Roles of peptidyl-prolyl isomerase Pin1 in disease pathogenesis

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Abstract

Pin1 belongs to the peptidyl-prolyl cis-trans isomerases (PPIases) superfamily and catalyzes the cis-trans conversion of proline in target substrates to modulate diverse cellular functions including cell cycle progression, cell motility, and apoptosis. Dysregulation of Pin1 has wide-ranging influences on the fate of cells; therefore, it is closely related to the occurrence and development of various diseases. This review summarizes the current knowledge of Pin1 in disease pathogenesis.

Key words: peptidyl-prolyl cis-trans isomerases, Pin1, pathogenesis of diseases, viral infection, neurodegenerative diseases

Introduction

Some proteins exhibit either a cis or a trans state due to the presence of proline, which imparts distinct conformations and biological functions. The peptidyl-prolyl cis-trans isomerases (PPIases) superfamily [1] comprises four families according to their structural differences: cyclophilins, FK506-binding proteins (FKBPs), parvulins, and the protein phosphatase (PPase) 2A phosphatase activator (PTPA) [2-6].

In the human parvulin family, there are two genes: PIN1 and PIN4 [7-9]. The coded product of PIN1, PPIase NIMA-interacting 1 (Pin1) protein, was identified in 1996 by Lu et al. as a protein interacting with NIMA kinase [7]. PIN4 encodes the isoforms parvulin 14 (Par14) and parvulin 17 (Par17) [9, 10]. Parvulin 14 consists of 131 amino acids, while parvulin 17 is an N-terminal extended version of Par14 with an additional 25 amino acids. Among the three members of the human parvulin family, current research on the function of Pin1 and its role in disease pathogenesis is the most in-depth. Pin1 consists of 163 amino acid residues with a relative molecular mass of 18 kDa and contains 1 nuclear localization signal and 2 functional domains. The amino terminus (N-terminus) is the tryptophan-tryptophan central domain (WW domain), which is responsible for recognition and binding to the pSer/Thr-Pro motif of the substrate, while the C-terminal PPIase catalytic domain performs the function of cis-trans isomerization [7, 11]. The two domains are fastened by a flexible linker of 15 residues. Although they belong to the same family, Pin1 differs from parvulin-type PPIases in that Pin1 specifically catalyzes the isomerization of phosphorylated Ser-Pro or Thr-Pro (pSer-Pro or pThr-Pro) peptides, whereas Par14/Par17 show no preference for phosphorylated substrates [9, 12, 13].

Since Pin1 isomerizes phosphorylated substrates and phosphorylation and post-phosphorylation events play important roles in cell signaling pathways, Pin1 is involved in a variety of cellular processes such as cell cycle, cell proliferation, cell motility, and apoptosis [13-18]. In most cases, Pin1
functions as a molecular timer or switch that modulates proteins or entire signaling pathways. Dysregulation of Pin1 is closely related to the development of multiple diseases. In this review, we will discuss the role of Pin1 in the pathogenesis of various related diseases.

**Pin1 and cancer**

Overall, Pin1 drives tumor progression and is negatively associated with clinical outcome in patients with cancer [19-21]. Pin1 has been shown to activate more than 50 oncogenic proteins and growth promoters and/or shut down at least 20 tumor suppressors and growth inhibitors through positive and negative feedback mechanisms [12, 22] (Table 1). Most tumors exhibit overexpression and/or activation of Pin1 compared with corresponding normal tissues, including breast, prostate, lung, ovarian, gastric, esophageal, cervical, and brain tumors and melanoma [21, 23-25]. Expression of Pin1 in tumor cell lines cultured *in vitro* has also been found to be significantly higher than that in normal cell lines. Knockdown of the Pin1 gene inhibits cancer cell growth both *in vitro* and *in vivo* and results in cancer cell apoptosis [26, 27]. In addition, emerging evidence suggests that inhibitors targeting Pin1 have significant anti-cancer effects. These inhibitors include juglone [27, 28], all-trans retinoic acid (ATRA) [29, 30], 2-[(4-(4-tert-butylbenzenesulfonamido) -1-oxo-1,4-dihydroronaphthalen-2-yl) sulfanyl] acetic acid (KPT-6566) [31], epigallocatechin-3-gallate (EGCG) [32], PiB [33], compound 20 [34], compound 23a [35], API-1 [36], arsenic trioxide (ATO) [37], and BJP-06-005-3 [38]. In a recent review [22], Chen *et al.* elaborated on how Pin1 contributes to all ten hallmarks of cancer [39] by dysregulating multiple cancer-driving pathways at various levels. Pin1 induces angiogenesis by facilitating expression of VEGF and inhibition of Pin1 by RNAi significantly suppresses angiogenesis [40, 41]; Pin1 sustains proliferative signaling and evades growth suppression by activating growth-promoting regulators and inactivating growth-inhibitory regulators [22]; Pin1 promotes migration and invasion by regulating NOTCH1 [42], TGF-β [43], β-catenin [44], and BRD4 [45]; Pin1 inhibits apoptosis of tumor cells by increasing the anti-apoptotic function of anti-apoptotic proteins and suppressing pro-apoptotic factors [46, 47]. This concept has recently been greatly expanded, demonstrating that overactivation of Pin1 disrupts the balance between carcinogenic proteins and tumor suppressors, which pushes cells towards carcinogenesis [12] (Figure 1).

**Table 1. Oncogenic proteins/growth-promoting regulators and tumor suppressors/growth-inhibitory regulators as Pin1 substrates**

| Substrate | Function | Activity of substrate | Ref. |
|-----------|----------|----------------------|------|
| AIB1      | Oncogenic protein | ↑ | [158] |
| AKT       | Oncogenic protein | ↑ | [159] |
| BCL2      | Oncogenic protein | ↑ | [160] |
| JUN       | Oncogenic protein | ↑ | [203] |
| CON2      | Oncogenic protein | ↑ | [162] |
| FOXO1     | Oncogenic protein | ↑ | [162] |
| FOXM1     | Oncogenic protein | ↑ | [163] |
| HIF2      | Oncogenic protein | ↑ | [164] |
| MYC       | Oncogenic protein | ↑ | [165] |
| Survivin  | Oncogenic protein | ↑ | [46]  |
| Tax       | Oncogenic protein | ↑ | [118] |
| XB1      | Oncogenic protein | ↑ | [166] |
| AR        | Growth-promoting regulator | ↑ | [167] |
| CDC25     | Growth-promoting regulator | ↑ | [168] |
| Cep55     | Growth-promoting regulator | ↑ | [169] |
| MYB       | Growth-promoting regulator | ↑ | [170] |
| Cyclin D1 | Growth-promoting regulator | ↑ | [23]  |
| ER        | Growth-promoting regulator | ↑ | [164] |
| FAK       | Growth-promoting regulator | ↑ | [171] |
| HBx       | Growth-promoting regulator | ↑ | [113] |
| HIF1      | Growth-promoting regulator | ↑ | [172] |
| HSFI      | Growth-promoting regulator | ↑ | [173] |
| IRAK1     | Growth-promoting regulator | ↑ | [174] |
| MCL1      | Growth-promoting regulator | ↑ | [175] |
| Nanog     | Growth-promoting regulator | ↑ | [176] |
| NF-kB     | Growth-promoting regulator | ↑ | [177] |
| NOTCH1    | Growth-promoting regulator | ↑ | [178] |
| NOTCH3    | Growth-promoting regulator | ↑ | [179] |
| NUR77     | Growth-promoting regulator | ↑ | [180] |
| OCT4      | Growth-promoting regulator | ↑ | [181] |
| p47phox   | Growth-promoting regulator | ↑ | [182] |
| p53M      | Growth-promoting regulator | ↑ | [183] |
| PKG1      | Growth-promoting regulator | ↑ | [115] |
| PKM2      | Growth-promoting regulator | ↑ | [184] |
| PLK       | Growth-promoting regulator | ↑ | [185] |
| PML-RARA  | Growth-promoting regulator | ↑ | [186] |
| PTP       | Growth-promoting regulator | ↑ | [187] |
| PTP-PEST  | Growth-promoting regulator | ↑ | [171] |
| RAF2A     | Growth-promoting regulator | ↑ | [188] |
| RAF1      | Growth-promoting regulator | ↑ | [189] |
| RSK2      | Growth-promoting regulator | ↑ | [190] |
| S642      | Growth-promoting regulator | ↑ | [189] |
| S6K       | Growth-promoting regulator | ↑ | [191] |
| Separase  | Growth-promoting regulator | ↑ | [192] |
| SEPT9     | Growth-promoting regulator | ↑ | [193] |
| BRD4      | Growth-promoting regulator | ↑ | [185] |
| STAT3     | Growth-promoting regulator | ↑ | [186] |
| v-Rel     | Growth-promoting regulator | ↑ | [194] |
| β-catenin | Growth-promoting regulator | ↑ | [183] |
| BAX       | Tumor suppressor | ↓ | [47]  |
| CDK10     | Tumor suppressor | ↓ | [195] |
| CHIP      | Tumor suppressor | ↓ | [107] |
| DAXX      | Tumor suppressor | ↓ | [196] |
| FADD      | Tumor suppressor | ↓ | [197] |
| FBX1W7    | Tumor suppressor | ↓ | [198] |
| FOXO4     | Tumor suppressor | ↓ | [199] |
| IRF5      | Tumor suppressor | ↓ | [200] |
| KLF10     | Tumor suppressor | ↓ | [201] |
| PML       | Tumor suppressor | ↓ | [202] |
| pRb       | Tumor suppressor | ↓ | [203] |
| RARα      | Tumor suppressor | ↓ | [186] |
| RUNX3     | Tumor suppressor | ↓ | [204] |
| SMRT      | Tumor suppressor | ↓ | [205] |
| AMPK      | Growth-inhibitory regulator | ↓ | [206] |
| ATR       | Growth-inhibitory regulator | ↓ | [207] |

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Pin1 and cardiovascular diseases

Atherosclerosis (AS) is a chronic disease and the main cause of coronary heart disease, cerebral infarction, and peripheral vascular disease [48]. The early stage of AS is mainly caused by endothelial dysfunction. Endothelial nitric oxide synthetase (eNOS) plays a key role in the control of blood pressure and prevention of atherosclerosis by producing the vasodilator and vascular protective molecule nitric oxide (NO) [49]. eNOS interacts with Pin1 in a phosphorylation-dependent manner in endothelial cells. Phosphorylation of eNOS at Ser116 enhances this interaction, thus inhibiting eNOS activity and reducing NO release [52]. These results indicate that Pin1 reduces NO synthesis by inhibiting eNOS and, thus, exerts a negative effect in cardiovascular disease.

However, in some conditions, Pin1 may protect vascular endothelial homeostasis. TGF-β stimulates synthesis of proteoglycan in vascular smooth muscle cells (VSMC), especially expression of disaccharide chain protein and extension of glycosaminoglycan (GAG) chain on biglycan, which increases lipoprotein binding and promotes early inflammation of atherosclerosis [53, 54]. It has been shown that Pin1 enhances degradation of Smad2/3 ubiquitin proteasome induced by Smurf2 and inhibits TGF-β signal transduction [55], effectively preventing early occurrence of atherosclerosis [56]. Another study showed that Pin1 inhibition significantly suppresses NO production in human periodontal ligament cells (PDLCs) [57]. Taken together, Pin1 potentially plays a double-edged role in regulating the pathogenesis of cardiovascular diseases under different circumstances. Similarly, both overexpression and downregulation of Pin1 can reduce cardiac hypertrophy [58]. Further detailed investigations are needed to reveal the function of Pin1 in cardiovascular disease.

Pin1 and metabolic diseases

Insulin dysregulation is associated with various metabolic diseases including obesity, NASH, and type 2 diabetes. Pin1 promotes insulin secretion of islet β cells by enhancing the activity of SIK2, and also promotes cell proliferation and transformation by regulating activation of API1 and ERK1/2 induced by insulin through interaction with p70S6K [59, 60]. Pin1 also positively regulates insulin-induced phosphorylation of IRS-1: Pin1 deletion inactivates IRS-1, thus leading to insulin resistance [61]. It can be concluded that Pin1 is involved in these metabolic...
diseases partially by controlling insulin signaling. However, Pin1 interacts with or regulates other key molecules involved in metabolic diseases, including obesity-related factors AMPK [62-65], PPARγ [66], and PRDM16 [67]; osteoporosis-related factors Runx2 [68-70] and BMP2 [71]; and Nash-related factors Smad2/Smad3 and the TGF-β1 pathway [72]. The detailed mechanisms by which Pin1 regulates metabolic diseases are summarized in other reviews [73, 74].

**Pin1 and neurodegenerative diseases**

Although emerging evidence has shown that Pin1 directly or indirectly regulates neuronal proteins such as Tau, amyloid precursor protein (APP), and α-synuclein, the physiological functions of Pin1 in neurodegenerative diseases remain to be elucidated. For example, in Parkinson’s disease (PD) and Huntington’s disease (HD), Pin1 is a pro-apoptotic factor in the process of neuronal degeneration, and high levels of Pin1 expression have been found in the brain tissue of patients [75-78]. In other studies, downregulation of Pin1 expression was found to increase the likelihood of developing Alzheimer’s disease (AD), and low expression of Pin1 was found in patients with AD [74, 78-80].

**Alzheimer’s disease**

Increased deposition of plaques and intracellular neurofibrillary tangles (NFTs) are the main mechanisms of AD pathogenesis. NFTs are microtubule aggregations produced by hyperphosphorylation of Tau protein [74]. Extracellular plaques are primarily composed of aggregates of amyloid-β-peptides (Aβ) derived from increased APP processing [74, 81, 82]. In the neuronal cells of patients with AD, Pin1 is usually underexpressed and exhibits a negative correlation with degeneration of neuronal fibers [83]. Pin1 catalyzes the conformational switch of GSK-3β-mediated phosphorylated Tau proteins from the dysfunctional cis structure to the functional trans structure, thus degrading Tau proteins [84-86]. Additionally, Pin1 catalyzes phosphorylation of APP Thr668-Pro from the cis to trans isomer and also transforms APP processing to healthy non-amyloid formation [84]. Pin1 can also directly inhibit activation of GSK-3β by binding to the phosphorylated Thr330-Pro motif of GSK-3β and catalyzing its isomerization [84, 87]. Evidence suggests that overexpression of Pin1 in mature neurons can prevent neurodegeneration caused by Tau hyperphosphorylation [79]. In general, events that decrease expression of Pin1 in the brain increase the likelihood of AD [88] (Figure 2A).

**Parkinson’s disease**

Lewy bodies (LBs) are the characteristic protein aggregates in tissues of PD. LBs are a characteristic protein polymer of PD. α-synuclein is the main component of LBs. Pin1 binds synphilin-1 phosphorylated by CKII and regulates its interaction with α-synuclein, thereby co-locating with α-synuclein intracellularly. (C) Pin1 binds and regulates p53 phosphorylated by mHTT. Subsequently, p53 is separated from the apoptosis inhibitor iASSP and is cascade activated, thus inducing neuronal apoptosis.
under the phosphorylation mediated by casein kinase II (CKII), Pin1 binds to phosphorylated synphilin-1 through Ser211-Pro and Ser215-Pro motifs, thus α-synuclein indirectly interacting with α-synuclein through indirect effects [75, 97].

Due to the absence of a pSer/Thr-Pro motif in mHTT, it was found to be expressed in 50-60% of LBs and was co-localized with α-synuclein in inclusion bodies [75]. From the immunohistochemical analysis of the brain tissue of patients with PD, Pin1 expression of α-synuclein and synphilin-1 was found to be expressed in 50-60% of LBs and was co-localized with α-synuclein in inclusion bodies [75].

α-synuclein causes the formation of debris inclusion bodies in the cytoplasm [93, 96]. From immunohistochemical analysis of the brain tissue of patients with PD, Pin1 was found to be expressed in 50-60% of LBs and was co-localized with α-synuclein in inclusion bodies [75].

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Therefore, it can be speculated that inhibitors targeting Pin1 may alleviate the process of PD.

**Huntington’s disease**

HD is a neurodegenerative disease caused by repeated amplification of the gene encoding CAG in huntingtin protein (HTT) [98]. The mutant huntingtin protein (mHTT) forms an endonuclear inclusion by misfolding and aggregating [99, 100]. mHTT is toxic, and its aggregation causes glial proliferation of astrocytes and selective loss of striatal neurons [101, 102]. mHTT can also cause DNA damage in neurons (DDR) [103, 104], which is a significant pathological feature of HD. Studies have found that p53 mediates this cytotoxicity in HD cells and transgenic animal models, while p53 inhibitors block this process [105]. mHTT promotes phosphorylation of p53 at Ser16 through HIPK2 and PKCδ, making it a target for Pin1 binding and regulation [76]. Pin1-mediated p53 isolates from the apoptosis-inhibiting factor iASPP, thus promoting the activation cascade of p53 in striatal neurons and increasing neuronal apoptosis [76, 106] (Figure 2C).

Conversely, when Pin1 is silenced, p53 binds to iASPP regardless of mHTT expression and p53 fails to induce apoptosis, thereby preventing mHTT-dependent neurodegeneration [76]. Pin1 is also associated with DDR in the regulation of DNA double-strand fracture repair [107]. In one study, DNA damage signal intensity in Pin1-knockout mice was significantly reduced by 20% compared with that of the wild-type HD mouse model [77]. However, another study revealed that Pin1 is a negative regulator of mHTT aggregation and that Pin1 overexpression reduces mHTT aggregates in HEK293 cells [108]. Nevertheless, experimental results from human neuronal cells and HD mice suggest that Pin1 is a potential therapeutic target for HD treatment.

**Pin1 and viral infection**

Viruses are common pathogens that cause infectious diseases. When a virus invades a host, the host activates its own immune system to fight or clear the infection [109]. But there are proteins in the host that help the virus reduce resistance from the host or promote the viral infection process. Some studies have found that Pin1 is one of these proteins and is closely related to viral infections [20, 110-119].

**HIV**

Acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV) infection [120]. Host protein Pin1 promotes HIV infection by mediating three key processes in the HIV replication cycle [121-123] (Figure 3A).

First, the HIV core relies on Pin1 to remove capsid proteins: The HIV core is composed of ribonucleic acid (RNA) molecules and capsid protein.

When HIV infects a host, it must remove the capsule and release RNA for subsequent reverse transcription, replication, and other processes [124]. The extracellular signal-regulated kinase 2 (ERK2) specifically phosphorylates Ser16-Pro17 residues on capsid proteins [124]. Pin1 then binds to the phosphorylated Ser16-Pro17 motif, which rearranges the structure of the capsid protein and removes the capsid from the HIV core [125].

Second, Pin1 facilitates reverse transcription of the HIV genome: Reverse transcription of the HIV genome is an important step in the life cycle of HIV, as DNA produced by reverse transcription can be incorporated into the host genome [126]. Host protein A3G (APOBEC3G) induces mutations in DNA during reverse transcription, which limits HIV replication [127]. But Pin1 downregulates A3G expression and prevents A3G from entering HIV [128]. HIV infection increases phosphorylation of Pin1 at Ser16 and enhances the inhibitory effect of Pin1 on A3G [111, 128].

Third, Pin1 helps integrate HIV cDNA into the host DNA: HIV needs to integrate its cDNA into the host genome to reliably transcribe its progeny RNA [129]. The cellular kinase JNK phosphorylates the pSer57 motif of HIV integrase [130]. Pin1 then binds to the phosphorylated pSer57-Pro motif to activate and stabilize HIV integrase activity, which helps it insert the HIV cDNA into the host genome [130, 131].
Figure 3. Roles of Pin1 in virus infection. (A) In HIV, the Ser16-Pro17 motif of the capsid protein is phosphorylated by ERK2. Pin1 specifically binds the motif and rearranges the capsid structure to release HIV RNA. Pin1 inhibits expression of catalytic polypeptide A3G to prevent incorrect coding of HIV cDNA during reverse transcription. Pin1 binds to the Ser57-Pro motif of integrase after its phosphorylation by the cellular kinase JNK, thus enhancing the stability of the integrase and promoting integration of HIV cDNA into the host cell DNA. (B) The viral protein NS5A/NS5B contains multiple phosphorylated Ser/Thr-Pro motifs. Interaction of overexpressed Pin1 with NS5A/NS5B increases HCV RNA replication and enhances HCV infection. (C) BALF5 is a key enzyme that regulates EBV DNA replication. Pin1 binds to the Thr178-Pro motif of BALF5 and actively regulates EBV DNA replication by regulating the conformation of the enzyme. Pin1 can also promote proliferation of EBV-infected nasopharyngeal carcinoma cells by upregulating expression of cyclin D1. (D) Viral oncoprotein Tax plays an important role in cell proliferation and viral replication. In HTLV-1-infected cells, Tax activates the RB/E2F pathway to increase expression of Pin1, which maintains the stability of Tax. Pin1 binds to the Ser160-Pro motif of Tax after its phosphorylation by mitotic kinase, which enhances the ability of Tax to directly bind IKKγ, activate NF-κB signaling, and finally promote cell proliferation and tumor occurrence. (E) In HPV-infected cells, overexpression of Pin1 causes NF-κB nuclear retention and activation of STAT3. Viral protein E2 can target and enhance the activity of Pin1 to increase the likelihood of cancer caused by HPV infection. (F) The viral protein HBx is a trans-activator of liver cancer. HBx activates cyclin D1 and the signaling pathway Wnt/β-catenin. Pin1 binds to the Ser41-Pro motif of HBx, which stabilizes the activity of HBx and induces overexpression of cyclin D1 and β-catenin, thus promoting liver cancer in HBV infection.

HCV

Hepatitis C virus (HCV) is the main pathogen of chronic hepatitis and hepatocellular carcinoma (HCC). HCV is an enveloped RNA virus [132]. The replication process of HCV depends mainly on the host cell cycle and requires participation of host proteins [133]. Pin1 has been shown to be a necessary cytokine for HCV replication and can increase HCV infection [114]. Overexpression of Pin1 increases intracellular HCV RNA and intracellular viral protein
EBV

Epstein-Barr virus (EBV) infection is associated with Burkitt lymphoma and production of T-cell malignancies [134]. BALF5, the EBV DNA polymerase subunit, is a key enzyme that affects replication during EBV cleavage [135]. Pin1 has been shown to be an important factor in regulating EBV replication. BALF5 interacts with Pin1 in a phosphorylation-dependent manner at Thr^{175}-Pro of the BALF5 subunit. In one study, Pin1 knockdown by shRNA significantly inhibited EBV replication [119]. Another study showed that Pin1 is overexpressed in all EBV-associated nasopharyngeal carcinoma (NPC) cells, xenografts, and primary tumors [20]. Overexpression of Pin1 induces tumor cell growth by promoting production of cyclin D1 and activating the MAPK/JNK pathway (Figure 3C). The Pin1 inhibitor Juglone has been shown to inhibit growth of nasopharyngeal carcinoma cells and induce their apoptosis [20].

HTLV-I

Human T-cell leukemia virus type 1 (HTLV-1) is the pathogen that causes adult T-cell leukemia (ATL) [136]. The oncoprotein Tax encoded by HTLV-1 plays an important role in cell proliferation, viral gene replication, transformation, and tumor generation [137, 138]. Expression of Tax may cause overexpression of Pin1 in ATL [116, 118]. In cells infected by HTLV-1, Tax activates the E2F/RB pathway to increase transcription and expression of Pin1. Pin1 binds to the Tax phosphorylation motif pSer^{160}-Pro in the presence of mitotic kinases. Pin1-regulated phosphorylated Tax then interacts with IKKγ to promote NF-κB activation [118, 139]. The activity of NF-κB plays an important role in cell transformation, cell proliferation and cancer development [140]. Pin1 can also inhibit both ubiquitination and lysosomal degradation of Tax, thus promoting its stability [116] (Figure 3D).

HBV

Hepatitis B virus (HBV) is a common pathogen in hepatocellular carcinoma (HCC) and HBV-encoded protein HBx is a trans-activator of liver cancer [147]. A study found that overexpression of Pin1 was most common in HBV-related HCC, and the majority of cases showed co-expression of Pin1 and HBx [113]. HBx contains two phosphorylated Ser-Pro motifs that are potential targets for Pin1 [148, 149]. Pin1 binds to the phosphorylated Ser^{41}-Pro motif of HBx, which increases HBx stability and transactivation [113, 149]. HBx activates the oncogenic transcription factor cyclin D1 and the β-catenin signaling pathway associated with oncogenesis [150]. Overexpression of Pin1 not only increases expression of cyclin D1 but also promotes intracellular accumulation of β-catenin in the Wnt/β-catenin signaling pathway [151, 152]. These two aspects can increase expression of oncogenes and promote occurrence of HCC in HBV infection (Figure 3F).

In summary, Pin1 promotes most viral infectious diseases by two broad mechanisms: (1) Pin1 is directly involved in the life cycle of the virus to promote viral infection. For example, Pin1 is involved in core exuviation, reverse transcription, and integration of the virus in HIV infection [111]. In HCV infection, Pin1 is involved in viral RNA replication [114]. Pin1 is also involved in viral DNA replication in EBV infection [119]. (2) Pin1 enhances the stability and production of oncogenic proteins. For example, Pin1 increases the stability of Tax in HTLV-1 infection and mediates Tax transactivation of NF-κB factor [116, 118]. In HBV infection, Pin1 stabilizes the oncoprotein HBx and increases expression of oncogenic proteins cyclin D1 and catenin [112, 113]. In HPV infection, Pin1 is involved in increased activation of transcription factors STAT3 and NF-κB [117]. Pin1 also increases expression of the oncogenic protein cyclin D1 in EBV infection [20]. Tanaka et al. also found that dipentamethylene thiram monosulfide, a specific inhibitor of Pin1, inhibited feline coronavirus (FCoV) replication [153], suggesting that targeting
Pin1 may provide new insights for antiviral therapy.

Conclusions and future directions

In summary, our review illustrates the potential roles of Pin1 in several common diseases. Due to the overexpression of Pin1 in tumor tissues and its role in promoting tumor progression, drugs currently under development for targeting Pin1, including natural products, chemical compounds, and peptide drugs, are mainly focused on cancer treatment. Although Pin1 inhibitors have shown tumor suppressive effects in cell lines, animal models, and even clinical trials, some inhibitors reveal a Pin1-independent mechanism and the side effects have yet to be clarified. For example, Pin1 inhibitor KPT-6566 may exert anti-cancer effects through at least two simultaneously acting mechanisms: inhibition of Pin1 and ROS production [31]. API-1 shows significant anti-HCC activity, but its low water solubility and in vivo bioavailability limit its clinical application [154]. Researchers have also identified some compounds or peptides such as PEPTIDE [155] and benzothiphene [156, 157] that suppress Pin1 activity at nanomolar concentrations but are inactive in cell-based assays because of their poor membrane permeability. One potential countermeasure is to increase the membrane bioavailability of these compounds by optimizing their structure or looking for corresponding derivatives. Research on the application of Pin1 inhibitors and agonists in other related diseases is limited, and more detailed investigations need to be carried out for therapeutic potential, especially in diseases such as viral infection and AD in which the role of Pin1 is relatively clear. Studies on the upstream regulatory signals and downstream targets of Pin1 can also provide ideas for expanding treatment strategies for the above-mentioned diseases.

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Competing Interests

The authors have declared that no competing interest exists.

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