

# Wnt/ $\beta$ -Catenin Signaling as a Driver of Hepatocellular Carcinoma Progression: An Emphasis on Molecular Pathways

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**Abstract:** Liver cancers cause a high rate of death worldwide and hepatocellular carcinoma (HCC) is considered as the most common primary liver cancer. HCC remains a challenging disease to treat. Wnt/ $\beta$ -catenin signaling pathway is considered a tumor-promoting factor in various cancers; hence, the present review focused on the role of Wnt signaling in HCC, and its association with progression and therapy response based on pre-clinical and clinical evidence. The nuclear translocation of  $\beta$ -catenin enhances expression level of genes such as c-Myc and MMPs in increasing cancer progression. The mutation of *CTNNB1* gene encoding  $\beta$ -catenin and its overexpression can lead to HCC progression.  $\beta$ -catenin signaling enhances cancer stem cell features of HCC and promotes their growth rate. Furthermore,  $\beta$ -catenin prevents apoptosis in HCC cells and increases their migration via triggering EMT and upregulating MMP levels. It is suggested that  $\beta$ -catenin signaling participates in mediating drug resistance and immuno-resistance in HCC. Upstream mediators including ncRNAs can regulate  $\beta$ -catenin signaling in HCC. Anti-cancer agents inhibit  $\beta$ -catenin signaling and mediate its proteasomal degradation in HCC therapy. Furthermore, clinical studies have revealed the role of  $\beta$ -catenin and its gene mutation (*CTNNB1*) in HCC progression. Based on these subjects, future experiments can focus on developing novel therapeutics targeting Wnt/ $\beta$ -catenin signaling in HCC therapy.

**Keywords:** liver cancer, drug resistance, immunotherapy, Wnt signaling, non-coding RNAs

## Introduction

Liver cancers are the fourth most common cancer worldwide.<sup>1,2</sup> Primary liver cancers are responsible for a major challenge in developed and developing countries and are correlated with clinical, economic, and psychological burden.<sup>3</sup> Hepatocellular carcinoma (HCC) is a troublesome problem for healthcare providers and comprises up to 85–90% of primary liver cancers. The risk factors for HCC are different based on region and country. For instance, chronic infection with hepatitis B virus (HBV), alcohol intake, and hepatitis C virus (HCV) lead to development of HCC. Risk factors are different in different countries, different genetic landscape and molecular subtype; and clinical emergence of HCC also varies based on region.<sup>4–7</sup> Antiviral treatment and HBV vaccination are considered as promising strategies to prevent HCC development.<sup>8,9</sup> Furthermore, advances in diagnosis and treatment of HCC have resulted in a significant decrease (20.3%) in mortality caused by HCC from 1990 to 2017.<sup>10</sup> There are some therapeutic strategies for HCC including liver resection, ablation and transplantation that show efficacy in

early stages of this malignant tumor. Unfortunately, in spite of advances in diagnostic methods, HCC patients are often diagnosed in advanced stages, when therapy is almost impossible.<sup>11,12</sup> Therefore, novel imaging methods should be applied in HCC diagnosis. For instance, patients who have cirrhosis, are advised to be screened in terms of HCC development.<sup>13</sup> Besides, plasma, serum, and urine can be considered valuable sources for HCC diagnosis.<sup>14</sup> Due to diagnosis of HCC at advanced stages, risk of recurrence and metastatic nature of cancer cells, HCC patients have a 5-year survival rate of less than 50%.<sup>15</sup> The incidence rate of HCC is more prevalent in developing countries compared to developed ones, so up to 85% of HCC cases are observed in Eastern Asia and Africa.<sup>11,16–18</sup> In addition to lifestyle (alcohol consumption) and environmental factors (infection) that were mentioned previously, genetic and epigenetic alterations play a key role in development of HCC.<sup>19</sup>

Recent experiments have been directed toward elucidating signaling networks involved in HCC progression and understanding their interaction as potential therapeutic targets.<sup>19,20</sup> The metastatic nature of HCC cells results in undesirable prognosis of patients. The epithelial-to-mesenchymal transition (EMT) is responsible for metastasis and migration of HCC cells.<sup>21,22</sup> Sphingosine-1-phosphate receptor-1 (S1PR1) undergoes upregulation in HCC to induce EMT-mediated migration.<sup>23</sup> The long non-coding RNA (lncRNA) SPRY4-IT1 regulates tumor necrosis factor (TNF) signaling in mediating EMT in HCC.<sup>24</sup> The matrix metalloproteinases (MMPs) also participate in invasiveness of HCC cells, so that ADAM17 induces MMP-21 expression that is in favor of increasing HCC progression.<sup>25</sup> As mentioned, lncRNAs regulate HCC progression. Notably, microRNAs (miRNAs) also affect malignancy of HCC cells. For instance, miRNA-16 and miRNA-375 undergo upregulation by thymoquinone as anti-tumor agent to suppress HCC progression.<sup>26</sup> Besides, circular RNA (circRNA)-102272 reduces expression level of miRNA-326 to enhance HCC growth and mediate their resistance to cisplatin chemotherapy.<sup>27</sup> The activation of PI3K/Akt axis enhances glycolysis of HCC cells to induce sorafenib resistance.<sup>28</sup> Each experiment provides a unique pathway that is responsible for HCC progression. For instance, SIX4 elevates migration and invasion of HCC cells via upregulating YAP1 and c-MET overexpression. Furthermore, hepatocyte growth factor as ligand of c-MET is capable of promoting SIX4 expression in aggravating HCC metastasis.<sup>29</sup> The

stabilization of STOML2 enhances PINK1 stability to induce metastasis of HCC cells and reduce their sensitivity to lenvatinib chemotherapy.<sup>30</sup> ENO1 can be transferred using exosomes to HCC cells and by enhancing integrin  $\alpha\beta4$  expression, ENO1 is involved in increasing migration and invasion.<sup>31</sup> The upregulation of SF3B1 favors HCC progression and significantly enhances survival of these malignant cells.<sup>32</sup> The interactions among signaling networks can affect HCC progression. For instance, circ-0001175 reduces miRNA-130a-5p expression to upregulate SNX5 that is of importance for promoting proliferation rate of HCC cells.<sup>33</sup> Down-regulation of RSK2 due to mutations result in MAPK signaling activation, promoting cholesterol metabolism and subsequent increase in proliferation of HCC cells.<sup>34</sup>

Therefore, a variety of genetic and epigenetic alterations can mediate the progression of HCC cells.<sup>35–38</sup> In respect to this, we allotted the present review to reveal the role of  $\beta$ -catenin signaling in HCC. First, we provided an overview of  $\beta$ -catenin signaling and its major role in oncology. Then, we examined activation of  $\beta$ -catenin in HCC and its association with proliferation, metastasis, and therapy response. Then, we shed some light on the regulation of  $\beta$ -catenin signaling in HCC by upstream mediators in which miRNAs, lncRNAs and circRNAs are the most well-known ones. Next, we demonstrated how  $\beta$ -catenin signaling can be affected via pharmacological and genetic approaches. Finally, we provided insights for clinical application of  $\beta$ -catenin as diagnostic and prognostic tool.

## Beta-Catenin: Signaling and Cancer Function

$\beta$ -catenin is encoded by *CTNNB1* gene in humans and is considered a multifunctional protein, as vertebrate homolog of *Drosophila Armadillo*.<sup>39</sup>  $\beta$ -catenin is a key member of catenin family proteins and is involved in intracellular adhesion.  $\beta$ -catenin is a part of Wnt signaling and participates in physiological processes including embryonic development and tissue homeostasis. Notably,  $\beta$ -catenin can function as a transcription activator upon coupling with T cell factor/lymphoid enhancer factor (TCF/LEF) proteins with capacity to bind to DNA.<sup>40</sup> Structurally,  $\beta$ -catenin in humans consists of 781 amino acids that have a central structural core containing 12 armadillo repeats and intrinsically disordered N- and C-terminal regions.<sup>41</sup> There is a positively charged groove in 12 superhelical armadillo repeats that provides a binding site for  $\beta$ -catenin

cooperators including TCF, Axin and APC.<sup>42</sup> The N-terminal domain can undergo phosphorylation by casein kinase-1 (CK-1) and glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), determining  $\beta$ -catenin stability. The C-terminal domain is responsible for interacting with transcriptional co-activators and co-repressors.<sup>43,44</sup> The biological investigations revealed that armadillo repeat domains are essential for interaction of  $\beta$ -catenin with its ligands. In fact, armadillo repeats provide protein-protein interaction capacity of  $\beta$ -catenin and its ability to form complexes. It has been reported that  $\beta$ -catenin can produce complexes with APC, Axin, ICAT, LEF1, TCF3, TCF4 and BCL9.<sup>45</sup>

Normally,  $\beta$ -catenin is present in cytoplasmic side of adherence junctions in epithelial cells with close contact with cadherins complex.<sup>46</sup> However, cytoplasmic  $\beta$ -catenin undergoes ubiquitination to be degraded by proteasomal route.<sup>47,48</sup> Therefore, the first impact of Wnt ligands is to enhance stability of  $\beta$ -catenin protein and prevent its degradation.<sup>49</sup> The Wnt ligands can bind to FZD-LRP5/6 receptors on surface of cells to prevent phosphorylation of  $\beta$ -catenin and mediate its dissociation from destruction complex.<sup>50</sup> The destruction complex consists of GSK-3 $\beta$ , Adenomatous polyposis coli (APC), Axin and CK1 that mediate proteasomal degradation of  $\beta$ -catenin protein.<sup>51</sup> Therefore, Wnt ligands inhibit  $\beta$ -catenin degradation, enhance its accumulation in cytoplasm, and mediate its nuclear translocation, where  $\beta$ -catenin can bind to transcription factors including TCF-LEF family.<sup>47,52–54</sup> This is called canonical or  $\beta$ -catenin dependent pathway of Wnt signaling (Figure 1).

The tumor-promoting role of  $\beta$ -catenin in different cancers has been revealed.  $\beta$ -catenin is able to reduce expression of miRNA-455-3p in mediating m6A modification of HSF1. Then, nuclear translocation of  $\beta$ -catenin occurs to enhance colorectal cancer progression.<sup>55</sup> UBE2T is able to induce ubiquitination of RACK1 at the lysine K172 to enhance its degradation, leading to activation of Wnt/ $\beta$ -catenin and subsequent increase in gastric cancer progression.<sup>56</sup>  $\beta$ -catenin signaling also participates in drug resistance feature of cancer cells.<sup>57</sup>  $\beta$ -catenin is able to stimulate autophagy and mediate temozolomide resistance of glioblastoma.<sup>58</sup> Furthermore, 5-fluorouracil (5-FU) increases stemness of colorectal tumor cells by triggering Wnt/ $\beta$ -catenin axis.<sup>59</sup> lncRNA SNHG11 interacts with Cullin 4A to mediate ubiquitination and degradation of GSK-3 $\beta$ , resulting in Wnt/ $\beta$ -catenin activation.<sup>60</sup> The interesting point is the interaction of  $\beta$ -catenin with the immune system. The expression level of programmed

death-ligand 1 (PD-L1) undergoes upregulation by  $\beta$ -catenin to reduce cytotoxicity and infiltration of CD8+ T cells, resulting in immune evasion of glioblastoma cells.<sup>61</sup> The inhibition of Wnt/ $\beta$ -catenin signaling by ISG12a leads to PD-L1 inactivation and subsequent cytotoxicity of natural killer (NK) cells.<sup>62</sup> Furthermore,  $\beta$ -catenin inhibition along with immunotherapy synergistically suppress colorectal tumor progression.<sup>63</sup> The Wnt/ $\beta$ -catenin axis can also promote migration and invasion of cancer cells via mediating EMT mechanism.<sup>64</sup> The knock-down of lncRNA AFAP1-AS1 by nanostructures can suppress  $\beta$ -catenin signaling to promote potential of radiotherapy in breast cancer suppression.<sup>65</sup> Hence,  $\beta$ -catenin has an oncogenic role and its inhibition should be performed to delay tumor growth.

## Beta-Catenin and Hepatocellular Carcinoma

### Beta-Catenin Expression Status and Mutation: Clinical Association

As  $\beta$ -catenin has an oncogenic role, its expression level should undergo upregulation in HCC. Furthermore,  $\beta$ -catenin mutation is an obvious finding that has been confirmed in various experiments.<sup>66,67</sup> An experiment has evaluated association between  $\beta$ -catenin mutation and HCC progression. This study demonstrated positive association between  $\beta$ -catenin mutation and high-grade differentiation in HCC. Furthermore,  $\beta$ -catenin mutation significantly enhances pseudoglandular proliferation and bile production in HCC.<sup>68</sup> Due to abnormal localization and  $\beta$ -catenin mutation, the generation of truncated  $\beta$ -catenin proteins increases, which favors HCC development.<sup>69</sup> Both conventional and missense mutations are able to affect  $\beta$ -catenin expression in HCC and mediate its progression. It has been reported that conventional mutations in codons 33, 37, 41 and 45 are observed in 12.8% of HCC patients. Other missense mutations can occur in codons 32, 34 and 35. Therefore, conventional and other missense mutations in *CTNBB1* gene can enhance  $\beta$ -catenin expression and trigger its nuclear translocation.<sup>70</sup> Another experiment has revealed somatic mutation of  $\beta$ -catenin in 12% of HCC cases. These mutations occurred in exon 3 that affects phosphorylation and ubiquitination of  $\beta$ -catenin, leading to a significant increase in its stability and expression. Furthermore, gene mutation results in increased nuclear translocation of  $\beta$ -catenin protein occurring in 17% of HCC cases. Finally,

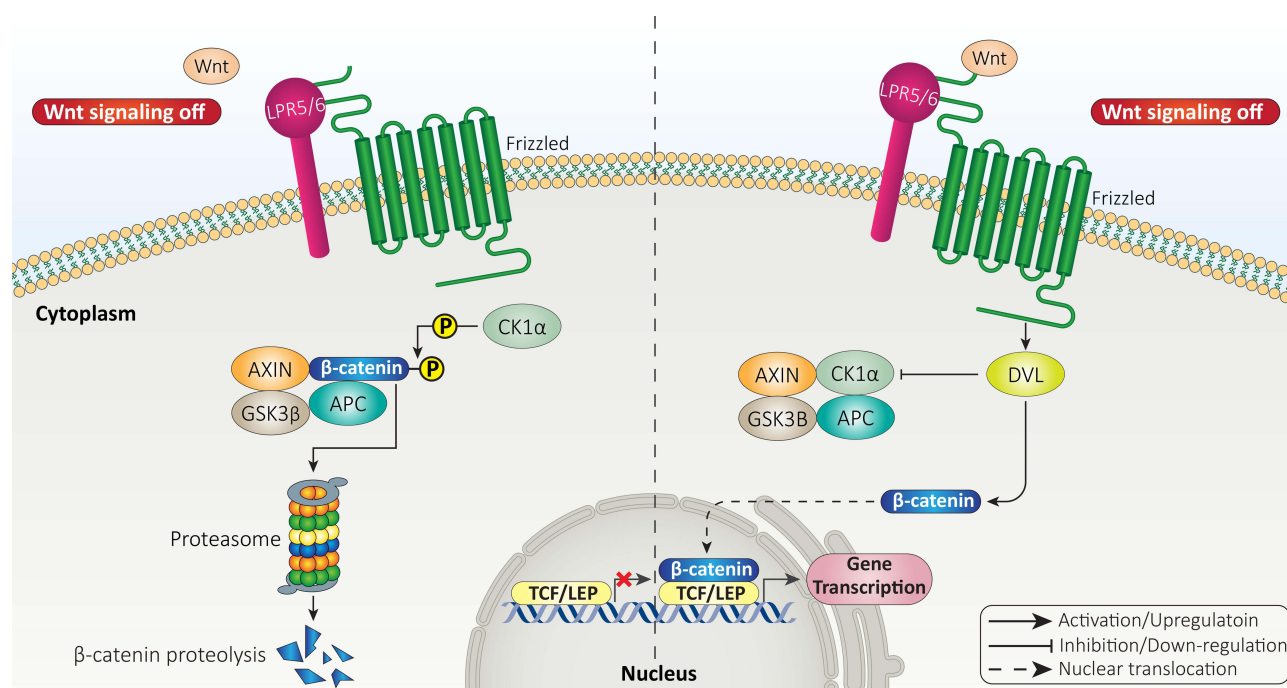
a nonnuclear type overexpression of  $\beta$ -catenin (cytoplasm or cytoplasmic membrane overexpression) can occur, showing that  $\beta$ -catenin upregulation in HCC is heterogeneous.<sup>71</sup>

As exon 3  $\beta$ -catenin mutation is common in HCC and enhances its progression, glutamine synthase staining can be utilized for its detection.<sup>72</sup> Another experiment has evaluated  $\beta$ -catenin mutation in Chinese people. The mRNA expression of  $\beta$ -catenin gene exon 3 undergoes overexpression in HCC compared to para-cancerous and normal liver tissues. The mutation of  $\beta$ -catenin occurs in 44.1% of HCC cases in Chinese people and its enhanced accumulation in cytoplasm or nucleus is observed in 61.8% of HCC cases.<sup>73</sup> However, an experiment provided contradictory results, showing that  $\beta$ -catenin mutation impairs HCC progression. This study revealed that cytokeratin 19 (CK19) overexpression leads to HCC progression and  $\beta$ -catenin mutation reduces its carcinogenesis impact.<sup>74</sup> Although this study provided controversial findings, it needs more investigation to show whether  $\beta$ -catenin mutation favors HCC progression or not. Furthermore, the incidence rate of  $\beta$ -catenin mutation varies based on region, race, and country. For instance,  $\beta$ -catenin mutation occurs in China, Japan and Europe, but its mutation does not occur in Southern African blacks with HCC.<sup>75</sup> The mutation of CTNNB1 gene occurs in

18.1% of cases of HCC, based on a new experiment, and its mutation frequency is higher in non-viral HCC (29.4%) compared to HBV-related cases (12.4%). There is a missense point mutation found in exon 3 of CTNNB1 gene with higher frequency in codons 32, 33, 38 and 45.<sup>76</sup> Notably, CTNNB1 gene mutation shows positive response with immune inhibitors in HCC. It also affects infiltration of neutrophils and natural killer cells in tumor microenvironment. Therefore, it can be considered as a reliable biomarker for HCC response to immunotherapy.<sup>77</sup> Next generation sequencing (NGS) seems to be beneficial in clinical course and for treatment of HCC patients, as it can provide predictions about advantages of immunotherapy in HCC patients. The mutation in CTNNB1 and abnormal activation of Wnt/ $\beta$ -catenin signaling reduce response of HCC patients to immune checkpoint inhibitors.<sup>78</sup> Hence, two conclusions can be made, first,  $\beta$ -catenin mutation should be highlighted based on region and race; second, most of the experiments demonstrated oncogenic role of  $\beta$ -catenin mutation in HCC.<sup>79–84</sup>

## Beta-Catenin and Cancer Stem Cells

Cancer stem cells (CSCs), also known as tumor-initiating cells, share similar features with normal stem cells, including self-renewal and differentiation capacities.<sup>85,86</sup> CSCs



**Figure I** The canonical pathway of Wnt signaling.



were first identified in acute myeloid leukemia and it was found that they can increase number of colony-formation capacitors.<sup>87</sup> CSCs are responsible for developing heterogeneous feature of tumors and is in contrast with conventional belief that tumor heterogeneity is mediated by genetic and epigenetic alterations.<sup>88,89</sup> CSCs have been isolated from various tumors including glioma, lung cancer, breast cancer, and liver cancer.<sup>90,91</sup> CSCs are recognized with a number of cellular markers including CD133, CD44, LGR5 and ALDH1, among others.<sup>92</sup> The CSCs play a significant role in increasing progression of HCC cells, and  $\beta$ -catenin is among the pathways that mediate stemness. Protein tyrosine kinase 2 (PTK2) is considered a tumor-promoting factor in HCC that enhances viability and survival rate of HCC cells and induces their sorafenib resistance. Furthermore, PTK2 elevates CSC features of HCC via activating Wnt signaling and promoting nuclear translocation of  $\beta$ -catenin.<sup>93</sup>

The macrophages that infiltrate tumor microenvironment (TME) are known as tumor-associated macrophages (TAMs).<sup>94</sup> Based on their stimulation by cytokines or chemokines, TAMs are divided into two major kinds, M1 and M2 macrophages. The M1 phenotype macrophages demonstrate tumor-suppressor activity, while M2 phenotype macrophages are able to secrete cytokines to enhance immune evasion, progression and angiogenesis.<sup>95,96</sup> A recent experiment revealed that M2 phenotype macrophages secrete tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) that subsequently promotes stemness and EMT in HCC. Investigation of molecular pathways revealed that M2 macrophage-derived TNF- $\alpha$  can induce Wnt/ $\beta$ -catenin signaling to promote CSC characteristics of HCC.<sup>97</sup> The positive association between  $\beta$ -catenin and HCC stemness has a clinical implication. It has been reported that increased stemness of HCC, due to  $\beta$ -catenin, predicts recurrence of this malignant condition.<sup>98</sup> Therefore, after treatment of HCC by chemotherapy, radiotherapy or immunotherapy, special attention should be directed toward complete eradication of CSCs in HCC and inhibiting  $\beta$ -catenin signaling to minimize risk of recurrence.

There is a close association between redox status and Wnt signaling in HCC. It is obvious that enhanced ROS generation can reduce viability of HCC cells via mediating apoptosis.<sup>99,100</sup> A recent experiment has shed more light on the role of ROS in HCC. It was reported that ROS overgeneration can suppress Wnt/ $\beta$ -catenin axis in decreasing survival rate of HCC cells. Glutaminase 1 (GLS1) is suggested to undergo upregulation in HCC

and be correlated with undesirable prognosis. GLS1 mediates clinicopathological characteristic of HCC and enhances stemness and CSC features. Upon GLS1 overexpression, the levels of stem cell markers such as KLF4, SOX2, Nanog, Oct4 and CD44 undergo an increase in expression. In this way, GLS1 reduces ROS levels to induce Wnt signaling and mediate nuclear translocation of  $\beta$ -catenin which favors HCC stemness.<sup>101</sup> As mentioned in the introduction section, GSK-3 $\beta$  is a negative regulator of Wnt signaling and inhibits its activation via mediating proteasomal degradation of  $\beta$ -catenin.<sup>102</sup> Recently, a novel pathway was revealed in which GSK-3 $\beta$  is inhibited to induce Wnt signaling. In this way, secretory clusterin (sCLU) increases expression level of protein kinase-B (Akt) as a tumor-promoting factor in HCC. Then, Akt induces GSK-3 $\beta$  phosphorylation to mediate its proteasomal degradation. Finally, this axis results in nuclear translocation of  $\beta$ -catenin and subsequent increase in stemness and CSC features of HCC that are of importance for mediating drug resistance (sorafenib resistance).<sup>103</sup> The diterpenoid ovatodiolide as anti-cancer agent, inhibits Wnt/ $\beta$ -catenin axis to impair CSC features of HCC cells and disrupt their progression.<sup>104</sup> Therefore,  $\beta$ -catenin signaling can be considered a novel target in HCC therapy and for reducing its stemness.

The role of ROS in regulating Wnt/ $\beta$ -catenin axis has been highlighted in another experiment. Aquaporin-9 (AQP9) shows low expression in CSCs and is able to diminish stemness. In this way, AQP9 induces ROS overgeneration to suppress  $\beta$ -catenin signaling, leading to a significant decrease in CSC features.<sup>105</sup> Besides, activation of  $\beta$ -catenin signaling can mediate transformation of hepatic progenitor cells to CSCs.<sup>106</sup> Hence, molecular pathways are divided into two major kinds, including tumor-suppressor and tumor-promoting factors that regulate  $\beta$ -catenin signaling in affecting CSC features of HCC cells. Future experiments will shed more light on signaling networks regulating  $\beta$ -catenin signaling in HCC.

## Beta-Catenin, Cancer Proliferation, and Migration

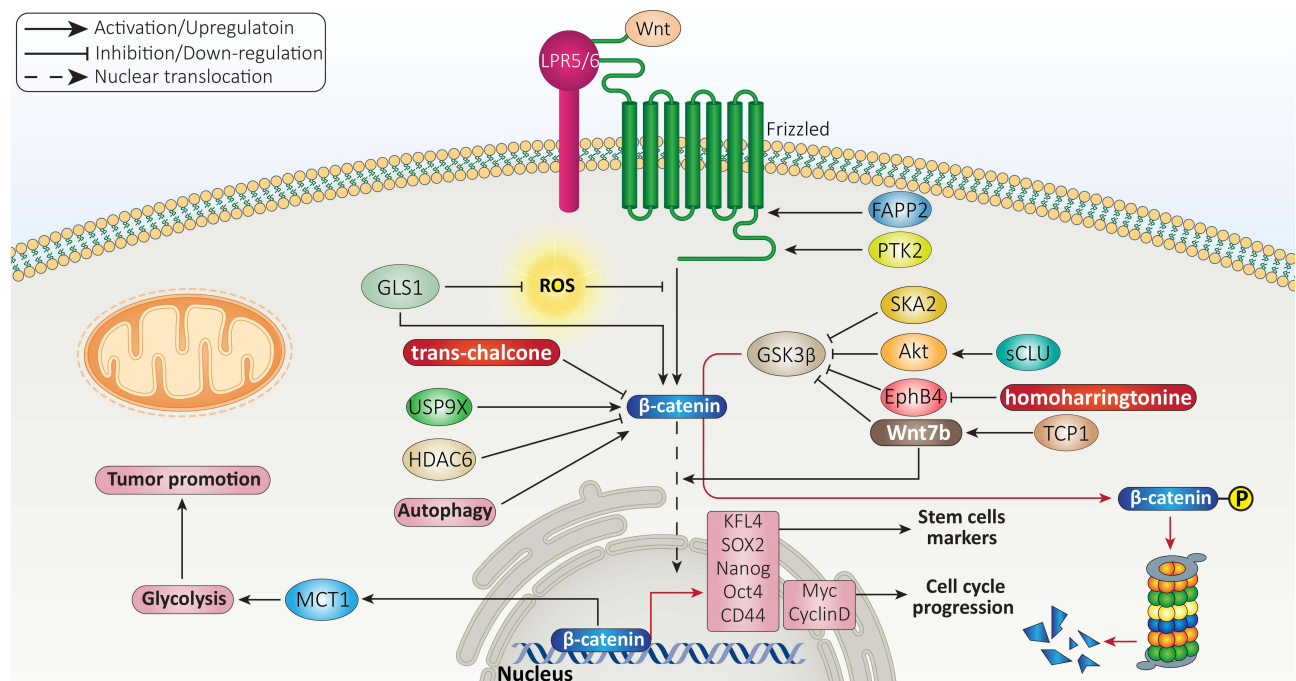
HCC cells have high capacity for proliferation and enhancing their number, mediating their aggressive behavior.<sup>107,108</sup> Microscopically, HCC demonstrates four distinct kinds of growth profiles including trabecular, pseudoglandular, solid and microtubular.<sup>109</sup> Various molecular pathways participate in enhancing proliferation rate

of HCC cells. For instance, COL4A1 is able to induce FAK/Src axis in elevating proliferation of HCC.<sup>110</sup> Hepatic stellate cells present in HCC can secrete GDF15 in increasing cancer growth.<sup>111</sup> Oxysophocarpine, as anti-tumor agent, inhibits STAT3 pathway to impair HCC progression and promotes anti-tumor immunity via mediating CD8+ T cell cytotoxicity.<sup>112</sup> As  $\beta$ -catenin has a tumor-promoting role, its activation enhances proliferation rate of HCC cells. Spindle and kinetochore-associated protein 2 (SKA2) shows overexpression in HCC and its silencing significantly diminishes capacity of HCC cells in colony formation and growth. Mechanistically, SKA2 induces phosphorylation of GSK-3 $\beta$  to mediate its degradation, leading to induction of  $\beta$ -catenin signaling and increased HCC growth.<sup>113</sup> Identification of factors affecting  $\beta$ -catenin signaling in HCC is of interest for developing novel therapeutics in the near future. For instance, phosphatidylinositol 4-phosphate adaptor protein 2 (FAPP2) mediates HCC carcinogenesis in vitro and in vivo via inducing Wnt/ $\beta$ -catenin axis. Targeting FAPP2 and reducing its expression result in  $\beta$ -catenin inactivation and reduced HCC progression.<sup>114</sup> Notably, there have been efforts in discovery of anti-tumor compounds capable of targeting  $\beta$ -catenin signaling in HCC therapy. In HCC patients, there is a positive association between EphB4 and  $\beta$ -catenin expression that promotes cancer progression. It has been reported that homoharringtonine down-regulates EphB4 expression to mediate phosphorylation and degradation of  $\beta$ -catenin, impairing HCC progression.<sup>115</sup> The trans-chalcone is another anti-tumor agent that can reduce  $\beta$ -catenin expression in impairing proliferation of HCC cells.<sup>116</sup> These examples were provided to show how  $\beta$ -catenin activation and inactivation can affect survival rate and growth of HCC cells and in the next sections, we specifically discussed targeting  $\beta$ -catenin with anti-cancer agents in HCC therapy.

Various ligands for Wnt signaling have been identified. A recent experiment has shown that Wnt7b ligand inhibits destruction complex activity (GSK-3 $\beta$ /APC/AXN) to prevent  $\beta$ -catenin phosphorylation and mediate its nuclear translocation. In the nucleus,  $\beta$ -catenin increases expression level of Myc and Cyclin D1 to promote cell cycle progression and increase growth of HCC cells. TCPI can function as upstream mediator of Wnt7b. Reducing TCPI expression diminishes Wnt7b and  $\beta$ -catenin expressions. Therefore, overexpression of TCPI is vital for  $\beta$ -catenin activation and increasing proliferation rate of HCC cells.<sup>117</sup>

USP9X is a deubiquitinating enzyme evolutionary conserved from *Drosophila* to humans.<sup>118,119</sup> The protein transportation, apoptosis, autophagy, cell growth and invasion are among biological mechanisms modulated by USP9X.<sup>120–122</sup> Recently, attention has been directed toward the role of USP9X in tumor cells. Overexpression of USP9X leads to cisplatin resistance of cancers and its suppression promotes drug sensitivity via inactivating  $\beta$ -catenin signaling.<sup>123</sup> There is also a close association between USP9X and  $\beta$ -catenin in HCC. USP9X enhances proliferation of HCC cells and is correlated with undesirable prognosis. At molecular level, USP9X induces  $\beta$ -catenin signaling to mediate HCC progression.<sup>124</sup> Therefore, mediating GSK-3 $\beta$  degradation and triggering  $\beta$ -catenin nuclear translocation can significantly enhance proliferation rate of HCC cells.<sup>125</sup> Besides, activation of  $\beta$ -catenin signaling induces resistance of HCC cells toward apoptosis.<sup>126</sup> Histone deacetylase 6 (HDAC6) acts as tumor-suppressor and diminishes  $\beta$ -catenin expression to induce apoptosis in HCC cells.<sup>127</sup> In addition to apoptosis, another programmed cell death mechanism, known as autophagy, is affected by  $\beta$ -catenin signaling in HCC. Briefly, autophagy is induced in cells to preserve homeostasis via degrading toxic and aged macromolecules and organelles. The autophagy function in cancer is controversial and no absolute recommendation can be made about activating or inactivating autophagy, as it has both tumor-suppressor and tumor-promoting roles.<sup>128–130</sup> A recent experiment has shown that autophagy induction enhances proliferation rate of HCC cells and mediates glycolysis. In this way, autophagy stimulates  $\beta$ -catenin signaling to increase expression level of monocarboxylate transporter 1 (MCT1), resulting in glycolysis-mediated HCC growth.<sup>131</sup> In this case, autophagy plays a tumor-promoting role and its inhibition impairs growth of HCC cells. An experiment has designed FH535 as a small molecule inhibitor of Wnt signaling. Exposing HCC cells to FH535 inhibits  $\beta$ -catenin to impair autophagy flux, leading to reduced HCC growth.<sup>132</sup> Overall,  $\beta$ -catenin is an oncogenic signaling in HCC and various signaling networks regulate its expression and nuclear translocation that can be the focus of future experiments (Figure 2).

The migration of HCC to distant organs is a complicated process and a variety of molecular pathways can regulate it, and  $\beta$ -catenin is one among them. The mutations and amplifications in genes are responsible for uncontrolled proliferation of HCC cells which was discussed in the previous section. When HCC cells grow,



**Figure 2**  $\beta$ -catenin association with stemness and proliferation rate of HCC cells.

they require a large amount of energy. Therefore, new vessels are formed to meet needs of HCC cells for energy. The HCC cells are able to degrade basement membrane to enhance their invasion and enter into circulatory system. In the blood circulation, the HCC cells should be able to escape immune surveillance and upon reaching new site, they colonize and new TME provides condition for rapid proliferation of HCC cells.<sup>133,134</sup>  $\beta$ -catenin signaling enhances metastasis of HCC cells via upregulating pyruvate dehydrogenase kinase isoenzyme 1 (PDK1) to stimulate Warburg effect. As a tumor-suppressor, PARP $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) suppresses Wnt/ $\beta$ -catenin axis via upregulating PARP $\gamma$  to impair PDK1 activation and suppress Warburg effect, leading to decreased HCC metastasis.<sup>135</sup> This experiment correlated Warburg effect and metastasis of HCC cells. However, Warburg effect is related to growth and glycolysis of HCC cells and if the authors have associated it with migration, it may be related to angiogenesis induction after Warburg effect to meet needs of HCC cells for energy. Therefore, more experiments should be performed in this case to highlight the relationship between Warburg effect and metastasis in HCC and role of  $\beta$ -catenin signaling.

Akt can function as upstream mediator of GSK-3 $\beta$  in cancers. For instance, Akt induces  $\beta$ -catenin signaling via down-regulating GSK-3 $\beta$  to enhance pancreatic cancer

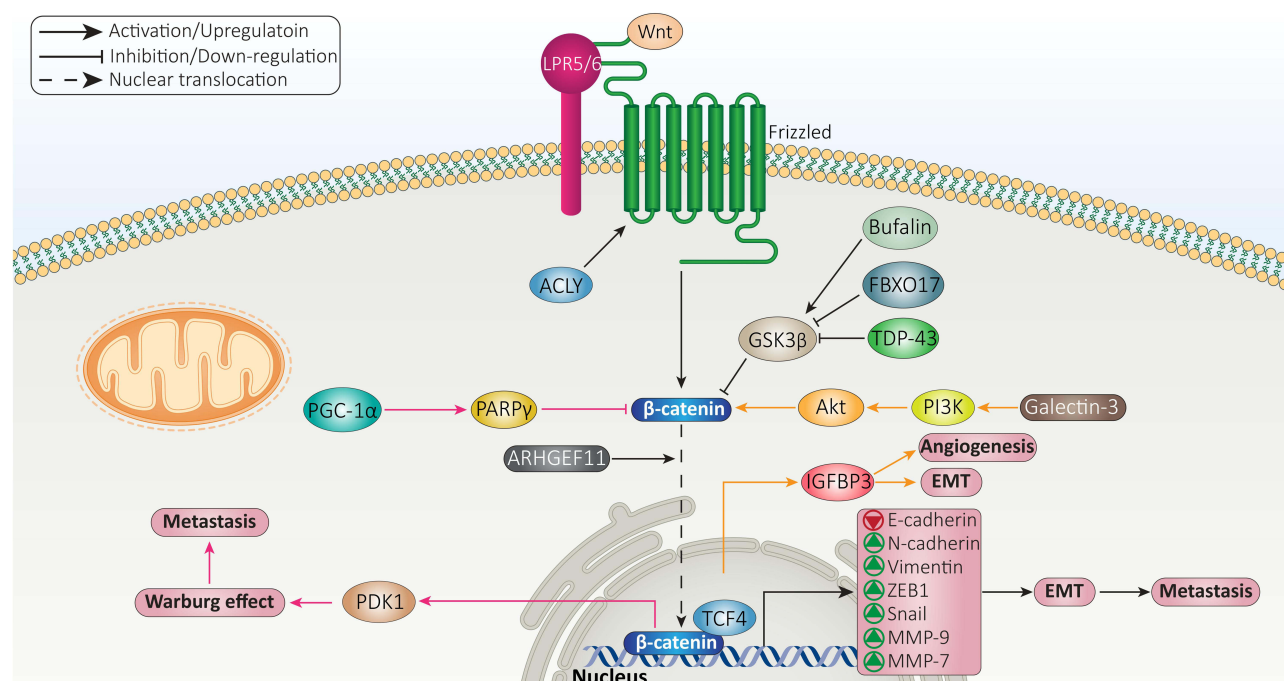
progression and induce drug resistance.<sup>136</sup> The same phenomenon also occurs in HCC, so galectin-3 increases migratory ability of HCC cells via inducing  $\beta$ -catenin signaling. In this way, galectin-3 induces phosphoinositide 3-kinase (PI3K)/Akt axis to stimulate  $\beta$ -catenin signaling via mediating GSK-3 $\beta$  degradation. Then,  $\beta$ -catenin interacts with TCF4 in nucleus to enhance expression level of IGFBP3, leading to angiogenesis and EMT in HCC.<sup>137</sup>

The most well-known factor responsible for enhancing migration and invasion of HCC cells, is EMT. Briefly, EMT is induced by EMT-inducing transcription factors (EMT-TFs) such as ZEB proteins (ZEB1/2), Snail, Slug and TGF- $\beta$ .<sup>138,139</sup> Furthermore, EMT is characterized by enhanced levels of vimentin and N-cadherin, and decreased levels of E-cadherin.<sup>140</sup> The induction of EMT in HCC significantly promotes metastasis and is mediated by various molecular pathways including miRNAs, SSR2 and ID1.<sup>141–144</sup> Recent experiments have shed some light on the association between  $\beta$ -catenin signaling and EMT in HCC cells. The trans-activation response DNA-binding protein of 43 kDa (TDP-43) is suggested to suppress translation of GSK-3 $\beta$  to induce Wnt/ $\beta$ -catenin axis. Then,  $\beta$ -catenin stimulates EMT and significantly enhances migration of HCC cells.<sup>145</sup> The molecular pathways that induce EMT are associated with unfavorable prognosis. For instance, ATP-citrate lyase (ACLY) shows

overexpression in HCC and is correlated with undesirable prognosis. ACLY induces canonical pathway of Wnt by mediating acetylation of  $\beta$ -catenin on Lys49, resulting in EMT-mediated metastasis of HCC cells.<sup>146</sup> The reduction of E-cadherin levels and enhanced vimentin and N-cadherin levels are mediated by  $\beta$ -catenin signaling in triggering EMT in HCC.<sup>147</sup> Noteworthy,  $\beta$ -catenin can also affect EMT-TFs in mediating EMT in HCC cells. Rho guanine nucleotide exchange factor 11 (ARHGEF11) stimulates nuclear translocation of  $\beta$ -catenin to enhance expression level of ZEB1, resulting in EMT induction and enhanced metastasis of HCC cells.<sup>148</sup> Furthermore, PI3K/Akt signaling mediates nuclear translocation of  $\beta$ -catenin via mediating GSK-3 $\beta$  degradation, resulting in Snail overexpression and EMT induction in HCC. Silencing PI3K/Akt axis results in GSK-3 $\beta$  overexpression, subsequent inhibition of  $\beta$ -catenin and prevents Snail/EMT in HCC.<sup>149</sup> Overall, increasing evidence has revealed a positive association of  $\beta$ -catenin with HCC metastasis and its capacity in triggering EMT.

In addition to EMT, matrix metalloproteinases (MMPs) also participate in increasing migration and invasion of cancer cells. Overall, MMPs are endopeptidases and their aberrant expression is observed in a variety of diseases including inflammation, fibrosis, tumors, and arthritis.<sup>150</sup> The expression level of MMPs can be modulated at

translational, transcriptional and post-transcriptional levels. Tissue inhibitors of MMPs (TIMPs) are considered suppressors of MMPs in cells.<sup>150,151</sup>  $\beta$ -catenin signaling shows interaction with MMPs in HCC that tightly regulates metastasis of these cells. MMP-9 is a target of  $\beta$ -catenin signaling that mediates progression of HCC cells. Furthermore,  $\beta$ -catenin induces EMT in promoting progression of HCC. As an anti-cancer agent, arctigenin suppresses Wnt/ $\beta$ -catenin axis and enhances GSK-3 $\beta$  expression to inhibit EMT in HCC and reduce MMP-9 expression in impairing migration.<sup>152</sup> MMP-7 is another factor that undergoes upregulation by  $\beta$ -catenin signaling to mediate HCC metastasis and migration. The administration of bufalin results in inhibiting phosphorylation of GSK-3 $\beta$  at Ser9 residue, leading to  $\beta$ -catenin degradation, suppressed Wnt signaling, down-regulated MMP-7 expression and subsequent decrease in migration and invasion of HCC cells.<sup>153</sup> In fact, activation of Wnt signaling and nuclear translocation of  $\beta$ -catenin are necessary for enhancing MMP expression and triggering HCC migration. A recent experiment has shown function of FBXO17 as a tumor-promoting factor in HCC. FBXO17 mediates nuclear translocation of  $\beta$ -catenin via down-regulating GSK-3 $\beta$  to increase expression level of its target genes including MMP-2 and MMP-9, resulting in HCC metastasis (Figure 3).<sup>154</sup>



**Figure 3**  $\beta$ -catenin signaling in regulation of HCC metastasis.



## Beta-Catenin and Therapy Response

In respect to role of  $\beta$ -catenin in mediating resistance feature to various therapies, this section focused on revealing  $\beta$ -catenin interaction with other molecular pathways in immune and drug resistance. The mutation in *CTNNB1* gene encoding  $\beta$ -catenin mediates low infiltration of cytotoxic immune cells at tumor microenvironment and poor clinical response of HCC cells to immunotherapy.<sup>155</sup> The suppression of  $\beta$ -catenin signaling along with anti-PD-1 therapy can exert a synergistic impact on HCC therapy. For this purpose, small interfering RNA (siRNA) was loaded on extracellular vesicles (EVs) as nanoparticles to mediate targeted delivery of siRNA, leading to down-regulation of  $\beta$ -catenin and subsequent enhancement in capacity of anti-PD-1 immunotherapy.<sup>156</sup> In HCC cells that are resistant to anti-tumor immunity, increasing expression level of CCL5 promotes immune surveillance and prevents immune escape caused by  $\beta$ -catenin signaling. The HCC cells that demonstrate high expression level of  $\beta$ -catenin are resistant to anti-PD-1 therapies. In mediating immune evasion feature of HCC cells,  $\beta$ -catenin signaling impairs recruitment of dendritic cells and decreases activity of T cells.<sup>157</sup> These studies highlight the role of  $\beta$ -catenin signaling in triggering immune evasion in HCC cells and subsequent strategies should focus on suppressing  $\beta$ -catenin expression in increasing anti-tumor immunity.

The participation of  $\beta$ -catenin signaling in chemoresistance feature of HCC cells is complex. The first reason is that a wide variety of molecular pathways have been recognized as upstream and downstream targets of  $\beta$ -catenin in mediating drug resistance, and second,  $\beta$ -catenin targets various mechanisms in HCC cells such as their metabolism, proliferation and migration to affect their response to chemotherapy. For instance, gankyrin is suggested to induce metabolic reprogramming of HCC cells to enhance carcinogenesis and mediate their migration and invasion. The underlying molecular pathway is overexpression of  $\beta$ -catenin by gankyrin that subsequently induces c-Myc signaling in triggering drug resistance.<sup>158</sup> The stimulation of Wnt/ $\beta$ -catenin axis was observed in 14.4% of HCC patients in a cohort study. The HCC patients with high expression level of  $\beta$ -catenin showed undesirable prognosis, confirming clinical association of Wnt signaling. Further investigation revealed that activation of  $\beta$ -catenin signaling by Akt leads to development of a subpopulation of cells with stem cell features and high

expression of CD44 that mediate chemoresistance.<sup>159</sup> Therefore,  $\beta$ -catenin can affect both metabolism and stem cell features of HCC cells in exerting their resistance to chemotherapy.

The upstream molecular pathways that can enhance stability of  $\beta$ -catenin are associated with drug resistance in HCC. Nek2 is considered a tumor-promoting factor in HCC and its overexpression prevents ubiquitination of  $\beta$ -catenin to increase its stability, leading to sorafenib resistance. Silencing Nek2 in xenograft tumor results in  $\beta$ -catenin inhibition and subsequent sorafenib sensitivity.<sup>160</sup> As drug resistance is an increasing challenge in HCC, experiments have focused on combination therapy. A combination of sorafenib (10 mg/kg) and refametinib (15 mg/kg) synergistically suppressed tumor growth in vivo (xenografts) and impaired proliferation of HCC cells that are attributed to suppressing Wnt/ $\beta$ -catenin axis.<sup>161</sup> Previously, it was mentioned that  $\beta$ -catenin signaling activation leads to enhanced CSC features in HCC. CDK1 increases PDK1 expression to induce  $\beta$ -catenin signaling which favors HCC progression. CDK1 overexpression is observed in 46% of HCC cases and is correlated with undesirable prognosis. The CDK1/PDK1/ $\beta$ -catenin axis increases CSC characteristics of HCC cells via upregulating Oct4, SOX2 and Nanog. Besides, this axis increases HCC migration via EMT induction and mediates cell cycle progression. As a CDK1 inhibitor, RO3306 down-regulates PDK1 expression to inhibit  $\beta$ -catenin signaling, leading to sorafenib sensitivity of HCC cells via EMT inhibition, decreased CSC features and impairing cell cycle progression (inhibiting S phase progression and enhancing number of cells in Sub-G1 phase).<sup>162</sup> These studies clearly demonstrate association between  $\beta$ -catenin and CSC feature, migration, proliferation, metabolism and cell cycle regulators in HCC in affecting therapy response.

Prospero-related homeobox 1 (PROX1) is a modulator of developmental and biological processes<sup>163</sup> and recently its role in cancer has been highlighted. The overexpression of PROX1 leads to enhanced migration and invasion of HCC cells via hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ) upregulation.<sup>164</sup> Notably, PROX1 can be involved in mediating sorafenib resistance of HCC cells. PROX1 elevates expression level of  $\beta$ -catenin by binding to its promoter and triggers its nuclear translocation which favors increasing HCC growth and progression, resulting in sorafenib resistance.<sup>165</sup> The anti-tumor compounds that promote drug sensitivity of HCC cells are able to affect  $\beta$ -catenin

signaling. The interaction between  $\beta$ -catenin and TCF in nucleus is of importance for increasing expression levels of ZEB1, c-Myc and cyclin D1 to induce EMT in HCC cells exposed to doxorubicin (DOX). Salinomycin administration is suggested to be beneficial in enhancing FOXO3a expression to interfere with  $\beta$ -catenin and TCF interaction, leading to EMT inhibition and increased drug sensitivity of HCC cells.<sup>166</sup>

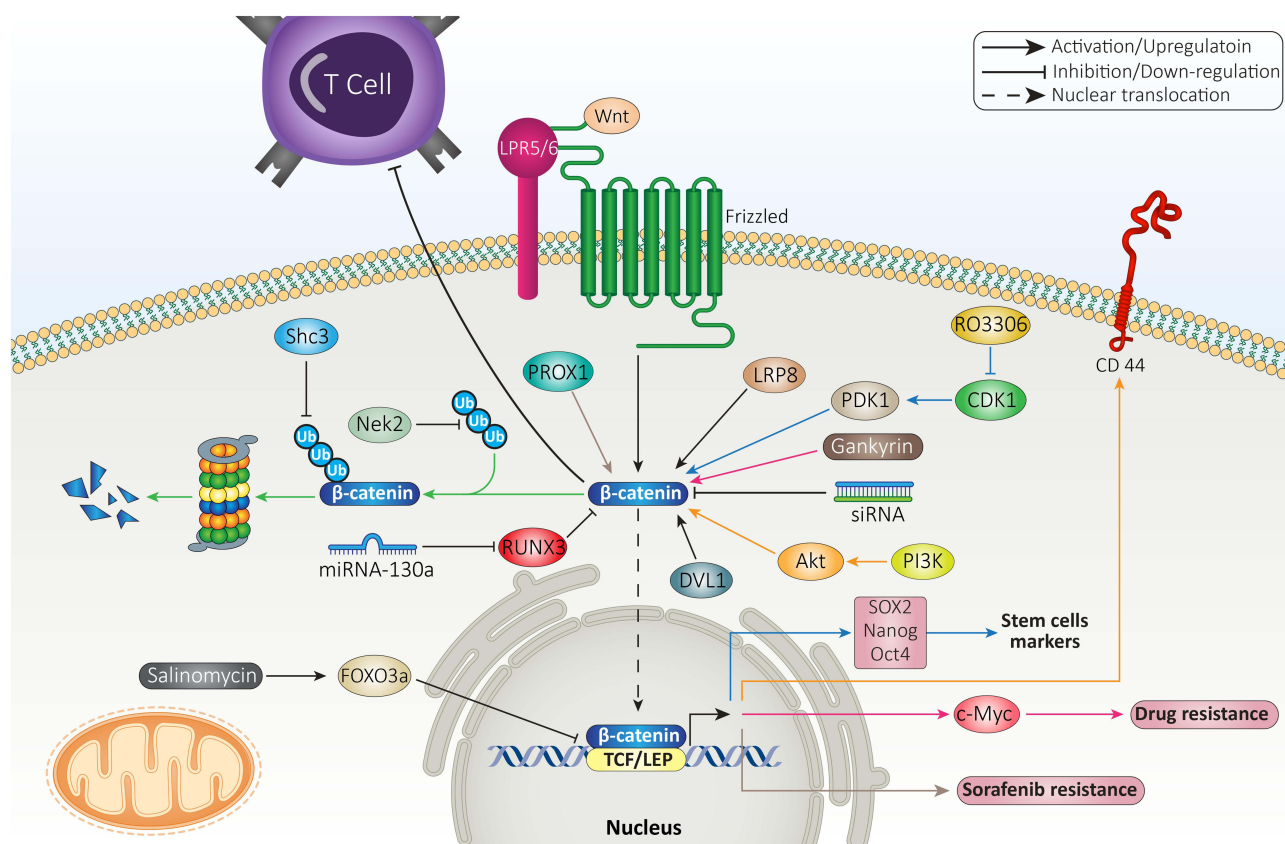
The previous sections revealed the potential role of  $\beta$ -catenin in stimulating the growth and metastasis of HCC cells to mediate their drug resistance and in this way,  $\beta$ -catenin interacts with various signaling networks. The drug efflux transporters are another option that can be considered in HCC. ATP-binding transporters (ABC) are the most well-known factors involved in mediating chemoresistance in HCC and they pump out anti-tumor agents to reduce their intracellular accumulation.<sup>167</sup> On the other hand,  $\beta$ -catenin signaling can function as upstream mediator of ABC transporters. Inhibition of  $\beta$ -catenin pathway enhances drug sensitivity via ABC transporter down-regulation.<sup>168</sup> In HCC cells, FZD7 induces Wnt/ $\beta$ -catenin signaling to enhance levels of ABC transporters (ABCB1,

ABCC1 and ABCC2), resulting in DOX and rhodamine-123 resistance. Quercetin administration as anti-tumor agent, inhibits Wnt/ $\beta$ -catenin signaling via FZD7 down-regulation to reduce levels of ABCB1, ABCC1 and ABCC2. Then, an increase occurs in drug sensitivity of HCC cells.<sup>169</sup> These experiments highlight the potential role of  $\beta$ -catenin signaling in mediating chemoresistance in HCC, confirmed by in vitro and in vivo experiments (Figure 4).<sup>170,171</sup> Table 1 summarizes the role of  $\beta$ -catenin signaling in therapy resistance of HCC cells.

## NcRNAs Regulating Beta-Catenin

### MicroRNAs

miRNAs can be found in various parts of genome, intragenic and intergenic. These non-coding RNAs (ncRNAs) have 19–24 nucleotides in length and can regulate gene expression at post-transcriptional level.<sup>172,173</sup> The miRNAs are able to decrease expression level of target gene by binding to 3'-untranslated region (3'-UTR). Sometimes, miRNAs bind to 5'-UTR and increase expression of target genes.<sup>174</sup> Regardless of their biological function, miRNAs have been implicated in development



**Figure 4**  $\beta$ -catenin signaling determines therapy response of HCC cells.

**Table I** The Oncogenic Function of  $\beta$ -Catenin in Mediating Therapy Resistance of HCC Cells

Therapy Resistance	Signaling Network	Remarks	Refs
5-Fluorouracil resistance	DVL1/Wnt	Overexpression of DVL1 in HCC cells Inducing $\beta$ -catenin signaling Triggering drug resistance	[269]
Sorafenib resistance	LRP8/ $\beta$ -catenin	Overexpression LRP8 in Huh7 cells Triggering $\beta$ -catenin signaling Apoptosis inhibition	[270]
Cisplatin resistance	miRNA-130a/RUNX3/Wnt	Increased expression level of miRNA-130a Down-regulating RUNX3 expression Inducing Wnt/ $\beta$ -catenin axis Mediating drug resistance	[271]
Immune resistance	$\beta$ -catenin	Triggering immune evasion Defective recruitment of dendritic cells Impairing T-cell activity	[157]
Sorafenib resistance	Gankyrin/ $\beta$ -catenin/c-Myc	Triggering metabolic reprogramming Enhancing growth and metastasis of HCC cells Inducing $\beta$ -catenin signaling Upregulation of c-Myc	[158]
Sorafenib resistance	PROX1/ $\beta$ -catenin	Increasing proliferation rate of HCC Overexpression of PROX1 in drug resistant cells Inducing nuclear translocation of $\beta$ -catenin	[165]
Sorafenib and doxorubicin resistance	Shc3/ $\beta$ -catenin	Increasing stemness feature of cancer cells Enhanced expression of Shc3 Inhibiting proteasomal degradation of $\beta$ -catenin	[272]

**Abbreviations:** DVL1, disheveled-1; LRP8, low density lipoprotein receptor-related protein 8; miRNA, microRNA; RUNX3, Runt-related transcription factor 3; HCC, hepatocellular carcinoma; PROX1, Prospero homeobox 1.

of various diseases. The aberrant expression of miRNAs occurs in cancers and in this case, miRNAs are divided into two groups including tumor-promoting and tumor-suppressor ones.<sup>174</sup> Recently, attention has been directed toward the role of miRNAs in HCC as biomarkers and how their expression profile undergoes alterations. The tumor-suppressor miRNAs reduce expression level of  $\beta$ -catenin by binding to its 3'-UTR.<sup>175</sup> The expression level of miRNAs with anti-tumor activity significantly diminishes in HCC tissues. The USP22 increases growth and metastasis of HCC cells via inducing Wnt/ $\beta$ -catenin signaling. Mechanistically, miRNA-329-3p reduces USP22 expression to suppress  $\beta$ -catenin signaling and improve prognosis of HCC.<sup>176</sup> These two experiments revealed that miRNAs can affect  $\beta$ -catenin signaling in HCC in two ways by directly binding to 3'-UTR of  $\beta$ -catenin or affecting its upstream mediators.

miRNA-466 is a new emerging miRNA in HCC with tumor-suppressor activity. miRNA-466 reduces expression

level of ROCK2 to impair metastasis of HCC cells.<sup>177</sup> miRNA-466 stimulates apoptosis and decreases growth capacity of HCC cells via down-regulating metadherin expression.<sup>178</sup> miRNA-466 can also affect Wnt/ $\beta$ -catenin signaling in HCC. Increasing miRNA-466 expression triggers apoptosis and diminishes growth and migration of HCC cells. At molecular level, miRNA-466 decreases FMNL2 expression to inhibit  $\beta$ -catenin signaling.<sup>179</sup> Notably, miRNA/ $\beta$ -catenin axis can also be affected by anti-tumor agents. A recent has revealed anti-tumor activity of astragaloside IV in HCC therapy. Exposing HCC cells to astragaloside IV (0–200  $\mu$ g/mL) increases expression level of miRNA-150-5p to induce apoptosis in HCC cells. Then, overexpressed miRNA-150-5p binds to 3'-UTR of CTNNB1 to inhibit  $\beta$ -catenin.<sup>180</sup>

miRNA-26b is another tumor-suppressor factor in HCC. Increasing evidence has revealed the role of miRNA-26b in decreasing HCC growth and metastasis, increasing anti-tumor immunity, and suppressing

angiogenesis.<sup>181–183</sup> Zinc ribbon domain-containing 1 (ZNRD1) is suggested to enhance progression of HCC in vitro and in vivo via inducing  $\beta$ -catenin signaling. miRNA-26b overexpression reduces ZNRD1 expression to impair Wnt/ $\beta$ -catenin axis, reducing growth and metastasis of HCC cells.<sup>184</sup> miRNA-342 and miRNA-186 can suppress  $\beta$ -catenin signaling via reducing expression levels of CXCL12 and MCERS1, respectively to impair HCC progression.<sup>185,186</sup>

On the other hand, there are tumor-promoting miRNAs that significantly enhance HCC progression. For increasing HCC progression, miRNAs can affect upstream mediators of  $\beta$ -catenin that reduce its expression. SOX transcription factors are able to regulate various molecular pathways in cancer and they possess both tumor-suppressor and tumor-promoting functions.<sup>187–190</sup> A recent experiment has shown that miRNA-19a-3p and miRNA-376c-3p can elevate progression of HCC cells via reducing SOX6 expression to induce Wnt/ $\beta$ -catenin signaling.<sup>191</sup> Furthermore, there are feedback loops that can regulate expression level of miRNAs targeting  $\beta$ -catenin signaling. The upregulation of miRNA-5188 is correlated with undesirable prognosis of HCC patients and its targeting (inhibition) can promote sensitivity of cancer cells to chemotherapy. Hepatitis X protein (HBX) is suggested to enhance expression level of miRNA-5188 in HCC. Then, overexpressed miRNA-5188 down-regulates FOXO1 expression to induce Wnt/ $\beta$ -catenin signaling, leading to EMT induction and c-Jun overexpression. Due to the presence of positive feedback loop, upregulated c-Jun also enhances miRNA-5188 expression to accelerate HCC progression.<sup>192</sup> The miRNA/ $\beta$ -catenin axis can significantly enhance growth and migration of HCC cells. miRNA-629-5p binds to 3'-UTR of secreted frizzled-related protein-2 (SFRP2) to diminish its expression. Then,  $\beta$ -catenin activation occurs and promotes both growth and migration of HCC cells.<sup>193</sup> The miRNA/ $\beta$ -catenin axis can be attributed to EMT induction and increasing HCC metastasis.<sup>194</sup> The capacity of miRNA/ $\beta$ -catenin axis in increasing HCC growth can be related to upregulating c-Myc and cyclin D1 expressions.<sup>195</sup>

In the previous section, it was discussed that Akt can function as upstream mediator of  $\beta$ -catenin signaling and induce its overexpression. miRNA-96 shows upregulation in HCC, while FOXO1 undergoes down-regulation, demonstrating their tumor-promoting and tumor-suppressor functions, respectively. FOXO1 inhibition by miRNA-96 significantly enhances growth rate and migration of HCC

cells. By FOXO1 down-regulation, miRNA-96 induces Akt phosphorylation to inhibit GSK-3 $\beta$  activity, resulting in nuclear translocation of  $\beta$ -catenin.<sup>196</sup> Another experiment revealed a novel pathway affected by miRNAs in enhancing HCC progression. ST7L is suggested to interact with carboxy terminal region of Akt to reduce its expression. miRNA-23b, as tumor-promoting factor, diminishes ST7L expression to induce Akt signaling, leading to GSK-3 $\beta$  inhibition and subsequent  $\beta$ -catenin-mediated HCC progression.<sup>197</sup> For activating  $\beta$ -catenin signaling, miRNA-500a can directly bind to 3'-UTR of GSK-3 $\beta$  to reduce its expression.<sup>198</sup> Therefore, the following key points can be concluded:

1. the miRNAs are divided into two groups capable of inhibiting or inducing  $\beta$ -catenin signaling,
2. the miRNAs can directly bind to  $\beta$ -catenin,
3. upstream mediators of  $\beta$ -catenin such as FOXO1 and GSK-3 $\beta$  can be affected by miRNAs to indirectly target  $\beta$ -catenin signaling,
4. anti-tumor compounds can affect miRNA/ $\beta$ -catenin axis,
5. the miRNA/ $\beta$ -catenin axis modulates growth, migration, and drug sensitivity of HCC cells.

### Long Non-Coding RNAs

Although it was first believed that lncRNAs are biologically inactive, these ncRNAs can modulate gene expression at transcription, post-transcriptional, and chromatin levels and have more than 200 nucleotides.<sup>199,200</sup> DNA methylation, histone modification and chromatin remodeling are affected by lncRNAs at epigenetic level.<sup>201,202</sup> Interaction of lncRNAs with DNA or transcriptional factors mediates lncRNA function at transcriptional level.<sup>203,204</sup> At post-transcriptional level, lncRNAs interact with proteins or mRNA. Recently, lncRNAs have been under noticed in cancer and they can affect growth, invasion, and therapy response of tumor cells.<sup>172,205</sup> lncRNAs possess valuable functions in HCC. For instance, lncRNA NBR2 can inhibit tumor-promoting autophagy in impairing HCC growth.<sup>206</sup> In contrast, lncRNA SNHG14 diminishes expression level of PTEN to increase HCC cell viability.<sup>207</sup> Besides, miRNAs can be affected by lncRNAs in HCC.<sup>208</sup> The current section focused on lncRNA and  $\beta$ -catenin interaction in HCC. HCC cells secrete Wnt ligands to induce  $\beta$ -catenin signaling and mediate polarization of macrophages into M2 phenotype.<sup>209</sup> Besides, differentiation of monocytes to



macrophages is modulated by  $\beta$ -catenin signaling.<sup>210</sup> A recent experiment has evaluated how lncRNA and  $\beta$ -catenin association can affect macrophage phenotype in HCC cells. LINC00662 is considered a tumor-promoting lncRNA that shows overexpression in HCC and is correlated with undesirable prognosis. As the first step, lncRNA LINC00662 decreases expression levels of miRNA-15a, miRNA-16 and miRNA-107. Then, an increase occurs in secretion of WNT3A to induce  $\beta$ -catenin signaling, leading to enhanced growth and migration of HCC cells and suppressing apoptosis. In a paracrine manner, LINC00662 stimulates  $\beta$ -catenin signaling in macrophages to mediate their M2 polarization, enhancing HCC proliferation and migration.<sup>211</sup> The lncRNA Linc00210 can increase self-renewal and tumor-initiating capacity of HCC cells via activating  $\beta$ -catenin signaling. In this way, Linc00210 inhibits CTNNBIP1 to induce Wnt/ $\beta$ -catenin signaling and provide its interaction with TCF/LEF complex in nucleus. Knock-down of Linc00210 inhibits HCC progression in vitro and in vivo.<sup>212</sup> The ligands of  $\beta$ -catenin signaling are under tight regulation by lncRNAs. The lncRNA FAM83H-AS1 is able to stimulate  $\beta$ -catenin signaling by increasing WNT1 expression in HCC.<sup>213</sup>

Identification of tumor-promoting lncRNAs targeting  $\beta$ -catenin signaling in HCC can pave the way to its treatment. EMT induction and apoptosis inhibition are mediated by lncRNA OGFRP1 via inducing Wnt/ $\beta$ -catenin signaling in HCC. Silencing OGFRP1 inactivates  $\beta$ -catenin signaling, impairing cell cycle progression, inducing apoptosis, and suppressing EMT-mediated metastasis of HCC.<sup>214</sup> lncRNA and miRNA interaction commonly occurs in HCC. The lncRNA ASB16-AS1 functions as tumor-promoting factor and increases growth and migration. miRNA-1827 functions at the opposite side and decreases FZD4 in HCC. ASB16-AS1 diminishes miRNA-1827 expression via sponging to upregulate FZD4, leading to  $\beta$ -catenin activation and increased HCC progression.<sup>215</sup> To date, a wide variety of upstream regulators of  $\beta$ -catenin signaling have been identified. CDK8 and LRP6 are considered inducers of  $\beta$ -catenin signaling. A recent experiment has revealed that lncRNA DLGAP1-AS1 increases expression levels of CDK8 and LRP6 to induce  $\beta$ -catenin signaling. Then, overexpressed  $\beta$ -catenin triggers EMT via reducing E-cadherin levels and enhancing vimentin, N-cadherin and Twist levels to promote HCC metastasis.<sup>216</sup> Therefore, lncRNAs stimulating  $\beta$ -catenin can significantly increase HCC progression.

On the opposite side, there are tumor-suppressor lncRNAs that prevent  $\beta$ -catenin signaling activation. PRDX4 is considered an inducer of  $\beta$ -catenin signaling in HCC to enhance EMT-mediated metastasis. lncRNA TP53TG1 stimulates PRDX4 degradation via mediating its ubiquitination, leading to  $\beta$ -catenin inactivation and subsequent inhibited EMT.<sup>217</sup> The lncRNA NEF is another tumor-suppressor factor that minimizes EMT in HCC. For this purpose, NEF interacts with GSK-3 $\beta$  to induce  $\beta$ -catenin phosphorylation and degradation, resulting in EMT inhibition.<sup>218</sup> In addition to metastasis, apoptosis is also regulated by lncRNA/ $\beta$ -catenin axis in HCC. The lncRNA ANCR shows down-regulation in HCC cells and tissues and it has a negative association with tumor size and lymph node metastasis. Investigation of molecular pathways revealed that ANCR enhances GSK-3 $\beta$  expression to inhibit  $\beta$ -catenin signaling. Furthermore, ANCR decreases Wnt1 expression to suppress  $\beta$ -catenin. These impacts lead to upregulation of Bax and caspase-3 in triggering apoptosis in HCC. Besides, ANCR inhibits EMT via affecting  $\beta$ -catenin signaling.<sup>219</sup> It should be noted that results of one study cannot be similarly translated to other experiments. In fact, it cannot be concluded that when a certain lncRNA suppresses  $\beta$ -catenin signaling in HCC, it will also inhibit  $\beta$ -catenin in other cancer types. A recent experiment has shown that lncRNA CASC2c suppresses  $\beta$ -catenin signaling in HCC and gastric cancer, while it induces  $\beta$ -catenin signaling in colorectal cancer.<sup>220</sup> Overall, the following keynotes can be concluded:

1. most of the studies have focused on tumor-promoting lncRNAs,
2. the miRNAs can be affected by lncRNAs in targeting  $\beta$ -catenin signaling,
3. although there are experiments showing that lncRNA/ $\beta$ -axis affects growth and invasion of HCC cells, there is no study about impact of drug sensitivity that can be the focus of future experiments,
4. finally, miRNAs can be considered as diagnostic and prognostic tools in HCC.

### CircRNAs

CircRNAs are another category of ncRNAs that were first recognized in plant studies.<sup>221</sup> CircRNAs have low expression in cells and they were first believed to be a result of RNA splicing.<sup>222</sup> CircRNAs are stable in multiple tissues and body fluids.<sup>217,223</sup> They lack protein encoding capacity and they have a closed loop structure.<sup>224</sup> Recent studies

have revealed the role of circRNAs in HCC. A variety of molecular pathways including miRNAs, Raf1, PDK1 and RAB1A are modulated by circRNAs in HCC. The proliferation and migration of HCC cells are affected by circRNAs. Furthermore, circRNAs can regulate HCC response to chemotherapy.<sup>225</sup> The following sections describe how circRNA and  $\beta$ -catenin interaction can determine HCC progression.

CircRNAs are divided into two types in HCC including tumor-promoting and tumor-suppressor. The most well-known pathway for affecting  $\beta$ -catenin signaling by circRNAs in HCC is to target miRNAs. hsa-circRNA-104348 enhances HCC proliferation and migration, and its knock-down sensitizes cancer cells to apoptosis. Mechanistically, stimulation of Wnt/ $\beta$ -catenin signaling by circRNA-104348 mediates its carcinogenesis impact in HCC.<sup>226</sup> circ-DENND4C is suggested to diminish expression level of miRNA-195-5p in HCC. Then, over-expression of transcription factor 4 (TCF4) occurs, resulting in  $\beta$ -catenin induction and apoptosis inhibition.<sup>227</sup> As it was mentioned in the introduction section, *CTNNB1* gene encodes  $\beta$ -catenin in HCC. circZFR decreases miRNA-3619-5p expression via sponging to enhance *CTNNB1* expression, resulting in Wnt signaling activation. Then,  $\beta$ -catenin induces EMT to increase migration and invasion of HCC cells.<sup>228</sup>

FZD5 is considered an oncogene in HCC. FZD5 over-expression can occur in an m6A-dependent manner that subsequently induces  $\beta$ -catenin signaling in increasing HCC progression.<sup>229</sup> A recent experiment has shown that circ-0067934 down-regulates miRNA-1324 expression to increase FZD5 expression. Next, FZD5 triggers  $\beta$ -catenin signaling to dually elevate growth and invasion of HCC cells.<sup>230</sup> Furthermore,  $\beta$ -catenin signaling induction by circRNA ZNF292 prevents apoptotic cell death and increases cell cycle progression via S phase.<sup>231</sup>

The previous statements revealed the role of tumor-promoting circRNAs in HCC. Similar to other ncRNAs, experiments have also recognized circRNAs capable of suppressing  $\beta$ -catenin signaling in HCC. circRNA-ITCH is suggested to decrease expression levels of miRNA-7 and miRNA-214 in suppressing  $\beta$ -catenin signaling, resulting in apoptosis induction and decreased colony formation capacity.<sup>232</sup> miRNA-626 induces  $\beta$ -catenin signaling in HCC via down-regulating DKK3 expression. As tumor-suppressor, hsa-circ-0004018 diminishes miRNA-626 expression to promote DKK3 expression. Then,  $\beta$ -

signaling inhibition occurs and HCC carcinogenesis is suppressed.<sup>233</sup>

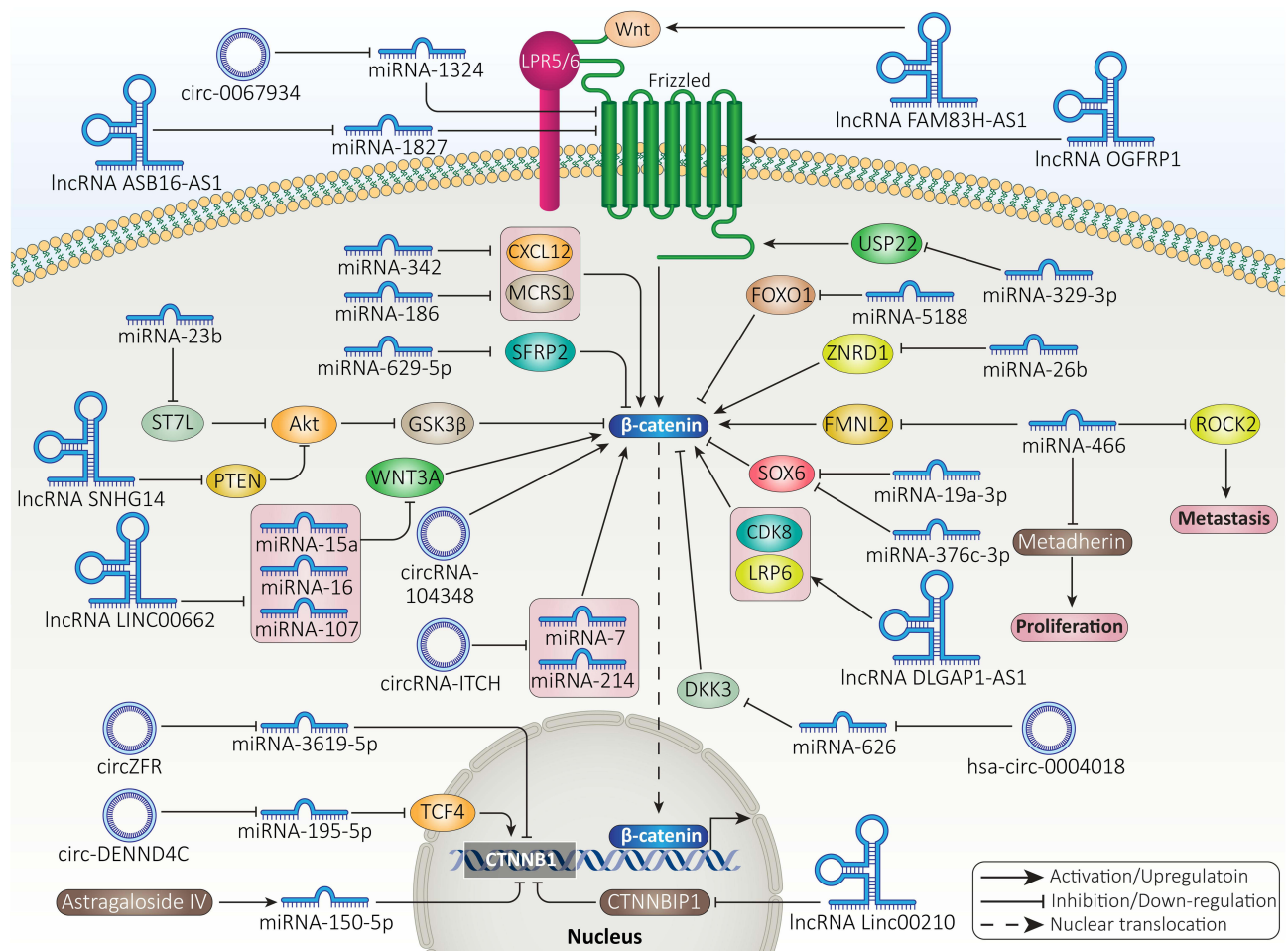
Cisplatin (CP) is a chemotherapeutic agent belonging to platinum compounds, capable of inhibiting DNA function, enhancing reactive oxygen species (ROS) levels and apoptosis induction.<sup>234–236</sup> One of the challenges in HCC therapy is the emergence of CP resistance, and overexpression of Nrf2 and HIF-1 $\alpha$  can lead to this condition.<sup>237</sup> The inhibition of PI3K/Akt axis by miRNA-27a-3p results in enhanced CP cytotoxicity against HCC cells.<sup>238</sup> The expression level of circ-0003418 undergoes down-regulation in HCC cells and tissues. Enhancing circ-0003418 expression suppresses Wnt/ $\beta$ -catenin axis to increase CP cytotoxicity.<sup>210</sup> Overall, the following keynotes can be concluded:

1. circRNAs mainly affect miRNAs in targeting  $\beta$ -catenin signaling.
2. Therapy response and progression of HCC cells are regulated by circRNA/ $\beta$ -catenin axis.

Figure 5 and Table 2 demonstrate the role of ncRNAs in regulating  $\beta$ -signaling in HCC.

## Pharmacological Targeting of Beta-Catenin

Due to the oncogenic role of  $\beta$ -catenin signaling in HCC, efforts have been made in targeting this pathway. To date, wide varieties of pharmacological compounds have been applied in HCC suppression via targeting different signaling cascades, including  $\beta$ -catenin signaling. Most of these anti-cancer agents are plant-derived, natural compounds which can modulate cancer progression,<sup>239–242</sup> and some of them are synthetic agents. As the first step, anti-tumor agents are able to decrease expression level of  $\beta$ -catenin. Then, Wnt signaling inhibition occurs, leading to a significant reduction in growth and metastasis of HCC cells.<sup>243</sup> Furthermore, anti-cancer agents can enhance expression level of GSK-3 $\beta$  to induce proteasomal degradation of  $\beta$ -catenin, resulting in a significant decrease in its cytoplasmic and nuclear levels.<sup>244</sup> At another stage, anti-cancer agents can affect upstream mediators of  $\beta$ -catenin signaling in HCC. For instance, propofol has been suggested to enhance expression level of miRNA-219-5p in impairing growth and migration of HCC cells. As a result, overexpressed miRNA-219-5p decreases glypican-3 expression to suppress Wnt/ $\beta$ -catenin signaling. The



**Figure 5** The ncRNAs modulate  $\beta$ -catenin signaling in HCC.

reduced invasion results from EMT inhibition.<sup>245</sup> Finally, it has been reported that urolithin B as anti-cancer agent, can inhibit nuclear translocation of  $\beta$ -catenin signaling in HCC.<sup>246</sup> Therefore,  $\beta$ -catenin signaling is affected in four stages including its expression level, GSK-3 $\beta$  upregulation for mediating its degradation and affecting upstream signaling pathways as well as inhibiting its cytoplasm to nuclear translocation.

Sevoflurane (Sevo) is a volatile anesthetic agent that has shown anti-tumor activity via apoptosis induction, triggering cell cycle arrest and metastasis inhibition.<sup>247</sup> Sevo is able to promote miRNA-29a expression to down-regulate Dnmt3a, impairing HCC growth.<sup>248</sup> In HCC cells, Sevo decreases expression level of miRNA-25-3p to induce PTEN signaling. Then, PTEN inhibits Akt to enhance GSK-3 $\beta$  expression, leading to  $\beta$ -catenin signaling inhibition and a decrease in expression level of its downstream targets including c-Myc and MMP-9.<sup>249</sup> In

addition to PTEN, MARCH1 can function as regulator of PI3K/Akt signaling in HCC. Exposing HepG2 cells to secalonin acid-F (SAF) is correlated with a significant decrease in MARCH1 expression. Besides, MARCH1 down-regulation by siRNA exerts similar anti-tumor effects. By down-regulation of MARCH1, SAF prevents PI3K/Akt signaling, leading to  $\beta$ -catenin inhibition and decreased HCC progression.<sup>250</sup> One of the interesting points is the anti-tumor activity of anesthetic agents. Similar to Sevo, propofol is an anesthetic agent that has been able to inhibit cancer progression via regulating molecular pathways such as miRNAs.<sup>226,251,252</sup> HMGA2 increases growth and metastasis of HCC cells via inducing Wnt/ $\beta$ -catenin signaling. In a concentration-dependent manner, propofol induces apoptosis and disrupts progression of HCC cells. Mechanistically, propofol reduces HMGA2 expression to inhibit Wnt/ $\beta$ -catenin signaling.<sup>253</sup> Therefore, more investigations should be performed in

**Table 2** Non-Coding RNAs Regulating  $\beta$ -Catenin Signaling in HCC

NcRNA	Function	Signaling Networks	Remarks	Refs
miRNA-182-5p	Tumor-promoting	FOXO3a/ $\beta$ -catenin	Reducing expression level of FOXO3a Inhibiting proteasomal degradation of $\beta$ -catenin Enhancing HCC progression and recurrence	[273]
miRNA-27a	Tumor-promoting	B-catenin/EMT	Enhancing metastasis of HCC cells Inducing $\beta$ -catenin signaling Decreasing E-cadherin levels and increasing vimentin levels in triggering EMT in HCC	[274]
miRNA-155	Tumor-promoting	PI3K/SGK3/ $\beta$ -catenin	P85 $\alpha$ suppression by miRNA-155 and increased SGK3 expression Eliminating inhibitory impact of PI3K on SGK3 Inducing $\beta$ -catenin signaling Mediating EMT mechanism	[275]
miRNA-885-5p	Tumor-suppressor	Wnt/ $\beta$ -catenin	Impairing growth rate of HCC cells Down-regulating expression level of CTNNB1 Suppressing $\beta$ -catenin signaling	[276]
miRNA-144	Tumor-suppressor	CLK3/ $\beta$ -catenin	Down-regulation of miRNA-144 in HCC and overexpression of CLK3 Enhancing miRNA-144 expression results in CLK3 down-regulation and subsequent inhibition of $\beta$ -catenin signaling	[250]
miRNA-1301	Tumor-suppressor	BCL9/Wnt/ $\beta$ -catenin	Suppressing angiogenesis, EMT and proliferation of HCC cells BCL9 down-regulation and subsequent inhibition of $\beta$ -catenin signaling	[277]
miRNA-122	Tumor-suppressor	Wnt/ $\beta$ -catenin/MDR1	Apoptosis induction Increasing sensitivity of cancer cells to oxaliplatin chemotherapy Inhibiting $\beta$ -catenin signaling to diminish expression level of MDR1	[278]
miRNA-122	Tumor-suppressor	Wnt/ $\beta$ -catenin	Disrupting migration and growth of HCC cells Inhibiting $\beta$ -catenin signaling	[279]
LncRNA-RUNX1	Tumor-suppressor	miRNA-632/GSK-3 $\beta$ / $\beta$ -catenin	Reduced miRNA-632 expression by RUNX1 via ceRNA action Enhancing GSK-3 $\beta$ expression to suppress $\beta$ -catenin signaling Impairing growth and invasion of HCC cells	[280]
LncRNA-MIR22HG	Tumor-suppressor	miRNA-10a-5p/NCOR2/ $\beta$ -catenin	Reducing miRNA-10a-5p expression Increasing NCOR2 expression Inactivating $\beta$ -catenin signaling	[281]
LncRNA-MUF	Tumor-promoting	ANXA2/ $\beta$ -catenin/EMT	Interaction between MUF and ANXA2 induces $\beta$ -catenin signaling Triggering EMT mechanism Increasing cancer migration and invasion	[282]
LncRNA-AWPPH	Tumor-promoting	Wnt/ $\beta$ -catenin	Increasing HCC growth and metastasis Inducing $\beta$ -catenin signaling	[283]
LncRNA-CRND	Tumor-promoting	Wnt/ $\beta$ -catenin/EMT	Increasing cancer metastasis via activating $\beta$ -catenin signaling and triggering EMT mechanism	[284]
LncRNA-DQ786243	Tumor-promoting	miRNA-15b-5p/Wnt3A/ $\beta$ -catenin	Reducing expression level of miRNA-15b-5p Enhancing Wnt3A expression to stimulate $\beta$ -catenin signaling Facilitating HCC progression	[285]

**Abbreviations:** miRNA, microRNA; lncRNA, long non-coding RNA; FOXO3a, forkhead box O3; HCC, hepatocellular carcinoma; EMT, epithelial-to-mesenchymal transition; BCL9, B-Cell CLL/Lymphoma 9; MDR1, multi-drug resistance 1; ceRNA, competing endogenous RNA; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; NCOR2, AnxA2, annexin A2.



revealing the true potential of anesthetic agents in HCC therapy via targeting  $\beta$ -catenin signaling.

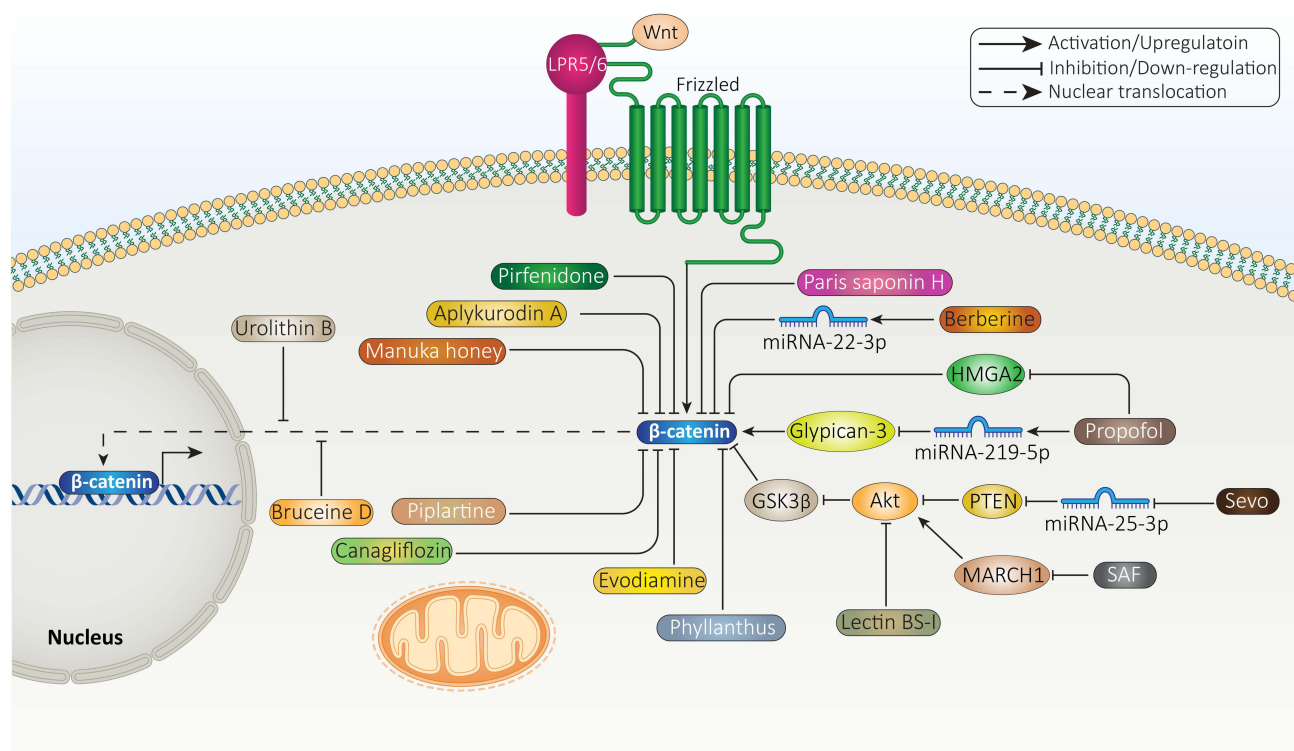
Berberine is a well-known phytochemical that has recently received attention for its anti-tumor activity.<sup>254,255</sup> Increasing evidence has revealed the role of berberine in HCC suppression. For instance, berberine increases miRNA-22-3p expression as tumor-suppressor to inhibit HCC progression.<sup>256</sup> Besides, berberine prevents inflammation and angiogenesis during non-alcoholic steatohepatitis to inhibit HCC development.<sup>257</sup> It is suggested that berberine prevents translation of  $\beta$ -catenin in HCC. In this way, berberine suppresses mTOR signaling to recruit eukaryotic translation initiation factor 4E-binding protein (4E-BP) 1, leading to  $\beta$ -catenin translation inhibition.<sup>258</sup> As  $\beta$ -catenin increases proliferation rate of HCC cells, its inhibition by pirfenidone leads to sensitizing tumor cells to apoptosis.<sup>259</sup> Each anti-tumor agent follows a unique pathway in affecting  $\beta$ -catenin signaling in HCC. For instance, lectin BS-I diminishes sGrp78 and p85 interaction via affecting its membrane localization to inhibit Akt signaling, resulting in GSK-3 $\beta$  overexpression and subsequent inhibition of  $\beta$ -catenin signaling.<sup>260</sup> Besides, the benefits of plant-derived, natural compounds is that they can inhibit  $\beta$ -catenin signaling to induce cytotoxicity against HCC

cells, while they are safe and have no toxicity on normal cells or hematological profile.<sup>116</sup>

A few experiments have evaluated synthetic small molecules as inhibitors of  $\beta$ -catenin signaling. C-82 is a small molecule and active form of PRI-724 that can induce cell cycle arrest at G0/G1 phase and prevents growth of HCC cells. Besides, C-82 elevates number of cells at sub-G1 phase. C-82 is also able to induce apoptosis in HCC cells. C-82 exerts its tumor-suppressor activity via inhibiting  $\beta$ -catenin signaling (Figure 6).<sup>261</sup> Future experiments are suggested to focus on small molecules regulating GSK-3 $\beta$  and also other upstream mediators of  $\beta$ -catenin signaling, described in aforementioned sections. Table 3 provides an overview of anti-cancer agents targeting  $\beta$ -catenin signaling in HCC therapy.

## Genetic Intervention in Beta-Catenin Targeting: Prospective and Future Remarks

The anti-tumor agents that were described in the previous section are able to suppress  $\beta$ -catenin signaling to effectively inhibit HCC progression. However, these anti-cancer agents, as most of them are phytochemicals, have problems including low bioavailability and less efficacy



**Figure 6** Selected anti-tumor compounds targeting  $\beta$ -catenin signaling in HCC therapy.

**Table 3** Regulation of  $\beta$ -Catenin Signaling by Anti-Cancer Agents in HCC Treatment

Anti-Tumor Agent	In vitro/In vivo	Cell Line/Animal Model	Study Design	Remarks	Refs
Aplykurodin A	In vitro	Hep3B and SNU475 cells	20 and 40 $\mu$ M	Apoptosis induction Decreasing proliferation rate of cancer cells Down-regulating $\beta$ -catenin expression	[286]
Manuka honey	In vitro	HepG2 cells	1.25–20% w/v	Apoptosis inhibition Enhancing sensitivity of cancer cells to doxorubicin Suppressing Wnt/ $\beta$ -catenin signaling	[287]
Phyllanthus urinaria L	In vitro In vivo	HepG2, SMMC-7721, Huh-7 cells Xenotransplantation model	30, 60 and 120 $\mu$ g/mL	Inducing proteasomal degradation of $\beta$ -catenin via autophagy inhibition Impairing metastasis of cancer cells	[288]
Piplartine	In vitro	HepG2 and SMMC-7721 cells	0, 5, 10, 15 and 20 $\mu$ M	Suppressing growth and metastasis of HCC cells Enhancing expression level of LINC01391 as tumor-suppressor factor Subsequent inhibition of Wnt/ $\beta$ -catenin axis	[289]
Canagliflozin	In vitro In vivo	Huh7 and Hep3B Huh7 xenograft tumor model	0–100 $\mu$ M 300 mg/kg/day	Increasing $\beta$ -catenin phosphorylation to mediate its proteasomal degradation Impairing tumor cell growth Enhancing survival rate of animal models	[290]
Evodiamine	In vitro In vivo	HepG2, SMMC-7721, and H22 cells Nude mice	20 mg/kg	Inhibiting $\beta$ -catenin signaling Suppressing angiogenesis via down-regulating VEGFa expression level Acting as anti-cancer agent	[291]
Bruceine D	In vitro In vivo	Huh7 and Hep3B HCC cell lines HCC xenograft model	0.75 and 1.5 mg/kg	Triggering proteasomal degradation of $\beta$ -catenin Inhibiting its nuclear translocation Down-regulation of Jagged 1 Suppressing tumor growth	[292]
Paris saponin H	In vitro In vivo	Huh7 and PLC/PRF/5 cells Nude mice	0–20 $\mu$ M 5 mg/kg	Exerting anti-tumor activity in a dose-dependent manner EMT inhibition Reducing $\beta$ -catenin expression Inhibiting tumor growth in vitro and in vivo	[293]

**Abbreviations:** VEGF, vascular endothelial growth factor; EMT, epithelial-to-mesenchymal transition; HCC, hepatocellular carcinoma.

in vivo compared to in vivo, showing that they have problems in reaching the tumor site and exerting their anti-tumor activity. Furthermore, plant-derived natural compounds have multitargeting capacity and along with  $\beta$ -catenin signaling, they can also affect other molecular pathways. Therefore, in order to be more specific, application of genetic tools in  $\beta$ -catenin targeting is suggested. Overall, there has been a general overlook toward using genetic tools for specific targeting of  $\beta$ -catenin signaling in HCC. Most of the experiments have focused on affecting other molecular pathways in context of  $\beta$ -catenin

signaling. Therefore, future experiments should consider  $\beta$ -catenin targeting in HCC therapy via genetic tools. siRNA is the most well-known genetic tool that can reduce expression of target gene with high application in tumor therapy.<sup>262,263</sup> A variety of experiments have used siRNA in targeting  $\beta$ -catenin signaling and providing HCC treatment. siRNA-CTNBB1 can suppress  $\beta$ -catenin signaling that in turn, reduces expression level of its target genes such as cyclin D1 and glutamine synthetase in impairing HCC growth.<sup>264</sup> Upon application of siRNA- $\beta$ -catenin, cell cycle arrest at G0/G1 phase occurs. Besides, siRNA- $\beta$ -

catenin enhances expression levels of Smad3, p-caspase-3 and Grp78, while it diminishes expression levels of TERT, caspase-3, XIAP, MMP-2, MMP-9, VEGF and bFGF protein. The application of siRNA- $\beta$ -catenin sensitizes HCC cells to apoptosis.<sup>265</sup> Short-hairpin RNA (shRNA) and CRISPR/Cas system are other genetic tools that have been applied in treatment of HCC. However, no specific targeting of  $\beta$ -catenin in these experiments has been performed. Hence, the first limitation is about using genetic tools for specific targeting of  $\beta$ -catenin. The next limitation is about gene therapy. Similar to anti-tumor compounds, genetic tools have their own drawbacks

including off-targeting and degradation by enzymes. Therefore, application of nanostructures for their delivery and increasing their efficacy in cancer suppression is suggested.<sup>235,266–268</sup> Table 4 summarizes recent efforts in revealing  $\beta$ -catenin's role in HCC.

## Conclusion and Remarks

In spite of significant advances in HCC management and treatment, there is still a long way to understanding factors responsible for HCC development. HCC has desirable prognosis at early stages, but its advanced stage is resistant to various therapies including immunotherapy,

**Table 4** An Overview of  $\beta$ -Catenin Signaling and Related Molecular Pathways in HCC

Signaling Network	Remarks	Refs
CDCA8/Akt/ $\beta$ -catenin	Acting as tumor-promoting factor and increasing HCC progression CDCA8 induces Akt/ $\beta$ -catenin axis to enhance HCC growth Increasing cancer stemness Knock-down of CDCA8 impairs HCC proliferation via inhibiting $\beta$ -catenin	[294]
UBE2T/Mule/Wnt/ $\beta$ -catenin	Overexpression of UBE2T in clinical samples and association with undesirable prognosis UBE2T interacts with Mule to induce its ubiquitination Increasing $\beta$ -catenin stability Promoting HCC progression	[295]
sFRP-4/Wnt/ $\beta$ -catenin	The down-regulation of sFRP-4 in HCC Suppressing HCC proliferation and inducing apoptosis Inhibiting $\beta$ -catenin signaling	[296]
RAD54B/Wnt/ $\beta$ -catenin	Association with poor prognosis Enhancing motility and growth of HCC cells Overexpression of RAD54B and inducing $\beta$ -catenin signaling	[297]
BAP31/Akt/ $\beta$ -catenin	Increasing HCC metastasis Upregulation of BAP31 and inducing Akt/ $\beta$ -catenin axis	[285]
TM2D1/Akt/ $\beta$ -catenin	TM2D1 induces EMT to enhance HCC migration and invasion Stimulating Akt/ $\beta$ -catenin axis	[298]
MNS1/PI3K/Akt/ $\beta$ -catenin	Association with unfavorable prognosis Enhancing cancer progression MNS1 induces Akt signaling to enhance nuclear translocation of $\beta$ -catenin	[299]
$\beta$ -catenin/miRNA-22-3p/TET2	Alcohol exposure enhances HCC progression $\beta$ -catenin elevates miRNA-22-3p expression to down-regulate TET2 expression	[300]
$\beta$ -catenin/KIF2C/mTORC1	Enhanced expression level of KIF2C by $\beta$ -catenin Upregulation of mTORC1 Increasing both growth and invasion of HCC cells	[301]
$\beta$ -catenin/NKG2D	Reduced expression level of NKG2D ligands by $\beta$ -catenin and association with malignant behavior of HCC cells	[302]
Wnt/ $\beta$ -catenin	Irradiated mesenchymal stem cells increase stemness of HCC via inducing $\beta$ -catenin signaling	[303]

**Abbreviations:** CDCA8, cell division cycle associated 8; Akt, protein kinase-B; HCC, hepatocellular carcinoma; UBE2T, ubiquitin conjugating enzyme E2 T; sFRP-4, secreted frizzled-related protein 4; PI3K, phosphoinositide 3-kinase; MNS1, Meiosis-specific nuclear structural 1; TET2, Tet methylcytosine dioxygenase 2; KIF2c, Kinesin family member 2C; mTORC1, mammalian target of rapamycin complex 1; NKG2D, Natural Killer Group 2D.

chemotherapy, and radiotherapy. HCC cells demonstrate high proliferation and migration rates at advanced stages. Hence, it is vital to identify factors responsible for aggressive behavior of HCC. Increasing evidence has revealed the role of interactions in TME for HCC development and progression. Such interactions promote HCC progression and mediate therapy resistance, threatening life of patients.  $\beta$ -catenin signaling is an oncogenic pathway that enhances HCC progression via cooperating with other molecular pathways and affecting TME components.

The present review focused on  $\beta$ -catenin affecting various aspects of HCC. As the first step,  $\beta$ -catenin signaling increases proliferation rate of HCC cells and prevents apoptosis. Inhibiting  $\beta$ -catenin signaling promotes expression level of pro-apoptotic factors such as Bax and caspases to induce apoptosis. The cell progression of HCC cells undergoes a significant increase by Wnt/ $\beta$ -catenin signaling. Silencing Wnt/ $\beta$ -catenin signaling suppresses proliferation rate and cell cycle progression, while it induces apoptosis in HCC cells. To increase growth ability of HCC cells,  $\beta$ -catenin elevates expression level of tumor-promoting factors such as c-Myc. Besides,  $\beta$ -catenin enhances stemness of HCC via improving CSC features. In addition to growth,  $\beta$ -catenin signaling increases migration of HCC cells via inducing EMT and promoting expression level of MMPs. Both proliferation and migration rates can be significantly enhanced by Wnt/ $\beta$ -catenin signaling and these factors are involved in therapy resistance of HCC cells, thus, knock-down of Wnt/ $\beta$ -catenin axis is beneficial in impairing progression and promoting chemosensitivity. Furthermore,  $\beta$ -catenin signaling can enhance number of macrophages with M2 phenotype in TME to mediate its oncogenic activity in HCC. The macrophages with M1 phenotype suppress HCC progression, while M2 polarization by Wnt/ $\beta$ -catenin signaling activation promotes HCC progression. When growth and migration increase, HCC cells are able to obtain resistance to therapy.  $\beta$ -catenin-mediated HCC progression leads to immuno-resistance and drug resistance in HCC. Hence, suppressing  $\beta$ -catenin signaling can promote therapy response and dually inhibit growth and invasion of HCC cells.

Since Wnt/ $\beta$ -catenin signaling activation significantly enhances proliferation and invasion of HCC cells, efforts have been made to target it using different pharmacological strategies. Anti-tumor compounds have been utilized in inhibiting Wnt signaling. Berberine, propofol, sevoflurane, and C-82 as anti-tumor agents are able to inhibit Wnt/ $\beta$ -catenin signaling in impairing HCC progression. On the other hand, siRNA as a nucleic acid drug can inhibit Wnt

signaling in reducing HCC proliferation and invasion. There are upstream mediators of Wnt signaling including miRNAs and lncRNAs that have also been found to regulate HCC progression. Moreover, in addition to the pre-clinical studies that have shown the role of Wnt/ $\beta$ -catenin signaling in HCC progression, clinical studies have also confirmed the role of Wnt overexpression, nuclear translocation of  $\beta$ -catenin and gene mutation (*CTNBB1*) in development and progression of HCC in patients.

## Abbreviations

PI3K, phosphoinositide 3-kinase; EMT-TFs, EMT-inducing transcription factors; TDP-43, trans-activation response DNA-binding protein of 43; ACLY, ATP-citrate lyase; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of MMPs; siRNA, small interfering RNA; EVs, extracellular vesicles; PROX1, prospero-related homeobox 1; HIF-1 $\alpha$ , hypoxia inducible factor-1 $\alpha$ ; DOX, doxorubicin; ABC, ATP-binding cassette; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; EMT, epithelial-to-mesenchymal transition; S1PR1, sphingosine-1-phosphate receptor-1; lncRNA, long non-coding RNA; miRNAs, microRNAs; circRNAs, circular RNAs; TCF, T cell factor; LEF, lymphoid enhancer factor; CK-1, casein kinase-1; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; APC, adenomatous polyposis coli; 5-FU, 5-fluorouracil; PD-L1, programmed death-ligand 1; NK, natural killer; CK19, cytokeratin 19; CSCs, cancer stem cells; PTK2, protein tyrosine kinase 2; TME, tumor microenvironment; TAMs, tumor-associated macrophages; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; GLS1, glutaminase 1; sCLU, secretory clusterin; Akt, protein kinase-B; AQP9, aquaporin-9; SKA2, spindle and kinetochore-associated protein 2; FAPP2, phosphatidylinositol 4-phosphate adaptor protein 2; HDAC6, histone deacetylase 6; MCT1, monocarboxylate transporter 1; PDK1, pyruvate dehydrogenase kinase isoenzyme 1; PGC-1 $\alpha$ , PARP $\alpha$  coactivator-1 $\alpha$ ; ncRNAs, non-coding RNAs; ZNRD1, zinc ribbon domain-containing 1; HBX, hepatitis X protein; SFRP2, secreted frizzled-related protein-2; TCF4, transcription factor 4; CP, cisplatin; ROS, reactive oxygen species; Sevo, sevoflurane; SAF, secalonic acid-F; 4E, BP, 4E-binding protein; shRNA, short hairpin RNA.

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## Disclosure

The authors declare no conflicts of interest for this work.

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