specimens.¹¹² Knockdown of MKP-4 in HCC cells increases cell proliferation, while ERK1/2 inhibition reverses the effect.¹¹¹ Mechanistically, MKP-4 negatively regulates the phosphorylation of ERK1/2, thereby reducing the expression of Cyclin D1 and *c-Myc*. Consistently, the expression of MKP-4 negatively correlates with p-ERK in clinical analyses of HCC patients.¹¹¹

The RBP sorbin and SH3 domain-containing 2 (SORBS2), also known as Arg/c-Abl kinase binding protein 2, is a member of a small family of adaptor proteins with sorbin homology (SOHO) domains.¹¹³ SORBS2 functions as a tumor suppressor in HCC. SORBS2 expression is substantially lower in HCC tissues than normal liver tissues, and low expression of SORBS2 is correlated with poor prognosis in HCC patients.¹¹⁴ SORBS2 overexpression suppresses cell migration, invasion, and EMT in HCC cells, whereas SORBS2 inhibition yields the opposite results. Mechanistically, SORBS2 suppresses HCC by inhibiting the *c-Abl*/ERK signaling pathway and stabilizing retinoic acid receptor-related orphan receptor alpha (RORA) mRNA.^{114,115} Myocyte-specific enhancer factor 2D binds to the promoter of SORBS2 and reduces its expression in HCC cells.¹¹⁴

3.2. Suppressors related to the PI3K/AKT pathway

The PI3K/AKT pathway plays a critical role in the development of HCC.¹¹⁶ A number of tumor suppressor genes inhibit HCC development by regulating the PI3K/AKT pathway. Protocadherin-10 (PCDH10), a member of the non-clustered protocadherin family, is one such gene. The expression of PCDH10 is noticeably downregulated in HCC due to the aberrant methylation status of the PCDH10 promoter. Low expression of PCDH10 in HCC is associated with shorter survival in HCC patients.¹¹⁷ The upregulation of PCDH10 inhibits cell growth and results in cell death in HCC cells by inhibiting the PI3K/AKT signaling.¹¹⁸

Placenta-specific 8 (PLAC8), a cysteine-rich protein, is notably decreased in HCC specimens compared with adjacent normal samples.¹¹⁹ Lower expression of the PLAC8 gene is associated with poorer prognosis in HCC patients.¹²⁰ The silencing of PLAC8 in HCC promotes cell viability, growth, and tumor formation through enhancing the PI3K/AKT/GSK3 β and Wnt/ β -catenin signaling pathways.¹¹⁹

Tat-interacting protein (30 kDa) (TIP30) is another tumor suppressor gene that regulates PI3K/AKT. Decreased TIP30 expression is inversely associated with prognosis in HCC patients with HBV infection.¹²¹ The loss of TIP30 increases EMT and tumor initiation in HCC through the regulation of SNAIL.¹²² It was also reported that decreased expression of TIP30 activates the AKT/mTOR signaling pathway, which increases SREBP1 expression and leads to increased fatty acid synthesis in HCC cells.¹²³

Triggering receptor expressed on myeloid cells 2 (TREM2), a cell surface receptor, was identified as a novel tumor suppressor in HCC. Expression of TREM2 is downregulated in HCC cells and tissues.¹²⁴ MiR-31-5p downregulates the expression of TREM2 in HCC cells.¹²⁴ Reduced TREM2 expression correlates with shorter survival and aggressive pathological features in HCC patients.^{124,125} TREM2 knockdown promotes cell growth, migration, and invasiveness, while TREM2 overexpression produces the opposite effect in HCC cells by targeting the PI3K/AKT/ β -catenin pathway.¹²⁴ Consistently, Trem2^{-/-} mice develop more liver tumors after diethylnitrosamine (DEN) administration and in fibrosis-associated HCC models.¹²⁵

3.3. Suppressors related to the transforming growth factor-beta (TGF- β) pathway

The TGF- β signaling pathway plays critical roles in cell proliferation, differentiation, and survival.¹²⁶ Despite the complicated functioning of TGF- β in HCC,^{126,127} several tumor suppressor genes related to the TGF- β pathway have been identified. CXXC finger protein 5 (CXXC5) was recently discovered as a novel TGF- β target gene in HCC cells.¹²⁸ Expression of CXXC5 is substantially reduced in HCC specimens compared to adjacent normal tissues.¹²⁸

Knockdown of *CXXC5* suppresses cell proliferation and invasiveness and reverses TGF- β -induced growth suppression and cell death in HCC cells.^{128,129} Mechanistically, *CXXC5* interacts with the histone deacetylase 1 (HDAC1) and competes for this association with Smad2/3, thus abolishing the inhibitory effect of HDAC1 on TGF- β signaling.¹²⁸

Forkhead box P3 (FOXP3) is a master regulator of the regulatory pathway in the development and function of regulatory T cells.¹³⁰ Elevated *FOXP3* expression is correlated with a better prognosis. Overexpression of *FOXP3* potently suppresses HCC tumor growth and metastatic ability via enhancing the TGF- β signaling pathway.¹³¹

3.4. Tripartite motif (TRIM) family

The *TRIM* gene family, characterized by the tripartite motif, is involved in pathogen recognition and regulation of transcriptional pathways in host defenses.¹³² Recent studies have shown that many *TRIM* superfamily members play essential roles in the development of HCC. *TRIM26* is significantly decreased in HCC tissues, and low expression of *TRIM26* is associated with poor prognosis in HCC patients.¹³³ *TRIM26* silencing promotes HCC cell growth and tumor metastasis and regulates sets of genes related to metabolism in cancer cells.¹³³

Similarly, *TRIM50* expression is also significantly lower in HCC tumors than adjacent normal tissues, and its lower expression associates with poorer survival in HCC patients.¹³⁴ Overexpression of *TRIM50* suppresses cell growth and metastasis, while *TRIM50* knockdown promotes these malignant behaviors. Mechanistically, *TRIM50* directly binds to SNAIL and induces K-48 linked poly-ubiquitous degradation of SNAIL protein, thereby decreasing EMT in HCC cells.¹³⁴

TRIM7 also acts as a tumor suppressor in HCC development. TRIM7 directly interacts with SRC and induces Lys48-linked poly-ubiquitination of the latter, and the subsequent degradation of SRC protein in HCC cells.¹³⁵ Consistent with this observation, TRIM7 protein expression is negatively associated with SRC protein expression in clinical HCC specimens.¹³⁵ However, another study indicated that TRIM7 promotes HCC cell proliferation via the DUSP6/p38 pathway.¹³⁶ These controversial results warrant further studies to more precisely specify the role of TRIM7 in HCC.

4. Conclusion

HCC remains one of the most lethal malignancies worldwide because of the immense challenges in preventing, diagnosing, and treating the disease.² HCC demonstrates a high degree of heterogeneity, including multiple induced factors, genetic background, and spatio-temporal molecular diversity.¹³⁷ Despite decades of advancements in targeted therapy, the currently approved medications for advanced HCC provide patients with limited clinical benefits.^{2,138} A major barrier to drug development has been a lack of understanding of the critical drivers of oncogenesis and tumor progression.¹³⁸ Although no primary drivers have been identified in HCC progression, many oncogenes and tumor suppressor genes have been discovered to be important in HCC.¹³⁹ This review summarized newly-identified putative oncogenes (Table 1) and tumor suppressor genes (Table 2) applicable to HCC from an analysis of the most recent five years of scientific study (Fig. 1). We hope that these findings may inspire the development of novel therapeutic strategies to improve HCC patient treatment outcomes going forward.

Table 1
Oncogenes in hepatocellular carcinoma (HCC).

Gene symbols ^a	Gene names	Did function validate using knockout mouse models?	References
<i>ABL1</i>	ABL proto-oncogene 1, non-receptor tyrosine kinase	Yes	12,13
<i>ANXA3</i>	Annexin A3		20
<i>ANXA4</i>	Annexin A4		21,22
<i>ANXA2</i>	Annexin A2		23–25
<i>FAK</i>	Focal adhesion kinase	Yes	29–32
<i>FOKK1</i>	Forkhead box k1		35–37
<i>FOXR2</i>	Forkhead box R2		38
<i>FOXA3</i>	Forkhead box A3		39
<i>KIF15</i>	Kinesin family member 15		42–44
<i>KIF2C</i>	Kinesin family member 2C		45,46
<i>KIFC1</i>	Kinesin family member C1		47–50
<i>NCAPG</i>	Non-SMC condensin I complex, subunit G		53,54
<i>NCAPG2</i>	Non-SMC condensin I complex, subunit G 2		55,56
<i>NCAPH</i>	Non-SMC condensin I complex subunit H		58,59
<i>NEK2</i>	Never-in-mitosis A-related kinase 2		66,67
<i>NEK7</i>	Never-in-mitosis A-related kinase 7		69
<i>PRMT1</i>	Protein arginine methyltransferase 1	Yes	71–74
<i>PRMT2</i>	Protein arginine methyltransferase 2		75
<i>PRMT5</i>	Protein arginine methyltransferase 5		76,77
<i>SIRT1</i>	Sirtuin 1		82,83
<i>SIRT5</i>	Sirtuin 5		84,85
<i>SIRT7</i>	Sirtuin 7	Yes	87–90
<i>TRIM31</i>	Tripartite motif containing 31		92,93
<i>TRIM32</i>	Tripartite motif containing 32		94
<i>TRIM44</i>	Tripartite motif containing 44		95
<i>USP5</i>	Ubiquitin-specific protease 5		98,99
<i>USP7</i>	Ubiquitin-specific protease 7		100–102
<i>USP11</i>	Ubiquitin-specific protease 11		103,104
<i>USP13</i>	Ubiquitin-specific peptidase 13		105
<i>USP14</i>	Ubiquitin-specific peptidase 14	Yes	106–108

^a All these genes have been validated as essential for HCC tumor initiation and/or progression using *in vitro* models and/or knockout animal models.

Table 2
Tumor suppressor genes in hepatocellular carcinoma (HCC).

Gene symbols ^a	Gene names	References
CXXC5	CXXC finger protein 5	128,129
FOXP3	Forkhead box P3	131
HPCAL1	Hippocalcin-like 1	110
MKP-4	Mitogen-activated protein kinase phosphatases-4	111,112
PCDH10	Protocadherin-10	117,118
PLAC8	Placenta-specific 8	119,120
SORBS2	RBP sorbin and SH3 domain-containing 2	114,115
TIP30	Tat-interacting protein (30 kD)	121–123
TREM2	Triggering receptor expressed on myeloid cells 2	124,125
TRIM26	Tripartite motif containing 26	133
TRIM50	Tripartite motif containing 50	134
TRIM7	Tripartite motif containing 7	135,136

^a All these genes have been validated as essential for HCC tumor prevention using *in vitro* models but not knockout mouse models.

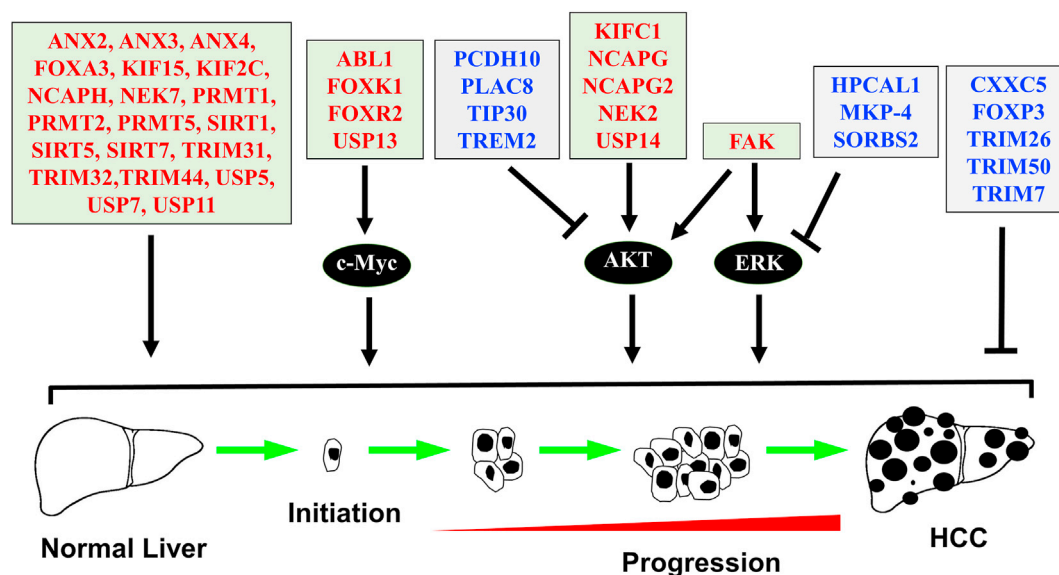


Fig. 1. Novel oncogenes and tumor suppressor genes in hepatocellular carcinoma (HCC) initiation and progression. HCC-related oncogenes (30 genes, highlighted with red) and tumor suppressor genes (12 genes, highlighted with blue) were discussed in this review. Abelson murine leukemia viral oncogene homolog 1 (ABL1), forkhead box (FOX) k1, FOXR2, and ubiquitin-specific proteases (USP) 13 function as oncogenes to promote HCC initiation and progression via regulating c-Myc. Kinesin family member C1 (KIFC1), non-structural maintenance of chromosomes condensin I complex subunit G (NCAPG), NCAPG2, never-in-mitosis A (NIMA)-related kinase (NEK) 2, and USP14 promote HCC initiation and/or progression via the regulation of the protein kinase B (AKT) signaling. Focal adhesion kinase (FAK) promotes HCC development via regulating both the AKT and extracellular signal-regulated kinase (ERK) signaling pathways. Annexin A2 (ANXA2), ANXA3, ANXA4, FOXA3, kinesin superfamily protein (KIF) 15, KIF2C, non-structural maintenance of chromosomes condensin I complex subunit H (NCAPH), NEK7, protein arginine methyltransferase (PRMT) 1, PRMT2, PRMT5, sirtuin (SIRT) 1, SIRT5, SIRT7, tripartite motif (TRIM) 31, TRIM32, TRIM44, USP5, USP7, and USP11 function as oncogenes and promote HCC initiation and/or progression via multiple mechanisms. Hippocalcin-like 1 (HPCAL1), mitogen-activated protein kinase phosphatases-4 (MKP-4), and the RBP sorbin and SH3 domain-containing 2 (SORBS2) function as tumor suppressors to suppress HCC initiation and/or progression through regulating the ERK signaling. Protocadherin-10 (PCDH10), placenta-specific 8 (PLAC8), tat-interacting protein (30KD) (TIP30), and triggering receptor expressed on myeloid cells 2 (TREM2) inhibit HCC development via regulating the AKT signaling. CXXC finger protein 5 (CXXC5), FOXP3, tripartite motif 26 (TRIM26), TRIM50, and TRIM7 suppress HCC initiation and progression through regulating multiple mechanisms, including the transforming growth factor-beta (TGF-β) signaling pathway.

Authors’ contributions

F. Wang and W. Qiu wrote the paper and made figure. P. Breslin S J critically edited the paper.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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