

Pin1 as a central node in oncogenic signaling: Mechanistic insights and clinical prospects (Review)

SHUNING LEI*, MIN LUO* and YUXUE WANG

Department of Laboratory Medicine, Hubei University of Chinese Medicine, Wuhan, Hubei 430065, P.R. China

Received August 25, 2024; Accepted January 14, 2025

DOI: 10.3892/mmr.2025.13445

Abstract. Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) is a specific phosphorylated serine/threonine-proline cis-trans isomerase, which is involved in the regulation of a variety of physiological and pathological processes, including cell cycle progression, proliferation and apoptosis. Pin1 plays a key role in tumorigenesis and tumor development and it promotes the proliferation and metastasis of cancer cells by regulating the cell cycle, signaling pathways and the function of tumor suppressors. Upregulated expression of Pin1 is closely associated with a poor prognosis in several types of cancers. Thus, Pin1 may have potential as a novel potential biomarker for tumor diagnosis and prognosis, as well as a promising anticancer target. The aim of the present review was to discuss the mechanism of Pin1 in tumors and recent research progress in this field.

Contents

1. Introduction
2. Mechanism of the Pin1 gene in regulating tumorigenesis
3. Role of Pin1 in multiple oncogenic signaling pathways
4. Pin1 inhibitors
5. Comparative novelty of the present review
6. Conclusions and future perspective

1. Introduction

Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) is an enzyme that belongs to the peptidyl-prolyl cis-trans

isomerase (PPIase) family (1). Pin1 induces conformational changes and functional transitions in target molecules by catalyzing the phosphorylation of serine/threonine (Ser/Thr) residues as well as the phosphorylation of Ser/Thr-Pro motifs (Fig. 1) (2).

The Ser/Thr-pro motif encompasses kinases such as CDKs, MAPKs (including P38, JNK and ERK) and GSK-3 β , as well as Ser/Thr phosphodiesterases such as PP2A, Fcp1 and Calcineurin. The former belongs to the proline-directed kinase family, whereas the latter belongs to the proline-directed phosphodiesterase family. ERK2, CDK2 and PP2A all exhibit trans-isomeric properties before and after phosphorylation. Previous studies have also confirmed the enhanced stability of CyclinD1, β -Catenin and P53 after cis- or trans-isomerization (3,4), which is closely related to tumor development (5).

Pin1 consists of 163 amino acids and contains two major functional domains: The WW structural domain located at the N-terminal end, which is primarily responsible for recognizing and binding phosphorylated Ser/Thr-proline motifs; and the PPIase structural domain located at the C-terminal, which catalyzes the cis- and trans-isomerization of proline residues (Fig. 1) (6).

Pin1 catalyzes the phosphorylation of the Ser/Thr-Pro motif through its C-terminal PPIase structural domain, which induces conversion of the proline residues between the cis and trans conformation. This cis-trans isomerization results in a change in protein conformation, which in turn affects protein function, stability, or interactions with other proteins (Fig. 2) (7). Pin1 can act on numerous phosphoproteins that regulate cell division (Table I). Previous studies have also shown that Pin1 is upregulated in several types of cancer where it promotes cell proliferation and inhibits apoptosis by regulating the Ser/Thr-Pro motifs of oncogenes and tumor suppressor genes (8,9). The present review focused on the mechanisms by which Pin1 acts on certain key proteins in tumorigenesis.

2. Mechanism of the Pin1 gene in regulating tumorigenesis

Pin1 not only exhibits upregulated expression in several types of cancer, but also plays a crucial role in tumorigenesis and is a known catalyst of tumorigenesis. Its overexpression can activate multiple oncogenic pathways (10).

Overactivation of Cdc25C or upregulated expression of Pin1 abrogates the cell cycle and promotes tumor growth and proliferation. Cdc25C is a cell cycle protein phosphatase that

Correspondence to: Professor Yuxue Wang, Department of Laboratory Medicine, Hubei University of Chinese Medicine, 16 Huangjiahuxi Road, Hongshan, Wuhan, Hubei 430065, P.R. China

E-mail: wangyuxue20012001@163.com

*Contributed equally

Key words: Pin1, tumor, cell cycle, signaling, apoptosis

is primarily responsible for removing the phosphate group and activating CDKs, especially CDK1 during the G₂/M phase transition, thus promoting entry into the mitotic phase (11).

In different types of cancer, the expression patterns of Pin1 and Cdc25C show significant differences. For example, in breast cancer and non-small cell lung cancer, upregulated expression of Pin1 and Cdc25C is associated with aggressive tumor behaviors and a poor prognosis (9,12,13). However, in colorectal cancer, this association is not as clear (14,15). After phosphorylation by Polo-like kinase (16), Cdc25C is activated, but stabilization of its activity requires the catalytic action of Pin1 to form the trans-isomer. This reversible process involves the specific action of PP2A, which dephosphorylates trans-Cdc25C, leading to its inactivation and thus preserving the equilibrium of Cdc25C activity. The regulatory role of Pin1 is multifaceted in modulating Cdc25C activity during the G₂/M phase. While insufficient Pin1 activity has been implicated in Cdc25C dysfunction, the context-dependent nature of Pin1's effects on Cdc25C activity suggests a more intricate relationship (11). Overexpression of Cdc25C or excessive Pin1 activity can lead to cell cycle deregulation, promoting uncontrolled cell proliferation, a hallmark of cancer development. This complex interplay is supported by studies showing both the inhibitory (17-19) and activating effects (20) of Pin1 on Cdc25C, highlighting the need for a nuanced understanding of the role of Pin1 in tumorigenesis. Studies have shown that Cdc25 is overexpressed in several types of cancer (21,22) and the two isoforms of Cdc25 phosphatase, Cdc25A (23) and Cdc25B (24) may be overexpressed either alone or in combination in a variety of cancers, including breast, lung, ovarian, colon, esophageal, gastric, hepatocellular (HCC), non-small cell lung, non-Hodgkin's lymphoma, pancreatic ductal, thyroid and head and neck cancer, among others (9,12). Upregulated expression of Pin1 and Cdc25C are typically associated with poorer prognostic outcomes, indicating that these proteins may serve as valuable prognostic indicators for certain types of cancer (25). Thus, assessing the expression of Pin1 and Cdc25C in tumors may provide critical insights into patient prognosis and guide therapeutic strategies.

Pin1 enhances Cyclin D1 stability and promotes cancer cell proliferation. In the course of performing the background research for the present review, >30 target proteins of Pin1 were identified (Table I), among which Cyclin D1 has received the most attention. Cyclin D1 is a key protein in cell cycle regulation and functions primarily in the G₁ phase (26). It facilitates the cellular transition from G₁ to S phase by binding to CDK4 or CDK6 to form the Cyclin D1-CDK4/6 complex (27). The stability and expression levels of Cyclin D1 are critical for cell cycle progression (Fig. 3).

Regarding the expression pattern of Cyclin D1, studies have shown that ~50% of patients with breast cancer exhibit upregulated expression levels of Cyclin D1 and it is also overexpressed in HCC and squamous cell carcinoma of the head and neck (26,28). These data suggest that the co-expression of Pin1 and Cyclin D1 may be a common feature of several types of cancer, highlighting it as a potential biomarker (9).

Phosphorylation of Cyclin D1 at the Thr286 site is a critical step in the regulation of its degradation and function (29). Pin1 recognizes and binds phosphorylated Cyclin D1 through its

WW structural domain. Subsequently, Pin1 uses its PPIase structural domain to cis-trans-isomerize Cyclin D1 and inhibit its binding to CRM1, a Cyclin D1 efflux factor and thus stabilizes Cyclin D1 (30). In addition to affecting the stability of Cyclin D1, Pin1 can also indirectly affect the expression of the Cyclin D1 gene by regulating the activity of transcription factors (such as c-Jun and AP-1) (31), further highlighting its role in cell cycle regulation.

Current studies have shown that 50% of patients with breast cancer exhibit upregulated expression levels of Cyclin D1 (26,27,32). Additionally, overexpression and gene amplification of Cyclin D1 have been associated with several types of cancer, including head and neck squamous cell carcinoma, esophageal cancer and HCC (33). Therefore, Pin1 inhibitors may pave the way for more precise management of breast cancer (34).

Pin promotes p53-mediated cell cycle arrest and apoptosis and suppresses tumorigenesis. P53 is an oncogenic protein that plays a key role in regulating cell cycle checkpoints, maintaining genomic stability and promoting apoptosis and is therefore known as the 'guardian of the genome' (35). In various malignant tumors, >50% of the cases show mutations in the P53 gene (36).

The frequency of P53 mutations varies significantly in different tumor types. For example, the incidence of P53 mutations is high in breast and colon cancers and relatively low in certain lymphomas (9). This difference may affect the role of Pin1 as it promotes the physiological function of P53, although its function may be inhibited in the case of mutations.

When DNA is damaged, upstream kinases such as checkpoint kinase 1/2, ataxia-telangiectasia mutated and ataxia telangiectasia and Rad3-related protein are activated, which phosphorylate multiple serine/threonine (Ser/Thr) sites of P53, including those preceding proline residues, thereby protecting P53 from ubiquitination (37), ensuring its high level of expression in the cell. This enhances the tumor suppressor function of P53. Increasing the levels of P53 promotes the expression of p21, leading to cell cycle arrest and favoring the repair of damaged DNA (38). When DNA damage persists, P53 also promotes the expression of proteins such as BAX, death receptor 5/killer, Fas and Fas ligand, which in turn triggers apoptosis (39).

Pin1 protein recognizes and binds phosphorylated P53 through its WW structural domain and this interaction leads to cis-trans isomerization of P53, further enhancing its stability and activity as a transcription factor (4). In tumor cells, Pin1 exerts its tumor suppressor effect by enhancing the function of wild-type P53, inhibiting tumor cell proliferation and promoting apoptosis (36). However, in certain types of cancer, mutations in the P53 gene result in the loss of its tumor suppressor function, at which point the role of Pin1 may vary, depending on the nature and location of the mutation (40).

Pin1 regulates the Ras/AP-1 signaling pathway and promotes cancer cell proliferation. Ras proteins belong to a family of small GTPases that serve a crucial role in numerous cell signaling pathways (41). When Ras binds to GTP, GTP is activated, which in turn activates a range of downstream effector

Table I. Pin1-interacting proteins.

Protein	Function
NIMA	Mitotic kinase
Cdc25C	Protein phosphatase for Cdc2
Plk 1	Mitotic kinase
Cdc27	Anaphase-promoting complex component
Rab4	GTP-binding protein
p70/S6 kinase	Protein kinase
Wee 1	Mitotic kinase
Myt 1	Mitotic kinase
CENP-F	Kinetokore protein
Incenp	Inner centromere protein
Tau	Microtubule-interacting protein
PolII	RNA polymerase II
Sin3-Rpd3	Histone deacetylase
NHERF-1	Na ⁺ /H ⁺ exchanger regulatory factor 1
KRMP 1	Kinesin-related protein
hSpt5	A DRB sensitivity-inducing factor component
Bcl-2	Anti-apoptotic factor
c-Jun	Transcription factor
β-catenin	Transcription activator
NFAT	Transcription factor
Cf-2	Transcriptional repressor
Cyclin D1	Cell cycle regulator
CK2	Protein kinase
P53	Transcription factor

Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; NIMA, never in mitosis gene A; Cdc25C, cell division cycle 25C; Plk 1, polo-like kinase 1; Cdc27, cell division cycle 27; Rab4, Ras-related protein Rab-4; p70/S6 kinase, ribosomal protein S6 kinase, 70 kDa; Wee 1, Wee1 G2 checkpoint kinase; Myt 1, myelin transcription factor 1; CENP-F, centromere protein F; Incenp, inner centromere protein; Tau, Tau protein; Pol II, RNA polymerase II; Sin3-Rpd3, Sin3 histone deacetylase complex; NHERF-1, Na⁺/H⁺ exchanger regulatory factor 1; KRMP 1, kinase regulatory protein 1; hSpt5, human SPT5 (suppressor of Ty); Bcl-2, B-cell CLL/lymphoma 2; c-Jun, c-Jun proto-oncogene; NFAT, nuclear factor of activated T-cells; Cf-2, C/EBP family member 2 (C/EBP is short for CCAAT/enhancer binding protein); CK2, casein kinase 2; P53, tumor protein P53.

molecules. By activating Raf kinase, Ras initiates the MAPK signaling cascade, which in turn activates MEK (MAPK/ERK kinase), which activates ERK. Activated ERK translocates to the nucleus and promotes activation of the AP-1 transcription factor (42).

In the Ras/AP-1 signaling pathway, Pin1 directly interacts with members of the AP-1 family (such as c-Fos and c-Jun) (31) and facilitates cis-trans isomerization by recognizing their phosphorylated Ser/Thr-Pro sequences, which enhances the ability of Jun proteins to dimerize, either in homo- or heterodimeric form and improves their DNA-binding activity, which in turn enhances transcriptional activity and stability. Furthermore, the role of Pin1 in the aberrant activation of the Ras/AP-1 pathway in cancer is critical, as it may contribute to the sustained proliferation and survival of cancer cells by

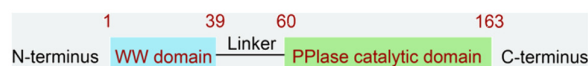


Figure 1. Schematic structure of the Pin1 protein. The figure, created with Adobe Illustrator, depicts Pin1, which consists of 163 amino acids with two functional regions: The amino-terminal tryptophan-tryptophan WW region (39 amino acid residues), characterized by two constant tryptophan residues that act as a specific linkage region for phosphorylated serine/threonine-proline motifs and the carboxy-terminal peptidyl prolyl isomerase region (120 amino acid residues), which contains activation sites and functions as an RNA polymerase II. The WW region is linked to the PPIase region by a variable sequence. Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; PPIase, peptidyl-prolyl cis-trans isomerase.

maintaining the oncogenic potential of AP-1 family members under pathological conditions (43,44).

Aberrant activation of the Ras/AP-1 signaling pathway is closely associated with the development of several types of cancer (31) and mutations in the Ras gene typically result in the persistent activation of downstream signaling pathways to promote uncontrolled cell proliferation and survival (45), particularly in pancreatic (46), colorectal (47) and lung cancer (48). Overexpression or overactivation of AP-1 signaling pathway members is also prevalent in several types of cancer, such as overexpression of c-Jun and c-Fos, which is associated with aggressiveness and a poor prognosis in breast cancer, osteosarcoma and other types of cancer (49) and mutations in other components of the Ras/AP-1 signaling pathway (for example, Raf, MEK and ERK), also result in sustained activation of the pathway, which enhances cell viability and the proliferative potential of cancer cells (50).

The activation pattern of the Ras/AP-1 pathway varies in different types of cancer. For example, in pancreatic cancer, Ras gene mutations lead to persistent activation of downstream signaling pathways, while in certain breast cancer subtypes, different regulatory mechanisms may be exhibited. This diversity underscores the importance of Pin1 in regulating the Ras/AP-1 pathway and its possibility as a potential therapeutic target (51-53).

Pin1 regulates the Wnt/β-catenin signaling pathway and promotes cancer cell proliferation. Pin1 recognizes and binds to the phosphorylation of the Ser/Thr-Pro motif on β-catenin and cis-trans isomerization β-catenin through its PPIase structural domain, altering its conformation and enhancing its stability (54). This isomerization protects β-catenin from ubiquitination and proteasome-mediated degradation, leading to increased stability and accumulation of β-catenin in the cytoplasm and facilitating its translocation to the nucleus.

In the nucleus, Pin1 enhances the binding of β-catenin to TCF/LEF transcription factors by elevating its stability and intranuclear translocation to form a transcriptional activation complex (55). A β-catenin/TCF complex activates the transcription of Wnt target genes (such as c-Myc and Cyclin D1 among others) in the nucleus and regulates the G₁/S transition of the cell cycle. The β-catenin/TCF complex promotes cell cycle progression, which in turn promotes the proliferation of cancer cells (56). This phenomenon can be seen in several types of cancer, including colon cancer (57), HCC (58) and breast cancer (59). There are also differences in the activation patterns of the Wnt/β-catenin signaling in different types of

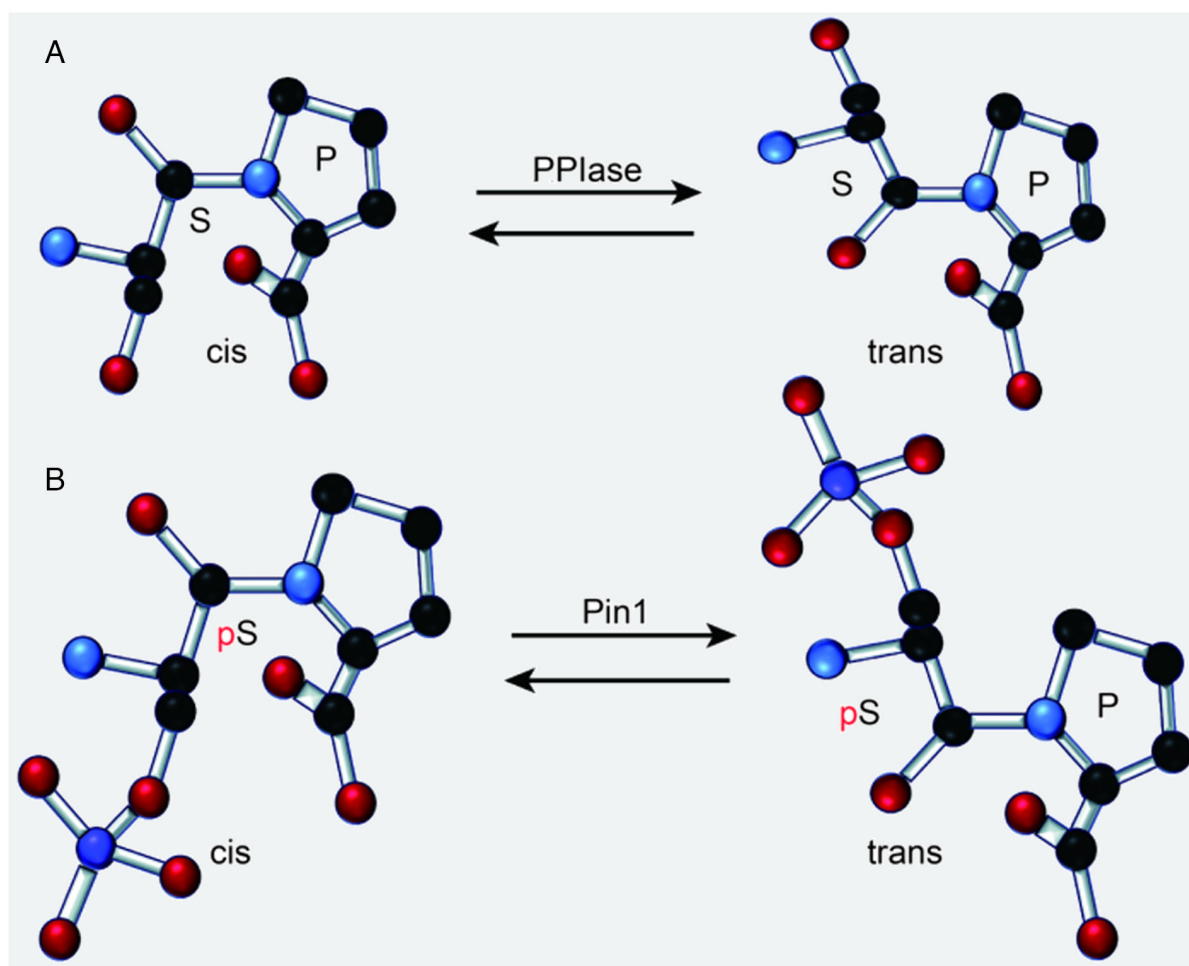


Figure 2. Functions of (A) PPlase and (B) Pin1. Adobe Illustrator was used to create this figure, which illustrates that PPlases are a class of enzymes that catalyze the cis-trans isomerization of proline residues within proteins. Pin1 is a specific member of the PPlase family that facilitates the conversion of phosphorylated Ser/Thr-Pro bonds from the cis to the trans conformation. This conformational change is crucial for regulating protein function, as it can induce alterations in protein structure, thereby affecting cellular signaling pathways, modulating neuronal activity, or promoting oncogenic processes. Specifically, Pin1 modulates the activity and interactions of phosphorylated proteins by altering their conformation, which may subsequently influence the activity of intracellular signaling pathways, inhibit neuronal function, or stimulate the proliferation of cancer cells. PPlase, peptidyl-prolyl cis-trans isomerase; Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1.

cancer. For example, in colon cancer, upregulated expression of β -catenin is closely associated with tumor progression and metastasis, while it manifests as dysregulation in certain types of HCC. The role of Pin1 in these different contexts may determine its specific role in tumor progression.

3. Role of Pin1 in multiple oncogenic signaling pathways

The promoter region of the Pin1 gene lacks a TATA box and a CAAT box, but contains two GC boxes and three E2F binding sites (60). Therefore, in breast cancer cells, due to the high expression of E2F (61), it increases the mRNA expression of Pin1 (62,63). This integration occurs as E2F, when activated, binds to the GC boxes in the Pin1 promoter, facilitating the recruitment of transcriptional co-activators that enhance Pin1 transcription. Aberrant upregulation of E2F is a key factor driving the upregulation of Pin1 in breast cancer cells, a phenomenon that has also been shown in other types of tumor cells (64,65). However, Pin1 activity is not only regulated by gene expression factors, but also by post-translational modifications, such as phosphorylation and dephosphorylation,

which can modulate its stability and interaction with target proteins (66). For example, when Pin1 is phosphorylated at specific residues, its conformational change enhances its ability to bind and isomerize target proteins such as Jun and β -catenin. This action not only stabilizes these proteins but also boosts their transcriptional activity, creating a feed-forward loop that escalates oncogenic signaling.

Previous studies highlight the critical role of the E2F/Rb pathway in regulating Pin1 expression (67,68), which is often upregulated in various cancers (69). The dysregulation of this pathway, particularly its aberrant upregulation, has been associated with increased Pin1 levels, resulting in a high oncogenicity rate of >80% (68,70). This suggests that Pin1 acts as an activator within oncogenic signaling pathways, contributing significantly to tumorigenesis (9,44,71).

Pin1 does not directly act on the E2F/Rb pathway, but rather indirectly influences the occurrence and development of tumors by regulating various proteins and signaling pathways, including p53, which is related to cell cycle regulation. A study by Yao *et al* (72) revealed the key role of the Rb-E2F bistable switch at the restriction point of the cell cycle, highlighting the

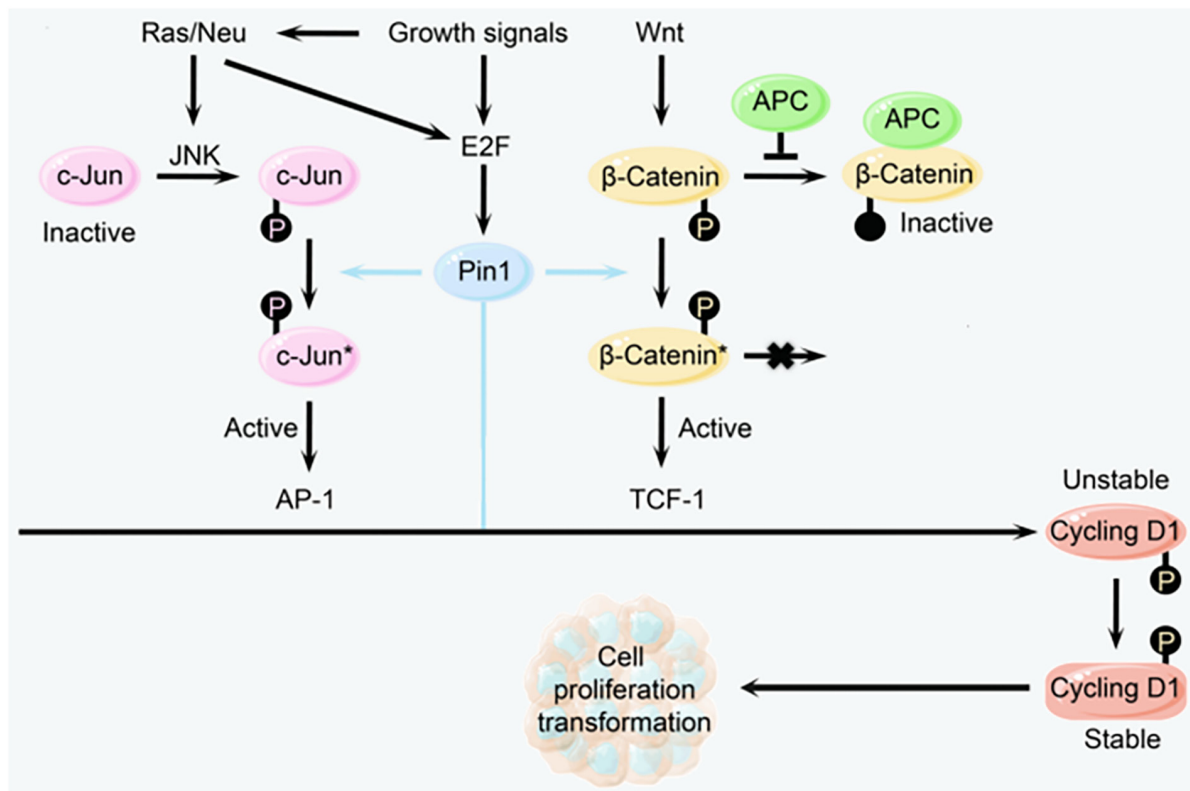


Figure 3. Pin1 regulation of cyclin D1. The figure, drawn using Adobe Illustrator, represents the role of Pin1 in regulating cyclin D1. Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; APC, adenomatous polyposis coli.

central position of the E2F/Rb pathway in cell cycle regulation. Dannenberg *et al* (73) further clarified the relationship between the retinoblastoma susceptibility gene-encoded nuclear phosphoprotein and DNA binding activity, which is a key link in the E2F/Rb pathway. The study by Engeland (38) provided novel insights into the regulation of RB function by monophosphorylation codes and RB, as a key component of the E2F/Rb pathway, its functional state is crucial for the control of the cell cycle. These studies together provide a solid scientific foundation for understanding the role of Pin1 in tumor pathways and emphasize the importance of the E2F/Rb pathway in the Pin1 regulatory network. Specifically, there have been studies that have specifically examined the association between the E2F/Rb pathway and Pin1 (74,75). For instance, it has been shown that Pin1 is a downstream target gene of E2F and plays an important role in the transformation of breast cancer cells induced by Neu/Ras (74,75). This finding highlights the importance of the E2F/Rb pathway in the Pin1 regulatory network. Additionally, studies have indicated that Pin1 can directly bind to phosphorylated Rb (67,76) and this binding is regulated by G₁-S phase-specific Cyclin/CDK complexes (74). These results suggest that Pin1 indirectly participates in the regulation of the E2F/Rb pathway through its interaction with Rb (74,75).

This process involves the following steps that ultimately lead to tumorigenesis: Growth factors induce expression of the Pin1 gene via the Ras signaling pathway and simultaneously contribute to JNK phosphorylation of Jun at the Ser63 and Ser73 sites (77). Then, Pin1 tautomerizes with phosphorylated Jun and enhances its transcriptional activity (78).

At the same time, Pin1 also tautomerizes with phosphorylated β-Catenin and prevents it from binding to adenomatous polyposis coli, thereby increasing the content of β-catenin in the nucleus and thus promoting Jun gene expression (79). As a result, β-catenin and Jun jointly promote the expression of CyclinD1; β-catenin also promotes the expression of Myc (80), which further induces the expression of CDK4 and E2F (65), which in turn promotes the expression of Pin1 through a positive feedback mechanism. Ultimately, these factors work together to promote abnormal cell proliferation and tumorigenesis (Fig. 4) (81).

Zheng *et al* (82) show the interplay between E2F/Rb pathway dysregulation and the upregulation of Pin1 expression, providing further evidence of their correlation in HCC. They identified that sorafenib, a multikinase inhibitor with proven efficacy in HCC treatment, downregulated the mRNA and protein expression levels of the peptidyl-prolyl isomerase Pin1, potentially through the Rb/E2F pathway (82). The Rb/E2F pathway is pivotal in cell cycle regulation and proliferation control and sorafenib may exert its antitumor effects in HCC by modulating this pathway, thereby inhibiting Pin1 transcription (82). Additionally, all-trans retinoic acid (ATRA), an anticancer agent, has been shown to suppress and induce the degradation of active Pin1 in cancer cells, effectively sensitizing HCC cells to sorafenib-induced cell death in a caspase-dependent manner. The combined use of ATRA and sorafenib demonstrated synergistic effects in mouse xenograft models, improving the inhibition of HCC tumor growth. These findings underscored the critical role of Pin1 in the antitumor activity of sorafenib and offered a scientific rationale for the

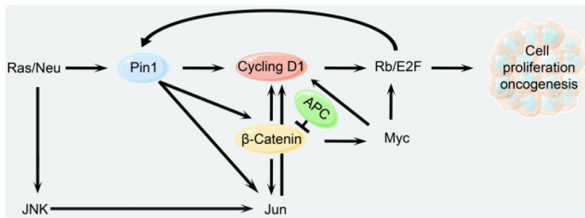


Figure 4. Pin1 acts as an important catalyst in the integration of multiple oncogenic signaling pathways. Created with Adobe Illustrator, this figure highlights Pin1's function as a significant catalyst in the convergence of various oncogenic signaling pathways. Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1.

use of Pin1 inhibitors as a novel approach to potentiate the therapeutic efficacy of sorafenib in HCC treatment (82).

In addition to the aforementioned signaling pathways, Pin1 plays a pivotal role in other key cancer-related signaling pathways. For example, the Hippo signaling pathway, which is critical for organ size regulation and tumor suppression, is positively regulated by the core components YAP and TAZ proteins through Pin1 (83). Specifically, Pin1 modulates the phosphorylation status of YAP and TAZ, which influences their localization and transcriptional activity in the nucleus, thus enhancing the expression of tumor-promoting genes. This modulation may contribute to tumor development and invasiveness in various types of cancer. Thus, Pin1-mediated regulation of the Hippo pathway presents another potential intervention point for cancer therapy.

4. Pin1 inhibitors

Pin1 knockout (Pin1^{-/-}) significantly affects cellular response capabilities, primarily in several key areas: First, Pin1 deficiency reduces the stability and accumulation of p53, subsequently inhibiting the expression of its downstream cell cycle regulator, p21. This alteration disrupts the normal activation of cell cycle checkpoints, allowing cells to continue dividing despite unresolved DNA damage, thereby increasing the risk of genetic mutations (84–86). Additionally, the loss of Pin1 induces morphological changes in cells and enhances sensitivity to DNA damage, potentially leading to cell death or transformation. While Pin1 is overexpressed in various types of cancer and influences the stability of phosphorylated proteins, its knockout may also suppress tumor progression (87–90). These findings underscore the critical role of Pin1 in maintaining genomic stability, regulating the cell cycle and its involvement in tumorigenesis, highlighting potential therapeutic targets for cancer treatment (84).

At the cellular level, the functions of Pin1 and its role in diseases have been extensively studied using a variety of cellular models (91). For instance, human embryonic kidney cell line HEK293, human cervical cancer cell line HeLa, human breast cancer cell line MCF-7 and human osteosarcoma cell line U2OS have been utilized to investigate the role of Pin1 in regulating the cell cycle, affecting p53 stability and promoting cancer development (91). Additionally, mouse embryonic fibroblast cell line NIH 3T3 and MEF cells have been employed to study the functional changes of Pin1 in knockout and over-expression models. Human neuroblastoma cell line SH-SY5Y

and rat adrenal pheochromocytoma cell line PC12 have been used to explore the role of Pin1 in neurodegenerative diseases and neural differentiation, respectively (91). These *in vitro* cell culture models provide important tools for understanding the mechanisms of Pin1 action in cellular signaling pathways (91). Studies have shown that Pin1 interacts with phosphorylated Ser/Thr-Pro motifs through its PPIase activity and WW domain (66,92), thereby affecting various cellular signaling pathways, revealing its significant role in tumorigenesis (93).

In terms of animal models, Pin1 knockout mice provide an important tool for studying Tau pathology and Alzheimer's disease (AD). Studies have shown that Pin1 knockout mice exhibit age-dependent neuropathy characterized by motor and behavioral deficits, Tau hyperphosphorylation, Tau fiber formation and neuronal degeneration (94). These mouse models were used to examine multiple aspects of neurodegeneration by means of behavioral tests, immunostaining and immunoblotting (94). In addition, the Pin1 knockout mouse model also revealed a role for Pin1 in regulating Tau stability and neurodegenerative phenotypes. For example, overexpression of mouse Pin1 (mPin1) promotes the degradation of phosphorylated Tau, whereas mPin1 knockout results in hyperphosphorylation of Tau, inhibition of Tau degradation and a neurodegenerative phenotype (91). For the P301L Tau mutant, the function of mPin1 is reversed and overexpression of mPin1 increases Tau hyperphosphorylation, inhibits Tau degradation and induces a neurodegenerative phenotype (91). Furthermore, Pin1 knockout mice crossed with Tau transgenic mice show increased cisP231-P Tau and reduced transP231-P Tau levels, further supporting the hypothesis that mPin1 inhibits tau-related neurodegenerative lesions in mice (91). In addition to the use of a Pin1 mouse model in Tau pathology studies of AD, Pin1 knockout mice were also found to affect starch precursor protein (APP) processing in mice overexpressing APP in the brain and mPin1 knockdown increased levels of the toxic insoluble Aβ peptide Aβ42 in an age-dependent manner (91).

Taken together, Pin1 knockout cell and animal models provide an important experimental basis for understanding the role of Pin1 in neurodegenerative diseases such as AD and provide potential targets for future therapeutic strategies.

Pin1 inhibitors inhibit tumor cell growth and proliferation by blocking Pin1 activity and interfering with its role in cell cycle regulation, signaling and protein isomerization (Table II) (95). Therefore, it is particularly crucial to develop effective Pin1 inhibitors to provide novel therapeutic options for the management of cancer (96).

Depending on how the inhibitor binds to the PPIase domain, Pin1 inhibitors can be classified into two main categories: Covalent and non-covalent (97). Covalent inhibitors bind to the active site of Pin1 by forming a covalent bond, thereby irreversibly inhibiting its isomerase activity. This mode of binding usually results in permanent inactivation of the enzyme activity, as the breaking of the covalent bond requires specific conditions such as a specific pH or further modification of the active center of the enzyme. Juglone, as the first identified covalent Pin1 inhibitor, was initially extracted from the walnut tree (98). It inhibits the isomerase activity of Pin1 by covalently binding to its catalytically active site, thus interfering with Pin1-mediated cis-trans isomerization of

Table II. Pin1 inhibitors.

Inhibitor Name	Mechanisms	Research phase
Juglone	Inhibits the isomerase activity of Pin1 by binding to its PPIase structural domain.	At the research stage
ATRA	Inhibits the activity of Pin1 by inducing its degradation.	Preclinical studies
PIB	Directly binds the PPIase structural domain of Pin1 and interferes with its interaction with the substrate.	Preclinical studies
GSK3 Inhibitors	Indirectly inhibits Pin1 function by reducing the phosphorylation state of Pin1.	At the research stage
AL-7	Inhibits the isomerization activity of Pin1 by non-competitively binding to its PPIase structural domain.	At the research stage
Nimbolide	Inhibits the isomerase activity of Pin1 by binding to its PPIase structural domain.	Preclinical studies
TAP	Directly binds to the PPIase structural domain of Pin1 and blocks the isomerization of Pin1.	Preclinical studies
CBU	Interferes with its interaction with substrates by binding to Pin1.	At the research stage

AL-7 is a specific compound in research, often related to its use in studies of kinase inhibition and protein degradation; it may not have a widely recognized full name. ATRA, all-trans retinoic acid; PIB, pyridinylhydrazone; GSK3, glycogen synthase kinase 3; TAP, transactivation response region RNA-binding protein; CBU, chlorambucil- β -ureidomethyl.

proteins, resulting in an inhibitory effect on tumor cell growth and also inducing apoptosis (99). This type of inhibitor has demonstrated potential for the long-term inhibition of Pin1 activity. However, concurrently, it might also induce nonspecific responses to other proteins within the cell due to covalent modification. Thus, the poor stability and high toxicity of Juglone *in vivo* restrict its clinical application (100).

Based on structural optimization, research has discovered a novel covalent Pin1 inhibitor, KPT-6566, which has higher specificity and biological activity. KPT-6566 inhibits the isomerase activity of Pin1 through covalent modification of its active site, interferes with its intracellular function and inhibits the proliferation and promotes apoptosis of cancer cells by inducing the degradation of the Pin1 protein (101). In animal experiments, KPT-6566 demonstrated good tolerability and safety, but its antitumor effect and safety in humans still needs to be further verified (102).

Notably, Pin1-targeting inhibitors, including Sulfopin and BJP-06-005-3, have exhibited promising therapeutic potential in preclinical *in vivo* studies (97,103). Sulfopin is a covalent inhibitor that blocks Myc-driven tumors by forming a covalent bond with Cys113 of Pin1 (103). Sulfopin is able to reduce the expression of Myc target genes and reduce tumor progression in N-Myc-driven neuroblastoma and pancreatic cancer models (103). Although Sulfopin has a moderate effect on tumor cell activity *in vitro*, it shows activity *in vivo* with very low toxicity (103), suggesting that higher doses or in combination with other therapies may be needed in the future in the treatment of MYC-driven malignancies (103). BJP-06-005-3 is another covalent Pin1 inhibitor designed to probe Cys113 at the Pin1 active site and inhibit cell viability in pancreatic ductal adenocarcinoma (91). Although BJP-06-005-3 is a promising tool, further chemical optimization may be required to improve its bioavailability and *in vivo* performance (91). These findings highlight the potential of Sulfopin and BJP-06-005-3 as Pin1 inhibitors in cancer therapy, especially in enhancing the sensitivity of cancer cells to radiotherapy and chemotherapy. The development of these inhibitors not only provides new

strategies for cancer treatment, but also provides an important theoretical basis for future clinical cancer treatment.

Noncovalent inhibitors bind Pin1 through noncovalent interactions, such as hydrogen bonding, hydrophobic interactions and van der Waals forces, competitively preventing substrate binding to Pin1. These inhibitors are often reversible, meaning that they can dissociate from the enzyme, allowing the enzyme activity to be restored after the inhibitor is removed. Subsequent studies reveal that ATRA, a drug used in the treatment of acute promyelocytic leukemia (104), also possesses Pin1 inhibitory activity (105). ATRA inhibits Pin1 activity indirectly by inducing degradation of Pin1 proteins that bind to the PPIase structural domain, indirectly inhibiting Pin1 activity. In a variety of cancer cell lines, ATRA shows inhibition of Pin1 expression and activity and can suppress tumor cell proliferation and induce differentiation (15).

The two types of inhibitors have potential applications in cancer therapy, but their mechanisms of action and potential side effects need to be elucidated in further studies. Covalent inhibitors may provide a more durable therapeutic effect due to their irreversibility, but they may also cause more non-specific side effects (106,107). Noncovalent inhibitors may be a safer treatment option because of their reversibility and specificity (105).

In the clinical trial NCT00599937, acute promyelocytic leukemia (APL) was highly curable when treated with a combination of ATRA and anthracycline-based chemotherapy (CT), although the long-term outcomes and the optimal timing for the addition of CT remain unclear (108). In the APL93 study, 576 newly diagnosed patients were followed for a median of 10 years, with a 10-year survival rate of 77%. Maintenance therapy significantly reduced the 10-year cumulative relapse rate from 43.2 to 13.4% through a regimen of intermittent ATRA, continuous 6-mercaptopurine and methotrexate, demonstrating particular efficacy in patients with high white blood cell counts ($>5 \times 10^9/l$). Early addition of CT markedly improves the 10-year event-free survival but had no significant effect on overall survival (108). These findings underscore the

importance of ATRA in conjunction with CT and maintenance therapy, especially in high-risk patients. However, ATRA has some drawbacks and limitations, such as the possibility of inducing serious side effects including Pseudotumor Cerebri syndrome, limiting its application in the clinic (108,109). Therefore, the development of safe and efficient Pin1 inhibitors may become an important direction for future research (110).

After conducting a thorough search on the clinical trials.gov website, it appears that only one clinical trial has been identified that is specifically investigating Pin1 inhibitors at present (108). The academic community has recognized the potential of Pin1 as a therapeutic target due to its role in regulating multiple oncogenic pathways and its overexpression in various cancers, which is associated with poor clinical prognosis (96). Despite the identification of several Pin1 inhibitors with promising anticancer activity in preclinical studies, the translation of these findings into clinical trials has been slow, probably due to challenges in drug solubility and the need for improved drug delivery systems (96). These clinical trials underscore the active investigation into the role of Pin1 inhibitors in cancer treatment and the ongoing quest for effective therapeutic strategies targeting this key regulatory enzyme (96).

5. Comparative novelty of the present review The present review provided an exhaustive examination of the critical role played by Pin1 in oncogenic signaling pathways, its regulatory mechanisms and its potential as a therapeutic target. Distinct from prior reviews (9,44,81,111), the present analysis introduces several innovative elements that enhance the comprehension of the complex role of Pin1 in cancer biology and its therapeutic implications.

The present review offered a comprehensive discussion on Pin1's modulation of multiple cancer-related signaling pathways, thereby elucidating its intricate mechanisms in tumorigenesis (112). This synthesis of recent research advancements afforded a novel perspective on the subject. Additionally, the present review underscored the potential of Pin1 as a clinical biomarker, with an in-depth analysis of the correlation between Pin1 expression levels and patient outcomes across a spectrum of types of cancer, highlighting its prognostic significance (69).

The development and application of Pin1 inhibitors in cancer therapy were thoroughly explored, including their effects on cancer cell growth and proliferation, an area of research with immediate clinical relevance (82). The present review also introduced the effect of Pin1 on the tumor immune microenvironment and its influence on resistance to cancer treatments, a relatively nascent domain in the field (6).

Furthermore, the present review discussed the potential for combining Pin1 inhibitors with existing cancer therapies to surmount treatment resistance, proposing a novel strategy to augment the efficacy of current therapeutic protocols (25). By incorporating the latest research and clinical trial outcomes, the present review presented a contemporary view on the role of Pin1 in cancer, addressing gaps that may have been overlooked in previous reviews due to the rapid evolution of this research area (108).

The present review extended its scope to analyze the function of Pin1 across various types of cancer, emphasizing the commonalities and specificities of its role, thereby enriching

the understanding of its oncogenic potential (33). The present review also incorporated structural insights into the function of Pin1, which are pivotal for the rational design of more potent inhibitors, a topic that has not been extensively covered in previous reviews (84-90).

Collectively, the innovation of the present review is reflected in its holistic and contemporary analysis of the multifaceted roles of Pin1 in cancer, its potential as a biomarker and the therapeutic potential of targeting Pin1, including advances in inhibitor design and overcoming therapeutic resistance (69). These contributions not only expanded the existing body of scientific knowledge but also chart new avenues for future research and clinical applications.

6. Conclusions and future perspectives

Pin1, as a novel regulatory enzyme following its phosphorylation, plays a crucial role in the regulation of cell cycle progression, cell proliferation and apoptosis. In particular, its highly active form is closely associated with tumor development (71). As a key molecular switch, Pin1 regulates numerous cancer-related signaling pathways and cellular processes (112) and is directly related to tumor aggressiveness and patient prognosis (7).

The expression level of Pin1 is significantly increased in a number of types of cancer, such as breast cancer, lung cancer and hepatocellular carcinoma, and is associated with poor prognosis of patients (9,12,82). For example, high Pin1 expression in breast cancer tissues is associated with tumor aggressiveness and chemotherapy resistance (9). In HCC, Pin1 overexpression is correlated with tumor size and lymph node metastasis, suggesting its important role in tumor progression. In addition, the expression level of Pin1 is also correlated with the survival time of patients with multiple cancers, which further confirms its potential as a prognostic biomarker. Pin1 expression levels vary not only among different types of cancer, but also among different subtypes of the same cancer type. This difference in expression pattern may be related to the biological behavior of the tumor and the responsiveness of the patient to treatment. For example, in non-small cell lung cancer, high Pin1 expression is associated with early tumor recurrence and poor overall survival (12). These findings suggest that the expression level of Pin1 may serve as a useful indicator for predicting patient outcome. Future studies are needed to further validate the clinical utility of Pin1 as a biomarker. The relationship between Pin1 expression level and patient prognosis can be more accurately evaluated by large-scale clinical sample studies. In addition, the combination of other biomarkers and clinical parameters may improve the accuracy and reliability of Pin1 as a prognostic assessment tool. In conclusion, Pin1, as an emerging biomarker, has shown great potential in the diagnosis, prognostic evaluation and therapeutic response monitoring of cancer. Future studies are expected to further underscore the potential of Pin1 as a biomarker for cancer diagnosis and prognosis assessment. By detecting Pin1 levels in tumor tissues or blood, it may be possible to achieve early cancer diagnosis, thereby improving patient survival (69).

In addition, Pin1 inhibitors show a broad potential for application in the field of cancer therapy (9). Future research directions may include the development of novel Pin1 inhibitors

with improved efficiency and greater specificity, improvement of the drug properties of existing inhibitors, exploration of the combined application of Pin1 inhibitors with other therapeutic means and further in-depth study of their molecular mechanisms and drug resistance mechanisms (113). Through systematic and in-depth research, Pin1 inhibition may emerge as a viable clinical approach and provide novel treatment options for patients with cancer, with the aim of improving treatment efficacy and patient survival.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

YW conceived and designed the present review. SL and ML wrote the manuscript. All authors revised and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Han HJ, Choi BY and Surh YJ: Dual roles of Pin1 in cancer development and progression. *Curr Pharm Des* 23: 4422-4425, 2017.
- Jeong J, Usman M, Li Y, Zhou XZ and Lu KP: Pin1-catalyzed conformation changes regulate protein ubiquitination and degradation. *Cells* 13: 731, 2024.
- Gurung D, Danielson JA, Tasnim A, Zhang JT, Zou Y and Liu JY: Proline isomerization: From the chemistry and biology to therapeutic opportunities. *Biology (Basel)* 12: 1008, 2023.
- Lanni C, Masi M, Racchi M and Govoni S: Cancer and Alzheimer's disease inverse relationship: an age-associated diverging derailment of shared pathways. *Mol Psychiatry* 26: 280-295, 2021.
- Marcolino TF, Pimenta CAM, Artigiani Neto R, Castelo P, Silva MS, Forones NM and Oshima CTF: p53, Cyclin-D1, β -catenin, APC and c-myc in tumor tissue from colorectal and gastric cancer patients with suspected lynch syndrome by the Bethesda criteria. *Asian Pac J Cancer Prev* 21: 343-348, 2020.
- Born A, Henen MA and Vogeli B: Activity and affinity of Pin1 variants. *Molecules* 25: 36, 2019.
- Stewart R, Sharma S, Wu T, Okuda S, Xie G, Zhou XZ, Shilton B and Lu KP: The role of the master cancer regulator Pin1 in the development and treatment of cancer. *Front Cell Dev Biol* 12: 1343938, 2024.
- Liu C, Dan L, Li Q, Bajinka O and Yuan X: The mechanisms of Pin1 as targets for cancer therapy. *Front Immunol* 15: 1482088, 2024.
- Yu JH, Im CY and Min SH: Function of PIN1 in Cancer development and its inhibitors as cancer therapeutics. *Front Cell Dev Biol* 8: 120, 2020.
- Ma JQ, Yang Y, Juan J, Guo CF, Tuerxun M, Ting W and Hasim A: Over-expression of prolyl isomerase Pin1 promotes cervical tumorigenesis and metastasis. *Int J Clin Exp Pathol* 11: 664-674, 2018.
- Liu K, Zheng M, Lu R, Du J, Zhao Q, Li Z, Li Y and Zhang S: The role of CDC25C in cell cycle regulation and clinical cancer therapy: A systematic review. *Cancer Cell Int* 20: 213, 2020.
- Wang JN, Zhang ZR, Che Y, Yuan ZY, Lu ZL, Li Y, Li N, Wan J, Sun HD, Sun N, *et al*: Acetyl-macrocyclic B, an ent-kaurane diterpenoid, initiates apoptosis through the ROS-p38-caspase 9-dependent pathway and induces G2/M phase arrest via the Chk1/2-Cdc25C-Cdc2/cyclin B axis in non-small cell lung cancer. *Cancer Biol Ther* 19: 609-621, 2018.
- Xia Z, Ou-Yang W, Hu T and Du K: Prognostic significance of CDC25C in lung adenocarcinoma: An analysis of TCGA data. *Cancer Genet* 233-234: 67-74, 2019.
- Wu C, Lyu J, Yang EJ, Liu Y, Zhang B and Shim JS: Targeting AURKA-CDC25C axis to induce synthetic lethality in ARID1A-deficient colorectal cancer cells. *Nat Commun* 9: 3212, 2018.
- Li Y, Yuan Z, Wang L, Yang J, Pu P, Le Y, Chen X, Wang C, Gao Y, Liu Y, *et al*: Prolyl isomerase Pin1 sculpts the immune microenvironment of colorectal cancer. *Cell Signal* 115: 111041, 2024.
- Maegawa S and Gopalakrishnan V: PLK inhibitors come of age in pediatric brain tumors. *Neuro Oncol* 24: 427-428, 2022.
- Crenshaw DG, Yang J, Means AR and Kornbluth S: The mitotic peptidyl-prolyl isomerase, Pin1, interacts with Cdc25 and Plx1. *EMBO J* 17: 1315-1327, 1998.
- Shen M, Stukenberg PT, Kirschner MW and Lu KP: The essential mitotic peptidyl-prolyl isomerase Pin1 binds and regulates mitosis-specific phosphoproteins. *Genes Dev* 12: 706-720, 1998.
- Zhou XZ, Kops O, Werner A, Lu PJ, Shen M, Stoller G, Küllertz G, Stark M, Fischer G and Lu KP: Pin1-dependent prolyl isomerization regulates dephosphorylation of Cdc25C and tau proteins. *Mol Cell* 6: 873-883, 2000.
- Stukenberg PT and Kirschner MW: Pin1 acts catalytically to promote a conformational change in Cdc25. *Mol Cell* 7: 1071-1083, 2001.
- Fei F, Qu J, Liu K, Li C, Wang X, Li Y and Zhang S: The subcellular location of cyclin B1 and CDC25 associated with the formation of polyploid giant cancer cells and their clinicopathological significance. *Lab Invest* 99: 483-498, 2019.
- Dakilah I, Harb A, Abu-Gharbieh E, El-Huneidi W, Taneera J, Hamoudi R, Semreen MH and Bustanji Y: Potential of CDC25 phosphatases in cancer research and treatment: Key to precision medicine. *Front Pharmacol* 15: 1324001, 2024.
- Wang C, Zeng J, Li LJ, Xue M and He SL: Cdc25A inhibits autophagy-mediated ferroptosis by upregulating ErbB2 through PKM2 dephosphorylation in cervical cancer cells. *Cell Death Dis* 12: 1055, 2021.
- Chen YC, Hsieh HH, Chang HC, Wang HC, Lin WJ and Lin JJ: CDC25B induces cellular senescence and correlates with tumor suppression in a p53-dependent manner. *J Biol Chem* 296: 100564, 2021.
- Khoei SG, Mohammadi C, Mohammadi Y, Sameri S and Najafi R: Prognostic value of peptidyl-prolyl cis-trans isomerase 1 (PIN1) in human malignant tumors. *Clin Transl Oncol* 22: 1067-1077, 2020.
- Montalto FI and De Amicis F: Cyclin D1 in cancer: A molecular connection for cell cycle control, adhesion and invasion in tumor and stroma. *Cells* 9: 2648, 2020.
- Cai Z, Wang J, Li Y, Shi Q, Jin L, Li S, Zhu M, Wang Q, Wong LL, Yang W, *et al*: Overexpressed Cyclin D1 and CDK4 proteins are responsible for the resistance to CDK4/6 inhibitor in breast cancer that can be reversed by PI3K/mTOR inhibitors. *Sci China Life Sci* 66: 94-109, 2023.

28. Lundberg A, Lindstrom LS, Li J, Harrell JC, Darai-Ramqvist E, Sifakis EG, Foukakis T, Perou CM, Czene K, Bergh J and Tobin NP: The long-term prognostic and predictive capacity of cyclin D1 gene amplification in 2305 breast tumours. *Breast Cancer Res* 21: 34, 2019.
29. Shi Q, Li Y, Li S, Jin Y, Lai H, Wu Y, Cai Z, Zhu M, Li Q, Li Y, *et al.*: LncRNA DILA1 inhibits Cyclin D1 degradation and contributes to tamoxifen resistance in breast cancer. *Nat Commun* 11: 5513, 2020.
30. Tchakarska G and Sola B: The double dealing of cyclin D1. *Cell Cycle* 19: 163-178, 2020.
31. Song D, Lian Y and Zhang L: The potential of activator protein 1 (AP-1) in cancer targeted therapy. *Front Immunol* 14: 1224892, 2023.
32. Mst Nazneen Nahar Rina D, Dr. Naba Kumar Saha P and Mostafa Kamal D: Significance of cyclin D1 immunoeexpression in breast carcinoma. *J Cancer Sci Clin Ther* 8: 321-326, 2024.
33. Fang M, Wu HK, Pei Y, Zhang Y, Gao X, He Y, Chen G, Lv F, Jiang P, Li Y, *et al.*: E3 ligase MG53 suppresses tumor growth by degrading cyclin D1. *Signal Transduct Target Ther* 8: 263, 2023.
34. Nashaat S, Henen MA, El-Messery SM and Eisa H: Synthesis, state-of-the-art NMR-binding and molecular modeling study of new benzimidazole core derivatives as Pin1 inhibitors: Targeting breast cancer. *Bioorg Med Chem* 28: 115495, 2020.
35. Zhang C, Liu J, Xu D, Zhang T, Hu W and Feng Z: Gain-of-function mutant p53 in cancer progression and therapy. *J Mol Cell Biol* 12: 674-687, 2020.
36. Hu J, Cao J, Topatana W, Juengpanich S, Li S, Zhang B, Shen J, Cai L, Cai X and Chen M: Targeting mutant p53 for cancer therapy: Direct and indirect strategies. *J Hematol Oncol* 14: 157, 2021.
37. Deng L, Meng T, Chen L, Wei W and Wang P: The role of ubiquitination in tumorigenesis and targeted drug discovery. *Signal Transduct Target Ther* 5: 11, 2020.
38. Engeland K: Cell cycle regulation: p53-p21-RB signaling. *Cell Death Differ* 29: 946-960, 2022.
39. Vaddavalli PL and Schumacher B: The p53 network: cellular and systemic DNA damage responses in cancer and aging. *Trends Genet* 38: 598-612, 2022.
40. Marei HE, Althani A, Afifi N, Hasan A, Caceci T, Pozzoli G, Morrione A, Giordano A and Cenciarelli C: p53 signaling in cancer progression and therapy. *Cancer Cell Int* 21: 703, 2021.
41. Tomazini A and Shifman JM: Targeting Ras with protein engineering. *Oncotarget* 14: 672-687, 2023.
42. Ullah R, Yin Q, Snell AH and Wan L: RAF-MEK-ERK pathway in cancer evolution and treatment. *Semin Cancer Biol* 85: 123-154, 2022.
43. Cheng CW and Tse E: PIN1 in cell cycle control and cancer. *Front Pharmacol* 9: 1367, 2018.
44. Chen Y, Wu YR, Yang HY, Li XZ, Jie MM, Hu CJ, Wu YY, Yang SM and Yang YB: Prolyl isomerase Pin1: A promoter of cancer and a target for therapy. *Cell Death Dis* 9: 883, 2018.
45. Sciacchitano S, Sacconi A, De Vitis C, Blandino G, Piaggio G, Salvati V, Napoli C, Marchetti P, Taurelli BS, Coluzzi F, *et al.*: H-Ras gene takes part to the host immune response to COVID-19. *Cell Death Discov* 7: 158, 2021.
46. Luo J: KRAS mutation in pancreatic cancer. *Semin Oncol* 48: 10-18, 2021.
47. Zhu G, Pei L, Xia H, Tang Q and Bi F: Role of oncogenic KRAS in the prognosis, diagnosis and treatment of colorectal cancer. *Mol Cancer* 20: 143, 2021.
48. Shalom B, Farago M, Salaymeh Y, Sebban S, Risling M, Pikarsky E and Katzav S: Vav1 accelerates Ras-driven lung cancer and modulates its tumor microenvironment. *Cell Signal* 97: 110395, 2022.
49. He Y, Ling Y, Zhang Z, Mertens RT, Cao Q, Xu X, Guo K, Shi Q, Zhang X, Huo L, *et al.*: Butyrate reverses ferroptosis resistance in colorectal cancer by inducing c-Fos-dependent xCT suppression. *Redox Biol* 65: 102822, 2023.
50. Degirmenci U, Wang M and Hu J: Targeting aberrant RAS/RAF/MEK/ERK signaling for cancer therapy. *Cells* 9: 198, 2020.
51. Liu J, Wang Y, Mu C, Li M, Li K, Li S, Wu W, Du L, Zhang X, Li C, *et al.*: Pancreatic tumor eradication via selective Pin1 inhibition in cancer-associated fibroblasts and T lymphocytes engagement. *Nat Commun* 13: 4308, 2022.
52. Lu KP and Zhou XZ: The prolyl isomerase PIN1: A pivotal new twist in phosphorylation signalling and disease. *Nat Rev Mol Cell Biol* 8: 904-916, 2007.
53. Luo ML, Gong C, Chen CH, Lee DY, Hu H, Huang P, Yao Y, Guo W, Reinhardt F, Wulf G, *et al.*: Prolyl isomerase Pin1 acts downstream of miR200c to promote cancer stem-like cell traits in breast cancer. *Cancer Res* 74: 3603-3616, 2014.
54. Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, Zhou Z, Shu G and Yin G: Wnt/beta-catenin signalling: Function, biological mechanisms, and therapeutic opportunities. *Signal Transduct Target Ther* 7: 3, 2022.
55. Koelman EMR, Yeste-Vazquez A and Grossmann TN: Targeting the interaction of β -catenin and TCF/LEF transcription factors to inhibit oncogenic Wnt signaling. *Bioorg Med Chem* 70: 116920, 2022.
56. Delgado-Bellido D, Zamudio-Martinez E, Fernandez-Cortes M, Herrera-Campos AB, Olmedo-Pelayo J, Perez CJ, Expósito J, de Álava E, Amaral AT, Valle FO, *et al.*: VE-Cadherin modulates β -catenin/TCF-4 to enhance vasculogenic mimicry. *Cell Death Dis* 14: 135, 2023.
57. Ji Y, Liu Y, Sun C, Yu L, Wang Z, Du X, Yang W, Zhang C, Tao C, Wang J, *et al.*: ADCK1 activates the β -catenin/TCF signaling pathway to promote the growth and migration of colon cancer cells. *Cell Death Dis* 12: 354, 2021.
58. Huang WJ, Tian XP, Bi SX, Zhang SR, He TS, Song LY, Yun JP, Zhou ZG, Yu RM and Li M: The β -catenin/TCF-4-LINC01278-miR-1258-Smad2/3 axis promotes hepatocellular carcinoma metastasis. *Oncogene* 39: 4538-4550, 2020.
59. Zhu L, Tian Q, Gao H, Wu K, Wang B, Ge G, Jiang S, Wang K, Zhou C, He J, *et al.*: PROX1 promotes breast cancer invasion and metastasis through WNT/ β -catenin pathway via interacting with hnRNPK. *Int J Biol Sci* 18: 2032-2046, 2022.
60. Wang JZ, Du WT, Bai J, Cheng SZ and Zhang YH: The association of rs2233679 in the PIN1 gene promoter with the risk of Coronary Artery Disease in Chinese female individuals. *J Stroke Cerebrovasc Dis* 29: 104935, 2020.
61. Yu S, Wang Y, Gong X, Fan Z, Wang Z, Liang Z, Wu R, Cao B, Wang N, Bi C, *et al.*: LncRNA AGPG confers endocrine resistance in breast cancer by promoting E2F1 activity. *Cancer Res* 83: 3220-3236, 2023.
62. Krishnan N, Titus MA and Thapar R: The prolyl isomerase pin1 regulates mRNA levels of genes with short half-lives by targeting specific RNA binding proteins. *PLoS One* 9: e85427, 2014.
63. Choi YJ, Kim I, Lee JE and Park JW: PIN1 transcript variant 2 acts as a long non-coding RNA that controls the HIF-1-driven hypoxic response. *Sci Rep* 9: 10599, 2019.
64. Kassab A, Gupta I and Moustafa AA: Role of E2F transcription factor in oral cancer: Recent insight and advancements. *Semin Cancer Biol* 92: 28-41, 2023.
65. Kim S, Armand J, Safonov A, Zhang M, Soni RK, Schwartz G, McGuinness JE, Hibshoosh H, Razavi P, Kim M, *et al.*: Sequential activation of E2F via Rb degradation and c-Myc drives resistance to CDK4/6 inhibitors in breast cancer. *Cell Rep* 42: 113198, 2023.
66. Chen D, Wang L and Lee TH: Post-translational modifications of the peptidyl-prolyl isomerase Pin1. *Front Cell Dev Biol* 8: 129, 2020.
67. Maggio J, Armando R, Balcone L, Vilarullo RN, Casco MDP, Gomez DLM and Gomez DE: Role of PIN1 in human pathology: Cellular regulation, pathogenesis and therapeutic implications (Review). *World Acad Sci J* 6: 5, 2023.
68. Zhou Y, Nakajima R, Shirasawa M, Fikriyanti M, Zhao L, Iwanaga R, Bradford AP, Kurayoshi K, Araki K and Ohtani K: Expanding roles of the E2F-RB-p53 pathway in tumor suppression. *Biology (Basel)* 12: 1511, 2023.
69. Chuang HH, Zhen YY, Tsai YC, Chuang CH, Huang MS, Hsiao M and Yang CJ: Targeting Pin1 for modulation of cell motility and cancer therapy. *Biomedicine* 9: 359, 2021.
70. Bao L, Kimzey A, Sauter G, Sowadski JM, Lu KP and Wang DG: Prevalent overexpression of prolyl isomerase Pin1 in human cancers. *Am J Pathol* 164: 1727-1737, 2004.
71. Caligiuri I, Vincenzo C, Asano T, Kumar V and Rizzolio F: The metabolic crosstalk between PIN1 and the tumour microenvironment. *Semin Cancer Biol* 91: 143-157, 2023.
72. Yao G, Lee TJ, Mori S, Nevins JR and You L: A bistable Rb-E2F switch underlies the restriction point. *Nat Cell Biol* 10: 476-482, 2008.
73. Dannenberg JH, van Rossum A, Schuijff L and te Riele H: Ablation of the retinoblastoma gene family deregulates G(1) control causing immortalization and increased cell turnover under growth-restricting conditions. *Genes Dev* 14: 3051-3064, 2000.
74. Tong Y, Ying H, Liu R, Li L, Bergholz J and Xiao ZX: Pin1 inhibits PP2A-mediated Rb dephosphorylation in regulation of cell cycle and S-phase DNA damage. *Cell Death Dis* 6: e1640, 2015.

75. Wulf G, Garg P, Liou YC, Iglehart D and Lu KP: Modeling breast cancer in vivo and ex vivo reveals an essential role of Pin1 in tumorigenesis. *EMBO J* 23: 3397-3407, 2004.
76. Zannini A, Rustighi A, Campaner E and Del Sal G: Oncogenic hijacking of the PIN1 signaling network. *Front Oncol* 9: 94, 2019.
77. Lepore A, Choy PM, Lee NCW, Carella MA, Favicchio R, Briones-Orta MA, Glaser SS, Alpini G, D'Santos C, Tooze RM, *et al*: Phosphorylation and stabilization of PIN1 by JNK promote intrahepatic cholangiocarcinoma growth. *Hepatology* 74: 2561-2579, 2021.
78. Poudel M, Bhattarai PY, Shrestha P and Choi HS: Regulation of Interleukin-36 γ /IL-36R Signaling Axis by PIN1 in epithelial cell transformation and breast tumorigenesis. *Cancers (Basel)* 14: 3654, 2022.
79. Jawanjal P, Salhan S, Dhawan I, Tripathi R and Rath G: Peptidyl-prolyl isomerase Pin1-mediated abrogation of APC- β -catenin interaction in squamous cell carcinoma of cervix. *Rom J Morphol Embryol* 55: 83-90, 2014.
80. Ma ZQ, Feng YT, Guo K, Liu D, Shao CJ, Pan MH, Zhang YM, Zhang YX, Lu D, Huang D, *et al*: Melatonin inhibits ESCC tumor growth by mitigating the HDAC7/ β -catenin/c-Myc positive feedback loop and suppressing the USP10-maintained HDAC7 protein stability. *Mil Med Res* 9: 54, 2022.
81. Pu W, Zheng Y and Peng Y: Prolyl isomerase Pin1 in human cancer: Function, mechanism, and significance. *Front Cell Dev Biol* 8: 168, 2020.
82. Zheng M, Xu H, Liao XH, Chen CP, Zhang AL, Lu W, Wang L, Yang D, Wang J, Liu H, *et al*: Inhibition of the prolyl isomerase Pin1 enhances the ability of sorafenib to induce cell death and inhibit tumor growth in hepatocellular carcinoma. *Oncotarget* 8: 29771-29784, 2017.
83. Khanal P, Yeung B, Zhao Y and Yang X: Identification of Prolyl isomerase Pin1 as a novel positive regulator of YAP/TAZ in breast cancer cells. *Sci Rep* 9: 6394, 2019.
84. Wulf GM, Liou YC, Ryo A, Lee SW and Lu KP: Role of Pin1 in the regulation of p53 stability and p21 transactivation, and cell cycle checkpoints in response to DNA damage. *J Biol Chem* 277: 47976-47979, 2002.
85. Zheng H, You H, Zhou XZ, Murray SA, Uchida T, Wulf G, Gu L, Tang X, Lu KP and Xiao ZX: The prolyl isomerase Pin1 is a regulator of p53 in genotoxic response. *Nature* 419: 849-853, 2002.
86. Zacchi P, Gostissa M, Uchida T, Salvagno C, Avolio F, Volinia S, Ronai Z, Blandino G, Schneider C and Del Sal G: The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults. *Nature* 419: 853-857, 2002.
87. Ryo A, Uemura H, Ishiguro H, Saitoh T, Yamaguchi A, Perrem K, Kubota Y, Lu KP and Aoki I: Stable suppression of tumorigenicity by Pin1-targeted RNA interference in prostate cancer. *Clin Cancer Res* 11: 7523-7531, 2005.
88. Kim JA, Kim MR, Kim O, Phuong NT, Yun J, Oh WK, Bae K and Kang KW: Amurensin G inhibits angiogenesis and tumor growth of tamoxifen-resistant breast cancer via Pin1 inhibition. *Food Chem Toxicol* 50: 3625-3634, 2012.
89. Polonio-Vallon T, Krüger D and Hofmann TG: ShaPINg cell fate upon DNA damage: Role of Pin1 isomerase in DNA damage-induced cell death and repair. *Front Oncol* 4: 148, 2014.
90. Steger M, Murina O, Hühn D, Ferretti LP, Walser R, Hänggi K, Lafranchi L, Neugebauer C, Paliwal S, Janscak P, *et al*: Prolyl isomerase PIN1 regulates DNA double-strand break repair by counteracting DNA end resection. *Mol Cell* 50: 333-343, 2013.
91. Lee YM, Teoh DE, Yeung K and Liou YC: The kingdom of the prolyl-isomerase Pin1: The structural and functional convergence and divergence of Pin1. *Front Cell Dev Biol* 10: 956071, 2022.
92. Jirawatnotai S, Dalton S and Wattanapanitch M: Role of cyclins and cyclin-dependent kinases in pluripotent stem cells and their potential as a therapeutic target. *Semin Cell Dev Biol* 107: 63-71, 2020.
93. Wang N, Chai T, Wang XR, Zheng YD, Sang CY and Yang JL: Pin1: Advances in pancreatic cancer therapeutic potential and inhibitors research. *Bioorg Chem* 153: 107869, 2024.
94. Kondo A, Albayram O, Zhou XZ and Lu KP: Pin1 knockout mice: A model for the study of tau pathology in Alzheimer's disease. *Methods Mol Biol* 1523: 415-425, 2017.
95. Nakatsu Y, Matsunaga Y, Ueda K, Yamamotoya T, Inoue Y, Inoue MK, Mizuno Y, Kushiya A, Ono H, Fujishiro M, *et al*: Development of Pin1 inhibitors and their potential as therapeutic agents. *Curr Med Chem* 27: 3314-3329, 2020.
96. He S, Li L, Jin R and Lu X: Biological function of Pin1 in vivo and its inhibitors for preclinical study: Early development, current strategies, and future directions. *J Med Chem* 66: 9251-9277, 2023.
97. Pinch BJ, Doctor ZM, Nabet B, Browne CM, Seo HS, Mohardt ML, Kozono S, Lian X, Manz TD, Chun Y, *et al*: Identification of a potent and selective covalent Pin1 inhibitor. *Nat Chem Biol* 16: 979-987, 2020.
98. Dos S Moreira C, Santos TB, Freitas RHCN, Pacheco PAF and da Rocha DR: Juglone: A versatile natural platform for obtaining new bioactive compounds. *Curr Top Med Chem* 21: 2018-2045, 2021.
99. Cai Y, Zou G, Xi M, Hou Y, Shen H, Ao J, Li M, Wang J and Luo A: Juglone inhibits listeria monocytogenes ATCC 19115 by targeting cell membrane and protein. *Foods* 11: 2558, 2022.
100. Li F, Li Y, Deng ZP, Zhu XJ, Zhang ZG, Zhang XD, Tian JL, Li W and Zhao P: Traditional uses, phytochemistry, pharmacology and clinical applications of Cortex Juglandis Mandshuricae: A comprehensive review. *J Ethnopharmacol* 285: 114887, 2022.
101. Zhang Z, Hu Q, Ye S and Xiang L: Inhibition of the PIN1-NRF2/GPX4 axis imparts sensitivity to cisplatin in cervical cancer cells. *Acta Biochim Biophys Sin (Shanghai)* 54: 1325-1335, 2022.
102. Guo YT, Lu Y, Jia YY, Qu HN, Qi D, Wang XQ, Song PY, Jin XS, Xu WH, Dong Y and Liang YY, Quan CS: Predictive Value of Pin1 in cervical low-grade squamous intraepithelial lesions and inhibition of Pin1 exerts potent anticancer activity against human cervical cancer. *Aging Dis* 11: 44-59, 2020.
103. Dubiella C, Pinch BJ, Koikawa K, Zaidman D, Poon E, Manz TD, Nabet B, He S, Resnick E, Rogel A, *et al*: Sulfopin is a covalent inhibitor of Pin1 that blocks Myc-driven tumors in vivo. *Nat Chem Biol* 17: 954-963, 2021.
104. Liang C, Qiao G, Liu Y, Tian L, Hui N, Li J, Ma Y, Li H, Zhao Q, Cao W, *et al*: Overview of all-trans-retinoic acid (ATRA) and its analogues: Structures, activities, and mechanisms in acute promyelocytic leukaemia. *Eur J Med Chem* 220: 113451, 2021.
105. Giuli MV, Hanieh PN, Forte J, Fabiano MG, Mancusi A, Natiello B, Rinaldi F, Del Favero E, Ammendolia MG, Marianucci C, *et al*: pH-sensitive niosomes for ATRA delivery: A promising approach to inhibit Pin1 in high-grade serous ovarian cancer. *Int J Pharm* 649: 123672, 2024.
106. Schaefer D and Cheng X: Recent advances in covalent drug discovery. *Pharmaceuticals (Basel)* 16: 663, 2023.
107. Bjiij I, Olotu FA, Agoni C, Adeniji E, Khan S, El Rashedy A, Cherqaoui D and Soliman MES: Covalent inhibition in drug discovery: Filling the void in literature. *Curr Top Med Chem* 18: 1135-1145, 2018.
108. Adès L, Guerci A, Raffoux E, Sanz M, Chevallier P, Lapusan S, Recher C, Thomas X, Rayon C, Castaigne S, *et al*: Very long-term outcome of acute promyelocytic leukemia after treatment with all-trans retinoic acid and chemotherapy: The European APL Group experience. *Blood* 115: 1690-1696, 2010.
109. Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E, Fey M, Rayon C, Huguet F, Sotto JJ, *et al*: A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood* 94: 1192-1200, 1999.
110. Zhang F, Zhang A, Xie Y, Wen H, Kankala RK, Huang J, Zhang A, Wang Q, Chen B, Dong H, *et al*: Nanocarrier of Pin1 inhibitor based on supercritical fluid technology inhibits cancer metastasis by blocking multiple signaling pathways. *Regen Biomater* 10: rbad014, 2023.
111. Wu W, Xue X, Chen Y, Zheng N and Wang J: Targeting prolyl isomerase Pin1 as a promising strategy to overcome resistance to cancer therapies. *Pharmacol Res* 184: 106456, 2022.
112. Fagiani F, Vlachou M, Di Marino D, Canobbio I, Romagnoli A, Racchi M, Govoni S and Lanni C: Pin1 as molecular switch in vascular endothelium: Notes on its putative role in age-associated vascular diseases. *Cells* 10: 3287, 2021.
113. Poli G, Di Stefano M, Estevez JA, Minutolo F, Granchi C, Giordano A, Parisi S, Mauceri M, Canzonieri V, Macchia M, *et al*: New PIN1 inhibitors identified through a pharmacophore-driven, hierarchical consensus docking strategy. *J Enzyme Inhib Med Chem* 37: 145-150, 2022.

