Wnt/β-Catenin Signaling Pathway in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide due to its high rates of tumor recurrence and metastasis. Aberrant Wnt/β-catenin signaling has been shown to play a significant role in HCC development, progression and clinical impact on tumor behavior.

Keywords: cancer metabolism ; drug resistance ; metabolic reprogramming ; hepatocellular carcinoma ; Wnt/β-catenin

1. Mutation and Expression Status of the Wnt/β-Catenin Pathway and Its Clinical Significance

Wnt/β-catenin signaling is crucial in contributing to HCC pathogenesis, where genetic mutations and epigenetic alterations are primarily revealed [1]. Activation of the Wnt/β-catenin signaling pathway was discovered in 20–35% of HCC cases, among which most are resulted by gene mutations of the key genes, including *CTNNB1*, *AXIN*, and *APC* [2][3][4]. In this case, *CTNNB1* is the gene that specifically encodes β-catenin. Mutation of β-catenin is positively related to HCC progression due to its oncogenic role [5]. To date, mutations at the serine/threonine sites of exon 3 of the β-catenin gene are mostly found to be involved in the phosphorylation and ubiquitination of β-catenin, thus enhancing its nuclear translocation in approximately 20% of HCC cases [6][7]. In addition, conventional and missense mutations have also been reported in other codons of β-catenin [8]. Previous reports showed that conventional mutations at codons 33, 37, 41, and 45 are discovered in over 12% of HCC patients, where missense mutations are observed at codons 32, 34, and 35 [8], which indicates the capability of mutated β-catenin proteins to evade degradation and enter the nucleus [6][9]. It is also noted that tumor cells with aberrant Wnt/β-catenin activation due to the mutation of β-catenin that tend to grow and spread more quickly in HCC [5].

Apart from β-catenin, deregulation of the Wnt/β-catenin signaling pathway is also caused by mutations in protein degradation complexes [10]. These mutations cause dysfunction of the destruction complex and accumulation of β-catenin in the nucleus in approximately 40–70% of HCC cases [1]. One example is the amino acid substitution in armadillo repeats domain 5/6 of β-catenin in human HCC cases [11]. This results in a reduction of APC binding to the degradation complex, which activates the Wnt/β-catenin signaling pathway and enhances targeted gene transcription [11]. It has been reported that a small amount of β-catenin accumulated in the nucleus is sufficient to activate Wnt target genes, suggesting the crucial role of β-catenin in HCC progression [12][13]. However, several studies have shown that the mutation of β-catenin alone is insufficient for promoting HCC in mice, which is different in comparison with humans [13][14], as the tumorigenic potential could be augmented when combined with other oncogenic pathways, such as H-RAS, MET, AKT, or chemicals such as diethylnitrosamine (DEN) [1][15].

In addition, high levels of E-cadherin have been reported to be correlated with the accumulation of β-catenin in both the cytosol and nucleus, that drives the transcription of Wnt target genes [16]. *C-Myc* and *cyclin D*, as key Wnt-target genes, not only perform their roles as proto-oncogenes for tumor formation but also regulate liver cancer stem cell (CSC) properties by mediating various signaling pathways involved in cellular differentiation and survival [5][6]. As previously mentioned, HBV and HCV are the causes of HCC, in which they lead to genetic mutations in genes involved in Wnt/β-catenin signaling [16][17]. It is common to find *CTNNB1* mutations in HCV-related HCC rather than HBV-related HCC or nonviral HCC [10]. However, mutation of *Axin1* is more often found in HBV-related HCC tumors [10]. Interestingly, apart from the mutations of the canonical pathway, Zucman-Rossi et al. suggested that *Axin1* mutation also plays a role in exerting oncogenic effects manifested by overexpressing glutamine synthase (GS), leading to β-catenin activation that correlates to the non-canonical pathway [18].

2. Regulation of Wnt/β-Catenin Pathway in HCC

2.1. Epigenetic Regulation of Wnt/β-Catenin

Several epigenetic dysregulations contribute to Wnt/β-catenin activation in HCC. DNA methylation is crucial in maintaining CSC properties, in which its inhibition can influence the fate of cells and gene expressions [19]. For instance, DNA methyltransferase (DNMT) plays a role in catalyzing the transition between a methyl group and DNA, mediating BEX1 expression in HCC [20]. A decrease in DNMT1 results in BEX1 hypomethylation that further enhances the transcription of β-catenin, which causes the activation of the Wnt/β-catenin signaling pathway [20]. Moreover, secreted frizzled-related proteins (SFRPs) negatively regulate Wnt/β-catenin signaling via DNA methylation, representing a leading cause of activating β-catenin activity in HCC [21]. Another study also consistently showed that downregulation of the SFRP family is correlated with Wnt/β-catenin signaling activation, in which SFRP1 and SFRP5 are also found to enhance the progression of HCC [22][23]. Similarly, downregulating Wnt inhibitory factor 1 (WIF1) or Dickkopf-related protein 3 (DKK3) has been proven to result in common consequences for SFRPs [24]. In addition, SOX17 is reported to take part in the aberrant activation of Wnt/β-catenin signaling due to promoter methylation [25]. Silencing of SOX17 could enhance Wnt activity due to the failure in interacting with TCF/LEF, which hinders Wnt-target gene transcription [26]. Apart from the genomic instability caused by DNA hypomethylation, another study showed the involvement of potassium channels in epigenetic regulation of the Wnt/β-catenin pathway [27]. Fan et al. revealed that a decrease in KCNQ1 (potassium voltage-gated channel subfamily Q member 1) causes an increment in Wnt/β-catenin activity via DNA hypermethylation [27].

Furthermore, several alterations through histone modification have been reported in HCC. Enhancer of zeste homologous 2 (EZH2) is a histone methyltransferase that plays a role in catalyzing methylation of histone H3 to achieve repression of Wnt antagonists, promoting Wnt/β-catenin signaling and hepatocarcinogenesis [28][29]. Histone deacetylases (HDAC) have been revealed to interact with EZH2 through its enzymatic role [30]. Specifically, for HDAC8, its upregulation due to the chromatin modifications is coexpressed with the lipogenic transcription factor SREBP1 in HCC mouse models, causing cell cycle arrest and β-catenin activation, which drives NAFLD-induced hepatocarcinogenesis [30]. Moreover, HDAC8 can also bind to pyruvate kinase M2 (PKM2) and subsequently deacetylate the residue K62, prompting the nuclear translocation of PKM2 and the binding of β-catenin that results in Wnt target gene transcription [31]. Similarly, EZH2 overexpression elevated the levels of the oncogene H3K27me3, which silenced Wnt inhibitors, leading to induced cell proliferation with activated β-catenin activity [28].

2.2. Non-Coding RNAs in Regulation of Wnt/β-Catenin

It has been suggested that microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are critical regulators associated with various tumors, in which they are negatively regulated [32]. Dysregulation of miRNAs and lncRNAs could lead to tumorigenesis in HCC. LncRNA-miRNA binding yields a complete endogenous RNA (ceRNA) that can avoid messenger RNA (mRNA) recognition and further silencing effects, known as the “sponge effect” [32]. Mounting evidence suggests that miRNA sponges are involved in Wnt/β-catenin signaling and are associated with HCC progression (**Table 1**). For example, LINC00355 and LINC01278 are negative regulators of miR-217-5p and miR-1258, respectively [33][34]. Overexpression of lncRNAs downregulate the corresponding miRNAs and further activates Wnt/β-catenin signaling, resulting in increased levels of Wnt target gene transcription and metastatic ability of HCC cells [33][34]. Additionally, upregulation of LINC00662 in HCC induced *WNT3A* secretion with miR-15a/16/107 binding, resulting in the activation of Wnt/β-catenin and polarizes M2 macrophage [35]. Similarly, overexpressing FEZF1-AS1 negatively regulates the level of miR-107, which inhibits the activation of Wnt/β-catenin signaling, while downregulation of FEZF1-AS1 enhances the expression of β-catenin [36]. Furthermore, both miR-122 and miR-148a were found to contribute to liver cancers by binding to the 3′-untranslated region (3′-UTR) site of *Wnt1*, suppressing the level of β-catenin and inhibiting Wnt-target gene transcription [37][38]. Furthermore, a decrease in these miRNA levels could cause excess Wnt/β-catenin signaling and increase EMT [37]. All the above mentioned enhance the progression of HCC. As a tumor suppressor, miR-34a is reported in mice and HCC patients and found to be upregulated through activated Wnt/β-catenin signaling [39]. In addition, overexpression of miR-145 has been shown to diminish the level of β-catenin, suppressing HCC cell growth [40]. To sum up, Wnt/β-catenin signaling is tightly regulated by DNA methylation, histone modification and non-coding RNAs in HCC (**Figure 1**).

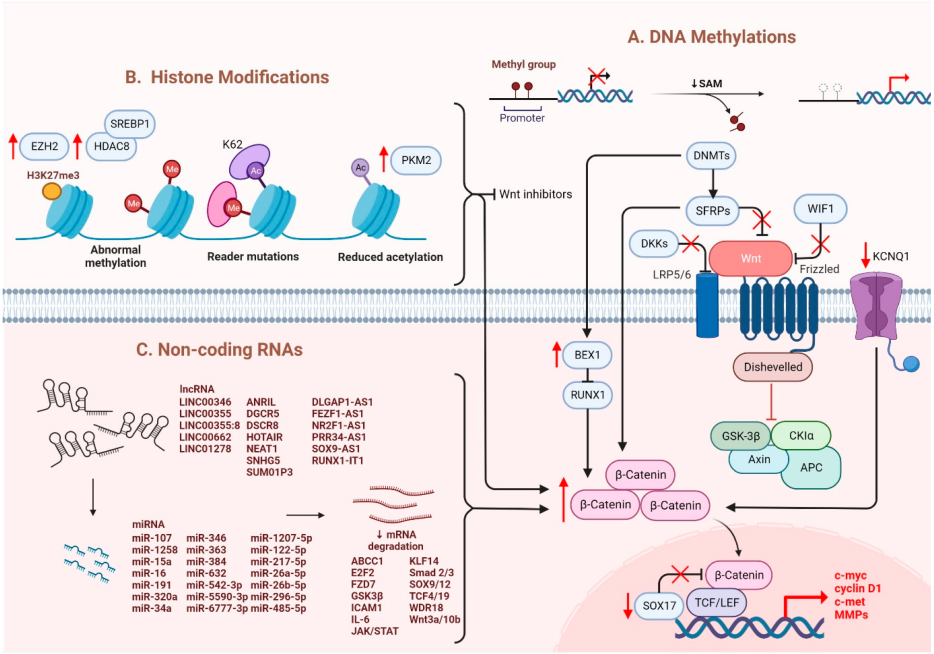

Figure 1. Regulation of Wnt/β-catenin signaling in HCC. Wnt/β-catenin signaling in HCC is regulated by (**A**) DNA methylation, (**B**) histone modification and (**C**) non-coding RNAs.

Table 1. The list of lncRNAs and their related miRNAs in regulation of Wnt/β-catenin signaling in HCC.

LncRNA	miRNA	Targets	Ref.
LINC00346	miR-542-3p	FZD7, WDR18	[41]
LINC00355	miR-217-5p	GSK3β, c-myc, CCND1	[33]
LINC00355:8	miR-6777-3p	Wnt10b	[42]
LINC00662	miR-15a, miR-16, miR-107	Wnt3a	[35]
LINC01278	miR-1258	TCF-4, Smad2/3	[34]
ANRIL	miR-191, miR-122-5p	CCND1, p53, p21, MMP-2, MMP-9, Vimentin	[43][44]
DGCR5	miR-346	KLF14	[45]
DSCR8	miR-485-5p	FZD7	[46]
DLGAP1-AS1	miR-26a-5p, miR-26b-5p	IL-6, JAK2, STAT3	[47]
FEZF1-AS1	miR-107	Wnt3a, ICAM1, Vimentin	[36]
HOTAIR	miR-34a	Akt	[48]
MIR194-2HG	miR-1207-5p	TCF19	[49]
NEAT1	miR-384	Wnt	[50]
NR2F1-AS1	miR-363	ABCC1	[51]
PRR34-AS1	miR-296-5p	E2F2, SOX12	[52]
RUNX1-IT1	miR-632	GSK3β	[53]
SNHG5	miR-26a-5p	GSK3β	[54]
SUMO1P3	miR-320a	C-myc, CCND1	[55]
SOX9-AS1	miR-5590-3p	SOX9	[56]

2.3. Other Molecules Involved in the Regulation of Wnt/β-Catenin

Apart from genetic mutations and epigenetic dysregulation, other molecules/pathways were identified to regulate Wnt/β-catenin signaling. In normoric environment, ROS is maintained at a low level; whereas a steady increase of ROS level

promotes cancer development and progression [57]. A recent study showed that Wnt/β-catenin signaling was suppressed upon elevation of intracellular ROS level [5][58]. In HCC, glutaminase 1 (GLS1) is upregulated which augmented liver CSC properties with increased expression of CSC markers via suppression of ROS level [5][58]. Likewise, another study also showed that ROS accumulation due to the overexpression of Cytochrome P450 2E1 (CYP2E1) decreased the activity of Wnt/β-catenin signaling through the degradation of DVL2 in HCC [59]. Hypoxia also plays a crucial role in the activation of Wnt/β-catenin signaling. Hypoxia-inducible factor 1-alpha (HIF1α), a hypoxia-inducible factor, regulates transcription in hypoxic environments and is also reported to mediate the expression of B-cell lymphoma 9 (BCL9) [16][60]. BCL9 can coactivate with HIF1α to enhance the transcriptional activity of β-catenin regardless of whether genetic mutations occur, resulting in activation of Wnt/β-catenin signaling and leading to HCC progression [60]. Furthermore, *ZBTB20* has been reported in liver tumorigenesis with its role in suppressing PPARG expression and inhibiting proteasomal degradation of the β-catenin destruction complex [61]. Overall, once the nuclear translocation of β-catenin is achieved, the expression levels of the downstream genes involved in EMT are modulated and enhanced, causing hepatocarcinogenesis [3]. *C-Myc* is the most critical gene induced by activated Wnt/β-catenin signaling, which enhances the mechanisms of glycolysis and glutaminolysis [62]. This is followed by cyclin D1, which has been reported to be enhanced in both mouse and human HCC [63][64]. Specifically, overexpression of c-Met and cyclin D1 triggers the development of liver tumors and decreases survival in mice [65]. It is also noted that upregulation of cyclin D1 enhances tumor metastatic ability [66]. Additionally, studies have discovered that GS and VEGF are also involved in modulating the downstream effects of activated Wnt and assisting in angiogenesis [67], as the upregulation of multiple matrix metalloproteinases (MMPs), including MMP2 and MMP9, is associated with tumor metastasis [68]. Apart from gene regulation, aberrant β-catenin signaling also negatively regulates certain signaling cascades: for example, the suppression of NF-κB cascade in the liver [69]. Moreover, the crosstalk between Wnt and Hippo signaling pathways has been observed in HCC. Recent study showed that Wnt-Hippo signature related genes may be a potential markers for prediction of immune infiltration in HCC [70]. Notably, aberrant activation of β-catenin caused by the deletion of mammalian STE20-like protein kinase 1/2 (Mst1/2) promotes tumor growth, indicating the co-expression of YAP and β-catenin in HCC [71].

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