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## Understanding the role of PIN1 in hepatocellular carcinoma

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### Abstract

PIN1 is a peptidyl-prolyl *cis/trans* isomerase that binds and catalyses isomerization of the specific motif comprising a phosphorylated serine or threonine residue preceding a proline (pSer/Thr-Pro) in proteins. PIN1 can therefore induce conformational and functional changes of its interacting proteins that are regulated

by proline-directed serine/threonine phosphorylation. Through this phosphorylation-dependent prolyl isomerization, PIN1 fine-tunes the functions of key phosphoproteins (*e.g.*, cyclin D1, survivin,  $\beta$ -catenin and x-protein of hepatitis B virus) that are involved in the regulation of cell cycle progression, apoptosis, proliferation and oncogenic transformation. PIN1 has been found to be over-expressed in many cancers, including human hepatocellular carcinoma (HCC). It has been shown previously that overexpression of PIN1 contributes to the development of HCC *in-vitro* and in xenograft mouse model. In this review, we first discussed the aberrant transcription factor expression, miRNAs dysregulation, *PIN1* gene promoter polymorphisms and phosphorylation of PIN1 as potential mechanisms underlying PIN1 overexpression in cancers. Furthermore, we also examined the role of PIN1 in HCC tumourigenesis by reviewing the interactions between PIN1 and various cellular and viral proteins that are involved in  $\beta$ -catenin, NOTCH, and PI3K/Akt/mTOR pathways, apoptosis, angiogenesis and epithelial-mesenchymal transition. Finally, the potential of PIN1 inhibitors as an anti-cancer therapy was explored and discussed.

**Key words:** Phosphorylation; Hepatocellular carcinoma; PIN1; Isomerization; Hepatocarcinogenesis

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**Core tip:** PIN1 specifically binds and catalyses isomerization of the pSer/Thr-Pro motif of target proteins, thereby modulating their functions. Many PIN1-interacting proteins are involved in cellular transformation and maintenance of malignant phenotype, and overexpression of PIN1 is frequently found in various cancer types, including hepatocellular carcinoma (HCC). Through interacting with regulatory proteins of key signalling pathways, such as  $\beta$ -catenin, cyclin D1, and HBx, PIN1 drives and amplifies the oncogenic signals essential for the development of HCC. Given its diverse oncogenic functions in hepatocarcinogenesis, PIN1

represents a potential therapeutic target in the treatment of HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth leading cancer in men and the ninth for women worldwide, with estimated 782000 new cases in 2012. It is one of the most common causes of cancer death, leading to 746000 deaths annually<sup>[1]</sup>. Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is the major risk factor<sup>[2]</sup>, accounting for 92% and 43% of HCC cases in developing and developed countries, respectively. HCC is an aggressive malignant tumour associated with a poor prognosis, and only a small proportion of HCCs is detected at an early stage. Early-stage HCCs are amenable to potentially curative treatments, such as surgical resection, liver transplantation, transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA)<sup>[3]</sup>. Nonetheless, HCCs are frequently diagnosed at advanced-stage and patients with advanced HCCs are not candidates for curative therapies. Conventional chemotherapy is ineffective for advanced HCCs because of the development of chemo-resistance and early occurrence of metastasis<sup>[4-6]</sup>. A thorough understanding of the pathogenesis and biology of HCC provides the mechanistic basis for designing effective HCC therapies.

Protein phosphorylation is a post-translational modification that plays an important role in the regulation of signalling pathways. Through activation of multiple protein kinases, such as cyclin dependent kinases (CDKs) and mitogen activated protein kinases (MAPKs), phosphorylation of proteins in serine or threonine residues preceding proline (pSer/ Thr-Pro) motif has been linked to dysregulated cell proliferation and malignant transformation<sup>[7,8]</sup>. The identification of peptidyl-prolyl *cis/trans* isomerase PIN1 provides a new post-phosphorylation regulatory mechanism in cell signalling<sup>[9-12]</sup>. PIN1 is a small and highly evolutionarily conserved 18-kDa protein, and is mainly localized in the nucleus<sup>[11,13,14]</sup>. It binds specific pSer/Thr-Pro motif in certain proteins through its amino-terminal WW domain, and isomerizes the pSer/Thr-Pro peptide bonds with its carboxyl-terminal prolyl isomerase (PPIase) domain<sup>[7,11,15]</sup> (Figure 1). PIN1-catalysed isomerization induces conformational changes of its target proteins, resulting in alterations of their enzymatic activities, phosphorylation status, protein-

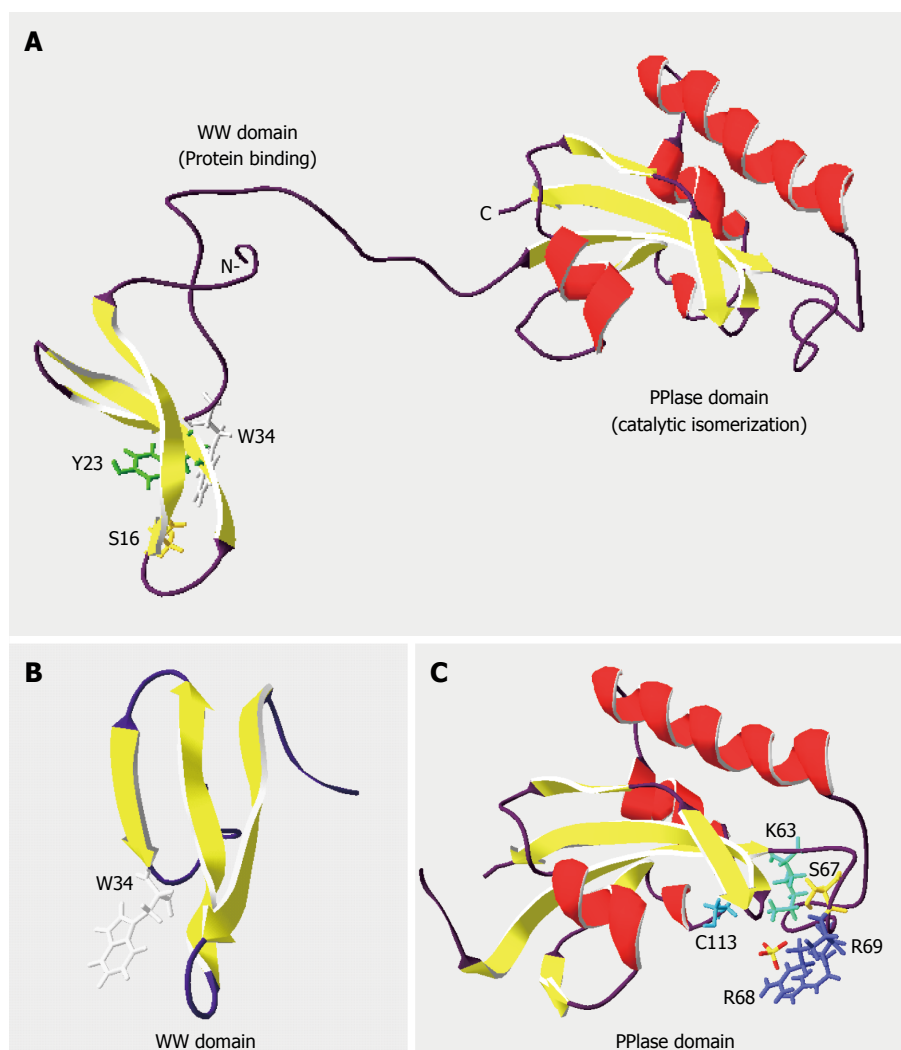
protein interaction patterns, subcellular localization, and protein stability. Conceivably, PIN1 plays an important role in diverse cellular processes, including cell cycle progression, differentiation, apoptosis and proliferation, as well as transformation<sup>[11,16-19]</sup>. Indeed, many PIN1-interacting partners, such as  $\beta$ -catenin, c-Jun, cyclin D1, cyclin E, Myc, nuclear factor-kappa B (NF- $\kappa$ B)-p65, p53 and p73, are important in regulating cell cycle progression and cell proliferation, and are often dysregulated in cancer<sup>[17,18,20-25]</sup>. Thus, the role of PIN1 in enhancing the oncogenic potential of these proteins *via* phosphorylation-dependent prolyl isomerization is important during cancer development.

In this article, we discuss the possible mechanisms underlying dysregulated PIN1 expression in cancer, the oncogenic roles of PIN1 in hepatocarcinogenesis, and the potential of PIN1 inhibitors as anti-cancer agents.

## REGULATION OF PIN1 EXPRESSION AND ACTIVITY

In normal cells, PIN1 expression is usually very low and is tightly regulated by the retinoblastoma protein (Rb)-E2F pathway<sup>[26,27]</sup>. The binding between Rb and E2F proteins is controlled by the phosphorylation of Rb. Hypophosphorylated Rb binds E2F transcription factors and inhibits its transcriptional activity towards the *PIN1* gene. In response to cell proliferative stimuli, CDK-cyclin complexes phosphorylate and inactivate Rb to release E2F. In turn, E2F binds to the E2F-binding sites of the *PIN1* promoter and directly activates transcription of the *PIN1* gene. Interestingly, PIN1 has also been found to interact with Rb and enhance its hyperphosphorylation<sup>[28,29]</sup>. Therefore, PIN1 inactivates Rb and promotes E2F target gene activation. Since dysregulation of the Rb-E2F pathway is frequently found in various cancers<sup>[30]</sup>, it is speculated that abnormalities of this pathway may contribute to PIN1 overexpression in cancers. Furthermore, PIN1 interacts with phosphorylated NOTCH1 to enhance NOTCH1 transcriptional activity, which in turn, increases the transcription of *PIN1*, resulting in a positive feedback loop for PIN1 overexpression in cancers<sup>[31]</sup>. In addition to E2F and NOTCH1, forkhead box transcription factor FOXC1 also enhances *PIN1* promoter activity, resulting in increased mRNA and protein expression of PIN1 in breast cancer cells<sup>[32]</sup>.

MicroRNAs (miRNAs) are small non-coding RNA that functions as a negative regulator of gene expression by binding to the 3'UTR of target mRNA to inhibit gene expression at the post-transcriptional level<sup>[33]</sup>. Dysregulation of miRNAs expression is frequently observed in cancers<sup>[34]</sup>. In HCC, a global reduction of miRNAs expression is associated with HCC progression<sup>[35]</sup>, suggesting that most of the expressed miRNAs in normal hepatocytes function as tumour suppressors. Some of these miRNAs may target the expression of PIN1 and their reduced expression may



**Figure 1 Structure of peptidyl-prolyl-isomerase PIN1 protein.** Ribbon diagrams of (A) PIN1 (NCBI Structure No. 1NMV), (B) WW binding domain (NCBI Structure No. 1I8H), and (C) PPIase catalytic domain (NCBI Structure No. 1NMW) were drawn with the Swiss-Pdb Viewer<sup>[11,15,116]</sup>.  $\alpha$ -helices and  $\beta$ -strands are denoted by coils and arrows, respectively. Residues Ser(S)<sup>16</sup>, Tyr(Y)<sup>23</sup> and Trp(W)<sup>34</sup> in the WW domain are critical for phospho-protein binding, while residues Lys(K)<sup>63</sup>, Ser(S)<sup>67</sup>, Arg(R)<sup>68/69</sup> and Cys(C)<sup>113</sup> contribute to the PPIase activity. Adapted from thesis: Identification and characterization of PIN1 binding partners, HKU 2010.

therefore result in the PIN1 overexpression observed in HCC. Currently, three miRNAs have been shown to negatively regulate PIN1 expression in cancers. miR-200b/c and miR-296-5p directly target and suppress PIN1 expression in breast cancer and prostate cancer cells, respectively<sup>[36-38]</sup>. However, no specific miRNA has been reported to target PIN1 expression in HCC.

Single nucleotide polymorphism (SNP) of the *PIN1* gene promoter may also contribute to the regulation of PIN1 expression. The promoter region of *PIN1* gene contains two SNPs [rs2233678 (-842G/C) and rs2233679 (-667C/T)] and one synonymous SNP [rs2233682 (Gln33GlnG>A)] in exon 2. Genotype -842CC is associated with lower PIN1 protein expression in peripheral mononuclear cells, whereas -677C/T genotype does not have significant effect on PIN1 expression<sup>[39]</sup>. Similar result was also found in squamous cell carcinoma of head and neck (SCCHN), with -842C genotype but not -677C/T associated with a lower *PIN1* promoter activity and a lower risk of

SCCHN<sup>[40]</sup>.

In addition to the transcriptional regulation, PIN1 level is also regulated through post-translational modification. Phosphorylation at Ser<sup>65</sup> by Polo-like kinase I (PLK1) inhibits ubiquitination of PIN1, resulting in decreased proteasomal degradation and increased protein level<sup>[41]</sup>. Moreover, multiple regulators have also been found to modulate the activity of PIN1 by post-translational modifications. Sumoylation of Lys<sup>6</sup> on the WW domain and Lys<sup>63</sup> on the PPIase domain suppress PIN1 protein-binding and catalytic abilities, respectively. De-sumoylation on those sites by SUMO1/sentrin specific peptidase 1 (SEN1) reverses the inhibitory function on PIN1 and increases PIN1 stability<sup>[42]</sup>. In addition, mixed-lineage kinase 3-induced phosphorylation of PIN1 at Ser<sup>138</sup> enhances PIN1 catalytic activity<sup>[43]</sup>, whereas death-associated protein kinase 1-induced phosphorylation of PIN1 at Ser<sup>71</sup> abolishes PIN1 catalytic activity<sup>[14]</sup>. Furthermore, protein kinase A, ribosomal S6 kinase 2 and Aurora

have also been shown to inhibit PIN1 function by phosphorylation at Ser<sup>16[13,44,45]</sup>.

## PIN1 OVEREXPRESSION IN HCC

As PIN1 regulates cellular signalling, PIN1 overexpression typically results in uncontrolled cell proliferation and tumour formation. A relationship between PIN1 and cancer was first demonstrated in breast cancer, in which PIN1 level positively correlated with tumour grade<sup>[20]</sup>. Moreover, PIN1 overexpression has been found in different cancers, including brain, breast, cervical, colon, lung and prostate<sup>[26,46]</sup>.

Consistently, several studies have confirmed that PIN1 mRNA and protein are over-expressed in HCC tumours, as compared with those of the adjacent non-tumourous liver tissues<sup>[47-50]</sup>. In one of the earliest studies, PIN1 overexpression was found in more than 50% of HCC samples<sup>[47]</sup>. In addition, a study from our group has also demonstrated that PIN1 overexpression is more frequently observed in HBV-related HCCs<sup>[51]</sup>. Shinoda *et al.*<sup>[52]</sup> has studied the association between PIN1 expression and clinicopathological characteristics in HCC. HCC tumours with higher PIN1 expression show significantly larger tumour size and higher frequency of portal vein invasion. Moreover, higher PIN1 expression is also significantly associated with poorer prognosis, lower overall survival and higher early recurrence rate (within 3 years) in patients with HCC. Thus, dysregulation of PIN1 expression is closely associated with HCC progression.

## ROLES OF PIN1 IN HEPATOCARCINOGENESIS

Through catalysing isomerization of signalling molecules, PIN1 functions as a critical catalyst in many signalling pathways in cancer. The oncogenic property of PIN1 was first demonstrated in breast cancer, as PIN1 can transform breast epithelial cells through up-regulation of cyclin D1<sup>[27]</sup>. Several studies have demonstrated that PIN1 expression is positively correlated with cyclin D1 expression in various types of cancer<sup>[20,47,53-56]</sup>. A positive correlation has also been shown between PIN1 expression and centrosome amplification in breast cancer. Both *in vitro* and *in vivo* studies have demonstrated that PIN1 induces centrosome duplication, resulting in chromosomes mis-segregation and genomic instability, which in turn promote cell transformation and tumour growth in transgenic mice<sup>[57]</sup>.

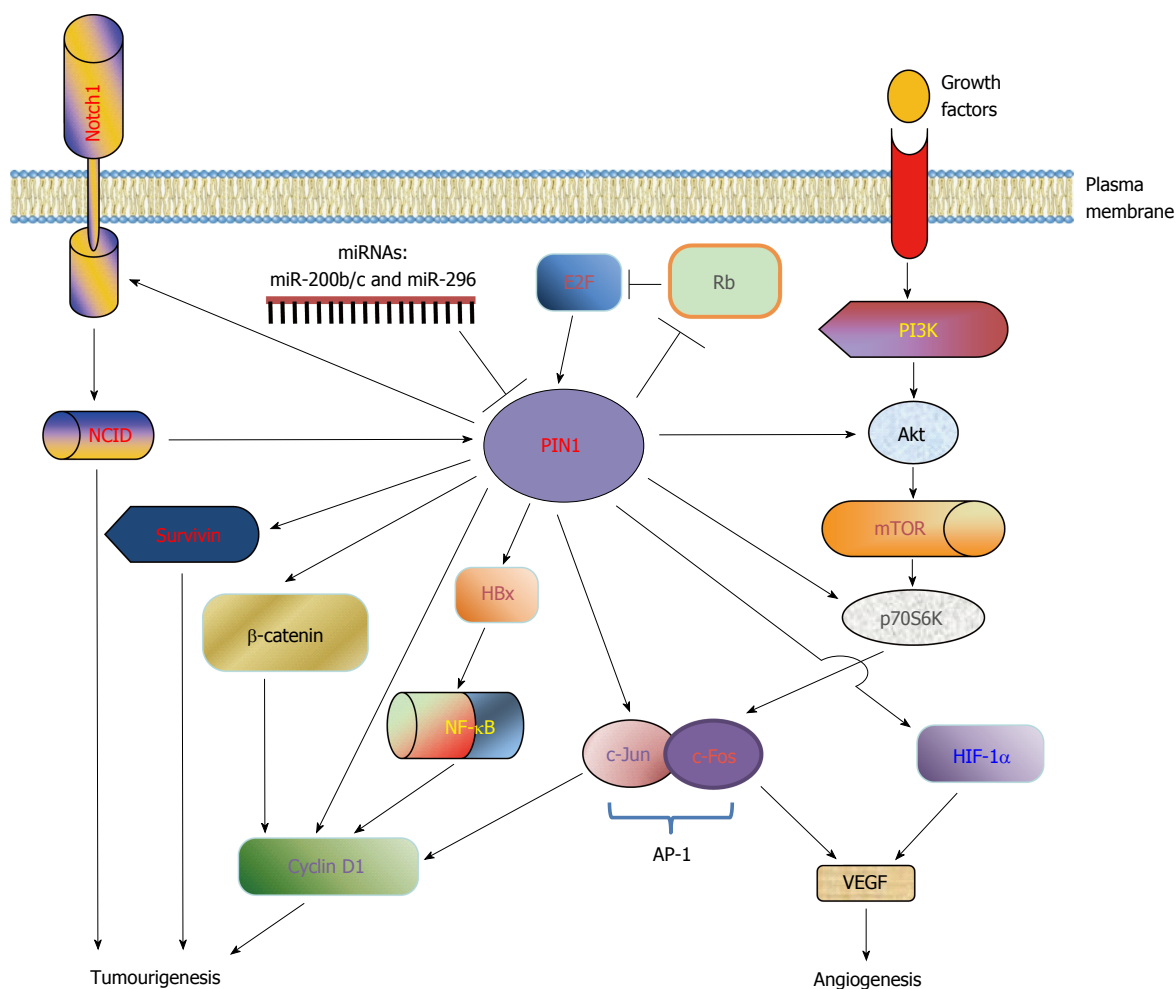
In hepatocytes, overexpression of PIN1 has been shown to promote malignant transformation. PIN1 overexpression in the immortalized but non-tumourigenic liver cell line MIHA leads to anchorage-independent colony formation in soft agar and tumour formation in nude mice *in vivo*<sup>[58]</sup>. The number of colonies in soft agar and the size of tumours in nude

mice are positively correlated with PIN1 expression levels. Similarly, PIN1 depletion in human HCC cells results in the suppression of cell proliferation, reduction of colony formation in soft agar and abrogation of tumour development in nude mice. Thus, PIN1 plays a critical role in hepatocarcinogenesis and the pathways involved are further discussed in the following sections (Figure 2).

## PIN1 AND $\beta$ -CATENIN/CYCLIN D1 SIGNALLING PATHWAY

Dysregulation of the  $\beta$ -catenin signalling pathway resulting from  *$\beta$ -catenin* gene mutations contributes to HCC development. Activation of the  $\beta$ -catenin signalling pathway results in nuclear translocation of  $\beta$ -catenin protein that in turn activates the transcription of its target genes, including cyclin D1 and c-Myc<sup>[59-62]</sup>. Up-regulation of cyclin D1 and c-Myc leads to uncontrolled cell proliferation, malignant transformation and tumour development. In addition to  *$\beta$ -catenin* gene mutations, PIN1 overexpression has been shown to increase the  $\beta$ -catenin transcriptional activity towards its target genes, such as cyclin D1, c-Myc, PPAR- $\delta$  and fibronectin<sup>[18]</sup>. The mechanism of PIN1 regulating  $\beta$ -catenin transcriptional activity is dependent on the direct interaction between PIN1 and the phosphorylated Thr<sup>246</sup>-Pro motif of  $\beta$ -catenin. Such interaction stabilizes  $\beta$ -catenin by inhibiting its binding with the adenomatous polyposis coli protein for nuclear export and subsequent glycogen synthase kinase-3 $\beta$ -mediated degradation of  $\beta$ -catenin. This leads to increased nuclear accumulation and transcriptional activity of  $\beta$ -catenin. We have previously demonstrated that overexpression of PIN1 in HCC is associated with  $\beta$ -catenin accumulation<sup>[47]</sup>. More importantly, PIN1 overexpression and  $\beta$ -catenin gene mutations are found to be mutually exclusive events, further underscoring the role of PIN1 overexpression in causing  $\beta$ -catenin accumulation in HCC. Therefore, in addition to the somatic mutations of  *$\beta$ -catenin* that occur only in 20% of HCCs<sup>[63,64]</sup>, PIN1 overexpression is the major mechanism leading to  $\beta$ -catenin accumulation in HCC.

In addition to  $\beta$ -catenin, PIN1 also binds other transcription factors to increase their transactivation activity towards the *cyclin D1* gene. In response to activated c-Jun N-terminal kinases or oncogenic Ras, PIN1 interacts with c-Jun *via* its phosphorylated Ser<sup>63/73</sup>-Pro motif and increases the transcriptional activity of c-Jun on its target genes, such as cyclin D1<sup>[20]</sup>. PIN1 binds the phosphorylated Thr<sup>254</sup>-Pro motif in the p65/RelA subunit of NF- $\kappa$ B<sup>[23]</sup>. This interaction stabilizes NF- $\kappa$ B by inhibiting its interaction with its inhibitor I $\kappa$ B to prevent the nuclear export and subsequent ubiquitin-mediated degradation of NF- $\kappa$ B. Moreover, PIN1 increases NF- $\kappa$ B transactivation activity by promoting phosphorylation of NF- $\kappa$ B at Ser<sup>276</sup> residue<sup>[52]</sup>. The



**Figure 2 PIN1 dysregulation and targets in hepatocellular carcinoma.** PIN1 functions as an amplifier to augment the oncogenic activities of key phosphoproteins involved in HCC tumourigenesis. PIN1 gene expression is up-regulated by various transcription factors, including E2F family and activated NOTCH1 intracellular domain (NICD), but is down-regulated by miRNAs (miR-200b/c and miR-296). In addition, PIN1 inactivates retinoblastoma protein (Rb), resulting in the release of E2F for activation of PIN1 expression. Through phosphorylation-dependent prolyl isomerization, PIN1 activates the  $\beta$ -catenin/cyclin D1 signalling pathway by induction of  $\beta$ -catenin transcriptional activity and stabilization of cyclin D1 protein. In parallel, PIN1 increases the transcriptional activities of c-Jun and NF- $\kappa$ B, leading to an increase in cyclin D1 transcription. Furthermore, PIN1 stabilizes hepatitis B virus X protein (HBx) and enhances its transactivating activity on downstream target nuclear factor-kappa B (NF- $\kappa$ B), which in turn increases cyclin D1 transcription. Up-regulation of cyclin D1 leads to uncontrolled cell proliferation and tumourigenesis. In addition, PIN1 increases the antiapoptotic function of survivin to inhibit apoptosis and contribute to tumourigenesis. Through interaction with Akt and ribosomal S6 kinase (p70S6K), PIN1 also activates the PI3K/Akt/mTOR pathway to promote tumourigenesis. PIN1 enhances the transcriptional activities of hypoxia-inducible factor (HIF)-1 $\alpha$  and activator protein (AP)-1, resulting in up-regulation of angiogenic factor vascular endothelial growth factor (VEGF) and promotion of angiogenesis.

PIN1-induced nuclear accumulation and activation of NF- $\kappa$ B result in increased cyclin D1 expression. Interestingly, PIN1 has also been shown to interact directly with cyclin D1 itself *via* its phosphorylated Thr<sup>286</sup>-Pro motif, resulting in protein stabilization and nuclear accumulation of cyclin D1<sup>[17]</sup>.

#### **PIN1 and HBx**

Chronic infection with HBV is a major cause of HCC<sup>[65,66]</sup>. HBV is a DNA virus that facilitates malignant transformation by integration into the host genome to induce chromosome instability<sup>[67,68]</sup> and to alter the expression of cancer-related genes by insertional mutagenesis<sup>[69]</sup>. In addition, HBV modulates cell proliferation through the expression of viral proteins, in particular, the hepatitis B virus X protein (HBx)<sup>[70]</sup>.

HBx is a gene transactivator that contributes to hepatocarcinogenesis through up-regulation of the proto-oncogenes such as c-myc, c-jun and NF- $\kappa$ B<sup>[71-73]</sup>. Studies have also shown that HBx interacts with p53 to inhibit the translocation of p53 into nucleus, resulting in the inhibition of p53-mediated cellular apoptosis and the development of liver tumour in transgenic mouse<sup>[74]</sup>.

PIN1 overexpression is more frequently observed in HBV-related HCCs. Moreover, PIN1 directly binds to the phosphorylated Ser<sup>41</sup>-Pro motif in HBx<sup>[51]</sup>. This interaction results in the stabilization of HBx protein, leading to augmentation of its transactivating activity on the downstream target genes Bcl-XL, c-myc, and NF- $\kappa$ B<sup>[51]</sup>. Overexpression of both PIN1 and HBx leads to synergistic increase in cell proliferation *in vitro*

and tumour growth *in vivo*, as compared with cells overexpressing PIN1 or HBx alone. These synergistic effects were totally dependent on the interaction between PIN1 and HBx. Neither the expression of the non-PIN1-binding HBx mutants nor PIN1 mutants that are defective for protein binding or isomerase activity cause any synergistic increase in cell proliferation and tumour growth.

### **PIN1 and survivin**

In addition to the dysregulation of cell proliferation, the tightly regulated programmed cell death (cellular apoptosis) is frequently impaired in cancers. PIN1 has also been found to affect cellular apoptosis in breast, prostate and cervical cancer cells<sup>[56,75,76]</sup>. A recent study by our group has demonstrated an interaction between PIN1 and phosphorylated Thr<sup>34</sup>-Pro motif of survivin, an inhibitor of apoptosis protein (IAP), in HCC cells<sup>[48]</sup>. The function of survivin is to inhibit apoptosis by facilitating its interaction with hepatitis B X-interacting protein (HBXIP) and pro-caspase-9, thereby blocking caspase-9 activation<sup>[77,78]</sup>. The antiapoptotic function of survivin is critical in a number of cancers, including HCC<sup>[79]</sup>. In our study, we showed that PIN1 overexpression increases the binding between survivin and pro-caspase-9 *via* HBXIP, leading to suppression of caspase-9 and caspase-3-dependent apoptosis in HCC cells. Moreover, PIN1 promotes HCC tumour growth through inhibition of apoptosis and PIN1 expression is positively correlated with survivin expression in HCC tumours. Therefore, PIN1 enhances the antiapoptotic function of survivin and plays an important role in hepatocarcinogenesis through inhibition of apoptosis.

### **PIN1 and phosphoinositide 3-kinase/serine/threonine-specific protein kinase B (Akt)/mammalian target of rapamycin pathway**

In addition to the  $\beta$ -catenin signalling pathway, the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is another important oncogenic pathway involved in HCC. Activation of this pathway is triggered by binding of multiple growth factors, including insulin and cytokines, to their respective cell surface receptors. This leads to the activation of PI3K and its subsequent downstream targets, including Akt, mTOR, translation initiation factor 4E-binding protein (4E-BP1) and ribosomal S6 kinase (p70S6K). Both 4E-BP1 and p70S6K regulate the translation of cell cycle regulatory proteins, and therefore, aberrant activation of the PI3K/Akt/mTOR pathway results in dysregulated cell cycle progression and tumourigenesis. It has been reported that mTOR phosphorylation is found in 15% of HCCs and total p70S6K expression is up-regulated in 45% of HCCs<sup>[80]</sup>. The occurrence of multiple serine and threonine phosphorylation events in this pathway suggests that PIN1 may be involved in and contribute to the development of HCC. Recently, PIN1 has been

found to interact with the phosphorylated Thr<sup>92/450</sup>-Pro motifs of Akt, resulting in the stabilization of both total and activated Akt (phosphorylated Ser<sup>473</sup>)<sup>[81]</sup>. Moreover, PIN1 expression is positively correlated with Akt activation in various types of human tumours including breast, nasopharynx and salivary gland<sup>[81]</sup>. Therefore, the PIN1-mediated Akt stabilization may be closely associated with tumourigenesis.

In addition, Lee *et al.*<sup>[44]</sup> revealed that PIN1 interacts with p70S6K and facilitates the insulin-induced phosphorylation of p70S6K as well as of its downstream target extracellular signal-regulated protein kinase (ERK)1/2 in human HCC cells. Through p70S6K-ERK signalling, co-expression of PIN1 and p70S6K leads to a synergistic increase in transcriptional activity of activator protein (AP)-1, as compared with expression of PIN1 or p70S6K alone<sup>[44]</sup>. The transcription factor AP-1 regulates gene expression through the formation of heterodimeric protein with other DNA binding proteins, such as c-Fos and c-Jun<sup>[82]</sup>. Activation of AP-1 regulates various cellular processes, such as cell proliferation, apoptosis and transformation, through activation of genes that encode the cell cycle regulatory proteins including cyclin D1, p53 and p21. Therefore, enforced expression of PIN1 enhances the insulin-induced neoplastic cell transformation, whereas the mTOR inhibitor rapamycin that blocks the activation of p70S6K suppresses PIN1-induced neoplastic cell transformation<sup>[44]</sup>. Hence, the PIN1-p70S6K signalling pathway enhances AP-1 activity and mediates the insulin-induced neoplastic cell transformation. Thus, PIN1 promotes hepatocarcinogenesis partly through the activation of the PI3K/Akt/mTOR pathway.

### **PIN1 and NOTCH1**

NOTCH1 signalling pathway plays a critical role in oncogenesis through the regulation of cell proliferation, differentiation and apoptosis. Ligand ( $\gamma$ -secretase)-induced cleavage of the membrane-bound NOTCH1 receptor releases its intracellular domain. This intracellular domain of NOTCH1 translocates into the nucleus and then activates the expression of target genes, including oncogenes c-Myc and HES1. Hence, activation of NOTCH1 signalling has been implicated in tumourigenesis. With immunohistochemistry and immunoblotting, NOTCH1 overexpression was found in 60% of HCCs<sup>[83]</sup>. In addition, enforced expression of the activated NOTCH1 intracellular domain completely rescues the inhibitory effect of  $\gamma$ -secretase inhibitor (GSI) on the cell proliferation of HCC cells<sup>[84]</sup>. As mentioned above, interaction between PIN1 and NOTCH1 stimulates the NOTCH1 signalling by releasing the activated NOTCH1 intracellular domain<sup>[31]</sup>. Therefore, PIN1 overexpression increases the transcriptional activity of activated NOTCH1 intracellular domain and enhances the colony formation *in vitro*. Likewise, down-regulation of PIN1 decreases NOTCH1 transcriptional activity, which in turn abrogates tumour

growth *in vivo*<sup>[31]</sup>. Taken together, both *in vitro* and *in vivo* studies demonstrate that activation of NOTCH1 signalling by PIN1 may potentially contribute to hepatocarcinogenesis.

### **PIN1 and angiogenesis**

Angiogenesis is the formation of new blood vessels that enhances the development and progression of tumours. HCC is a highly aggressive vascular tumour that relies on active angiogenesis. Tumour angiogenesis is mainly regulated by the expression of an angiogenic factor, vascular endothelial growth factor (VEGF). VEGF functions to stimulate vascular permeability and subsequently promotes tumour angiogenesis<sup>[85,86]</sup>. Its expression is positively correlated with the angiogenic activity or tumour progression in HCCs<sup>[87-91]</sup>. Recently, PIN1 has been found to interact with hypoxia-inducible factor (HIF)-1 $\alpha$  under hypoxic conditions<sup>[92,93]</sup>. HIF-1 $\alpha$  is an important transcription factor for VEGF gene expression. Down-regulation of PIN1 or suppression of PIN1 activity reduces the protein stability of HIF-1 $\alpha$  under hypoxic conditions, resulting in decreased transcriptional activity of HIF-1 $\alpha$ , down-regulation of VEGF expression and inhibition of angiogenesis *in vivo*<sup>[92]</sup>. In addition, PIN1 overexpression has been found to increase the transcriptional activity of AP-1 and the protein level of VEGF in breast cancer cells<sup>[94]</sup>. The transcriptional activity of AP-1 is regulated through the formation of heterodimer with c-Fos and c-Jun<sup>[82]</sup>. Since PIN1 binds c-Fos and c-Jun, and increases their transcription activity<sup>[20,95]</sup>, it also enhances the transactivation activity of AP-1 (c-Jun/c-Fos dimer), leading to increased VEGF gene transcription. Therefore, PIN1 may facilitate VEGF-mediated angiogenesis of HCCs through the regulation of AP-1 activity.

## **ROLES OF PIN1 IN TUMOUR INVASIVENESS**

Several studies have reported that PIN1 is involved in cell motility and contributes to cancer cell invasiveness. PIN1 overexpression promotes migration of immortalized human breast epithelial cells and induces epithelial-mesenchymal transition (EMT) with up-regulation of the mesenchymal markers including N-cadherin, Zeb1 and vimentin, and down-regulation of the epithelial marker E-cadherin<sup>[37]</sup>. Moreover, the protein binding WW domain and catalytic isomerization PPIase domain of PIN1 are essential for the induction of EMT in breast cancer cells. Consistently, PIN1 silencing suppresses protein expression and promoter activity of EMT regulator SNAIL, leading to increased expression of its downstream effector E-cadherin in tamoxifen-resistant breast cancer cells<sup>[96]</sup>. In epidermal growth factor receptor (EGFR) Thr<sup>790</sup>Met mutant lung cancer tissues, PIN1 expression is also positively correlated with the mesenchymal markers vimentin and Zeb1<sup>[97]</sup>. PIN1 expression enhances the survival of

EGFR-mutant lung adenocarcinoma cells with an EMT phenotype. In prostate cancer, PIN1 induces cellular migration and invasion by interacting with Smad2/3<sup>[98]</sup>, while PIN1 depletion by siRNA inhibited migration, invasion and wound healing ability<sup>[75]</sup>. In addition to EMT, PIN1 also regulates focal adhesion kinase (FAK), which is a critical focal adhesion component for cell-cell interaction and migration. By binding to protein tyrosine phosphatase (PTP)-PEST, PIN1-induced isomerization enhances the interaction of PTP-PEST with FAK and dephosphorylates FAK at the Tyr<sup>397</sup> site<sup>[99]</sup>. Dephosphorylation of FAK promotes migration, invasion and metastasis of Ras-induced transformed cells. In conclusion, PIN1 enhances cancer cell motility by controlling the EMT regulating proteins expression as well as focal adhesion protein activity.

## **PIN1 AS A NEW DRUG TARGET FOR HCC TREATMENT**

The oncogenic role of PIN1 makes it an attractive target for the development of anticancer drugs. Most of the PIN1 inhibitors developed are small molecules that inhibit its isomerase activity by binding to its catalytic active site<sup>[100]</sup> (Table 1). The first described PIN1 inhibitor is Juglone, which irreversibly inhibits the PIN1 PPIase activity<sup>[101]</sup>. Juglone was found to suppress tumorigenicity in human cancer cells by inducing apoptosis<sup>[102]</sup> and reducing number and size of colonies in human HCC cells in soft agar assay<sup>[44]</sup>. However, in addition to its PIN1-inhibitory activity, Juglone also directly inhibits RNA polymerase II<sup>[103]</sup>, rendering it not suitable for clinical treatment of human cancers. Tataru *et al.*<sup>[104]</sup> and Uchida *et al.*<sup>[105]</sup> have also screened for additional PIN1 PPIase inhibitors using a chemical compound library. PiB and dipentamethylene thiuram monosulfide (DTM) were identified to exhibit specific inhibitory activity toward PPIase through binding to the active site of PIN1. Both PiB and DTM inhibit proliferation of colon carcinoma HCT116 cells by delaying or blocking cell cycle progression. Moreover, the same concentration of PiB inhibits proliferation of wild-type mouse embryonic fibroblasts (MEFs), but not *Pin1-null* MEFs, suggesting that PiB is more specific in suppression of cell proliferation through inhibition of PIN1. Recently, all-trans retinoic acid was also found to inhibit PIN1 activity and to suppress cell proliferation in breast cancer and acute promyelocytic leukaemia<sup>[106]</sup>. However, the specificity of those PIN1 inhibitors remains a concern as some of them also possess parvulin-type PPIases inhibitory activity<sup>[100]</sup>. In addition to directly inhibiting PIN1 activity, miRNA-mediated gene silencing may also be used to knock-down PIN1 expression in cancer cells. The first miRNA mimic MRX34 has already been tested in phase I clinical trial for HCC<sup>[107]</sup>. PIN1 silencing by miR-200b/c or miR-296-5p may provide a new approach for HCC treatment.

The application of PIN1 inhibitors or miRNAs in the



**Table 1 Potential PIN1 inhibitors for cancer treatment**

Drug	Details	Status
Juglone	First PIN1 inhibitor	Preclinical
PiB	Irreversibly inhibits PIN1 PPIase activity Specifically inhibits PIN1 PPIase activity Inhibits colon cancer cell proliferation	Preclinical
Dipentamethylene thiuram monosulfide	Specifically inhibits PIN1 PPIase activity Inhibits colon cancer cell proliferation	Preclinical
All-trans retinoic acid	Binds PIN1 and inhibits its activity Inhibits breast cancer and APL cell proliferation	FDA approved for treatment of APL Preclinical
miRNAs miR-200b/c miR-296-5p	Bind to the 3'UTR of PIN1 mRNA Suppress PIN1 expression in breast cancer and prostate cancer cells	Preclinical
Sorafenib	Multi-kinase inhibitor targeting Raf/Mek/Erk signalling pathway and tyrosine receptors Inhibits angiogenesis and growth of HCC tumours <i>in vivo</i> Inhibits phosphorylation of PIN1-interacting proteins (Mcl-1 and p70S6K) Improves overall survival and increases time to progression in HCC patients	FDA approved for treatment of HCC
Bortezomib	Proteasome inhibitor Suppresses expression of PIN1 and its transcription factor E2F Inhibits HCC cell proliferation <i>in vitro</i>	FDA approved for treatment of multiple myeloma

APL: Acute promyelocytic leukaemia; FDA: Food and Drug Administration; HCC: Hepatocellular carcinoma; PPIase: Peptidyl-prolyl isomerase.

treatment of human cancers may be challenged by the fact that PIN1 is also expressed in normal cells for the regulation of cell division. PIN1 interacts with p53 to enhance protein stability and transactivation activity of p53 to promote cellular apoptosis in response to DNA damage<sup>[16,24,108]</sup>. Depletion of PIN1 has also been reported to induce transformation and tumorigenesis of MEFs through stabilization of oncogenic proteins Myc and cyclin E<sup>[21,22]</sup>. Therefore, it remains uncertain whether PIN1 inhibitors would have any adverse effect on normal tissues. To minimize the detrimental effects of PIN1 inhibitors on normal cells, a targeted delivery system may be employed to ensure specific drug delivery to HCC cells. More importantly, preclinical or clinical studies are necessary to examine the safety and effectiveness of the PIN1 inhibitors in cancer treatment.

Sorafenib is the only approved small molecular targeting agent for the treatment of advanced stage HCC. It is a multi-kinase inhibitor that blocks the Raf/Mek/Erk signalling pathway and inhibits several receptor tyrosine kinases, including VEGF receptor 2 and 3. In clinical studies, patients who received sorafenib had longer overall survival and time to progression<sup>[109,110]</sup>. Recently, *in vitro* and *in vivo* studies have provided further evidence of the efficacy of sorafenib in suppressing the growth of HCC cells<sup>[111,112]</sup>. Through inhibition of Raf/Mek/Erk signalling, sorafenib suppresses proliferation and enhances apoptosis of HCC cells. Moreover, sorafenib inhibits the angiogenesis and growth of patient-derived HCC tumour xenografts in mice. Sorafenib has also been shown to block the Erk-mediated phosphorylation of Mcl-1, which is required for interaction with PIN1 and subsequent protein stabilization<sup>[76]</sup>. Indeed, sorafenib also inhibits the phosphorylation of another PIN1 target, p70S6K, which induces cell transformation through

enforced PIN1 expression. Therefore, inhibition of the phosphorylation of oncogenic PIN1 interacting partners may be an effective treatment strategy for PIN1-overexpressing tumours. Furthermore, proteasome inhibitor bortezomib (BZB) has been shown to suppress HCC cell growth through down-regulation of PIN1 and its transcription factor E2F<sup>[113]</sup>. As a single agent, however, the benefit of BZB in advanced HCC patients is limited<sup>[114]</sup>. Combination of BZB with other agents as treatment for HCC should be further evaluated.

## CONCLUSION

HCC is an aggressive cancer associated with a poor prognosis. Conventional treatment options available for advanced HCC patients are very limited. Identification of important molecular targets in HCC may lead to the development of a new therapeutic approach. Dysregulation of PIN1 expression is associated with HCC and its expression is positively correlated with tumour size. Through phosphorylation-dependent prolyl isomerization, PIN1 functions as an amplifier to augment the oncogenic activities of its interacting proteins in hepatocarcinogenesis. The diverse oncogenic effects exerted by PIN1 overexpression in HCC render PIN1 as an attractive therapeutic target for treatment. In fact, several studies have already demonstrated that inhibiting PIN1 activity results in the suppression of cell growth and tumour development. Further studies and clinical trials are required to examine the safety and efficacy of PIN1 inhibition in the treatment of HCC.

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