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Pharmacological Inhibition of Pin1 for Cancer Therapy

Min SH[1]* and Kim BM[2]*

[1]New Drug Development Center, DGMIF, Republic of Korea

[2]Severance Integrative Research Institute for Cerebral & Cardiovascular Diseases (SIRIC), Yonsei University College of Medicine, Republic of Korea

*Corresponding author(s): Byeong Mo Kim (PhD), Severance Integrative Research Institute for Cerebral & Cardiovascular Diseases (SIRIC), Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea, Tel: 82-2-2228-0789; Fax: 82-2-2227-7906; E-mail: bkim2@yuhs.ac

Sang-Hyun Min, New Drug Development Center, DGMIF, 80 Cheombok-ro, Dong-gu, Daegu 41061, Republic of Korea, Tel: 82-53-790-5228; Fax: 82-53-790-5219; Email: shmin03@dgmif.re.kr

ABSTRACT

Most standard chemotherapies act on rapidly dividing cells, including both normal and cancerous cells. In contrast, targeted chemotherapies act on specific molecular targets involved in the growth, progression, and spread of cancer. Many different candidate small-molecule therapeutics have been developed for use in cancer treatment, as targeted chemotherapies spare healthy cells due to their selectivity and efficiency. Pin1, a cis/trans isomerase, is the only identified enzyme known to catalyze pSer/Thr-Pro motif isomerization. Pin1 deregulation is implicated in a number of age-related diseases, including cancer and Alzheimer's disease. In particular, Pin1 promotes cell cycle progression and cell proliferation, acting as proto-oncogene in cancer cells. Here, we describe the principal role of Pin1 in cancer and present the various pharmacological approaches to inhibiting Pin1 for cancer treatment. Domain-directed inhibitors have been developed to target peptidyl-prolyl cis/trans isomerase (PPIase) activity and/or the WW domain in Pin1.

INTRODUCTION

During the last three decades, the paradigm in cancer treatment has shifted from the use of nonspecific agents to selective therapeutics. Targeted therapeutics attack cancer cells specifically while imposing less damage to healthy cells, which results in milder side effects than traditional and standard chemotherapy drugs. Whereas most standard chemotherapeutic agents are cytotoxic, targeted chemotherapies are often cytostatic, meaning that they block only tumor cell proliferation with no harm to normal cells. Therefore, a current trend in drug discovery for cancer therapy is to develop inhibitors that target proteins involved in cancer activation and tumorigenesis. Various types of targeted therapies are currently available such as apoptosis inducers, angiogenesis inhibitors, signal transduction modulators, and immune modulators.

Phosphorylation of proteins on serine or threonine residues preceding proline (Ser/Thr-Pro) is a major trigger of intracellular signal transduction. The peptidyl-prolyl cis-trans isomerase (PPIase) Pin1 binds to and isomerizes this specific phosphorylated Ser-Pro or Thr-Pro (pSer-Pro or pThr-Pro) motif in proteins, resulting in conformational changes in protein that transfer a profound impact on the activity of protein and diverse phosphorylation signals [1-5]. These Pin1-induced conformational changes regulate a variety of biological processes such as the cell cycle and cell proliferation, motility, apoptosis, and survival; the altered activities of target proteins play a pivotal role in tumorigenesis [1,2,6-9]. Pin1 has two distinct domains, consisting of an N-terminal WW domain that binds only specific pSer-Pro or pThr-Pro motifs and a C-terminal PPIase domain that isomerizes specific pSer/Thr-Pro motifs; they affect protein function by controlling their conformation [5, 10].

Pin1 is overexpressed and/or activated in various human cancers including lung, ovary, breast, brain, prostate, gastric, and cervical cancers [11-15]. Pin1 overexpression is correlated with poor clinical outcomes in patients with cancer, including with disease progression in those with oral squamous cell carcinoma and lymph node metastasis in non-small-cell lung cancer [15-18]. Pin1 activates at least 33 oncoproteins/growth-promoting proteins and inactivates multiple tumor suppressors/growth-inhibitory proteins [13,19]. Knockdown of Pin1 mediated by RNAi, eliminates xenograft growth, and Pin1 knockout mice are resistant to breast cancer induced by overexpression of Ras or ErbB2, implying that Pin1 function is required for tumor development [13,19-22].

Here, we describe the implication of Pin1 in cancer in terms of the cell cycle and cell apoptosis and metabolism. In addition, we describe the pharmacological inhibitors of Pin1 for cancer therapy.

ROLE OF PIN1 IN CANCER

Pin1 is overexpressed in various types of cancers, and the dysregulation of this protein contributes to cancer development, suggesting that Pin1 is a useful and attractive target for cancer therapy [11-15]. Pin1 acts on cancer cells cycle, apoptosis, and metabolism.

Role of Pin1 in the Cell Cycle

Pin1 regulates a number of proteins implicated in cell-cycle progression, operating as a molecular timer of the cycle. Cyclin D1 is a critical target of Pin1-mediated cell-cycle control in cancer cells. Pin1 promotes cell-cycle progression, cell proliferation, and tumorigenesis by inducing cyclin D1 expression [14,23,24]. It binds to phosphorylated transcription factors such as c-Jun and β-catenin, causing them to undergo conformational changes. These fully activated transcription factors turn on their specific target genes AP-1 and TCF1, which results in the elevated expression of cyclin D1 (Figure 1). Under certain circumstances, Pin1 inhibits the interaction between β-catenin and the tumor suppressor APC protein, representing another mechanism for cyclin D1 activation. Pin1 can also directly stabilize cyclin D1 protein [24]. In this way, it has a positive role in G0-G1-S progression in addition to its originally proposed role in mitotic progression.
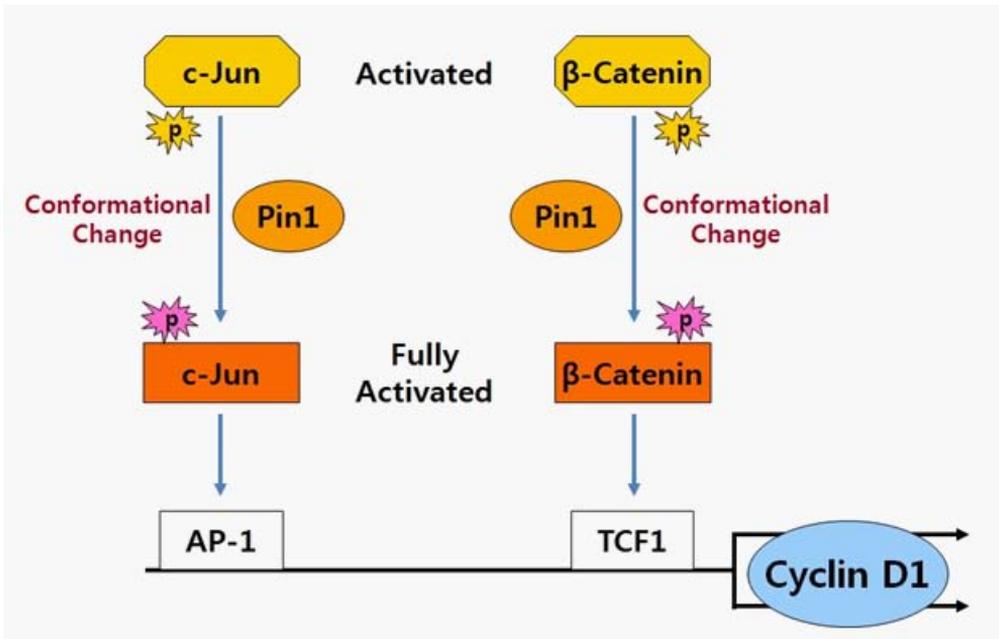

Figure 1: Pin1-mediated cyclin D1 induction. Pin1 binds phosphorylated and activated c-Jun and β-catenin and induces conformational changes in these transcription factors. These fully activated transcription factors, induced by conformational changes, bind to their specific cyclin D1 promoter target sites AP-1 and TCF, respectively. In this manner, cyclin D1 expression is elevated, which contributes to cell cycle progression.

Pin1 binds to many hyperphosphorylated proteins implicated in cell-cycle regulation such as Myt1, Wee1, and Cdc25C. Both Myt1 and Wee1 prevent entry into mitosis by inhibiting Cdc2 through phosphorylation at Thr14 and Tyr15 sites. In contrast, Cdc25C phosphatase triggers entry into mitosis by dephosphorylating and activating the cyclin B-Cdc2 complex. Pin1 binds to the C-terminal domain of phosphorylated Myt1 and potentially modulates Myt1-regulated mitosis entry, which leads to blockage of mitosis initiation [25]. In addition, Pin1 interacts with phosphorylated Cdc25C, thereby promoting a conformational change in Cdc25C and increasing its ability to activate and maintain cyclin B/Cdc2 activity [26,27]. However, sometimes Pin1 also inhibits the activity of Cdc25C [25]. Thus, it functions as a double-edged mitotic regulator that negatively regulates entry into mitosis but is required for progression through mitosis.

Role of Pin1 in Cancer Cell Apoptosis

Pin1 affects cancer cell apoptosis by directly regulating pro-apoptotic proteins such as Bax and death-domain associated protein (Daxx) or anti-apoptotic proteins such as Bcl-2 and Mcl-1. Although it regulates mitochondrial apoptosis by unleashing the pro-apoptotic response triggered by p53 and its sibling p73 in response to chemotherapeutic treatments [28], it also has anti-apoptotic activities in a variety of circumstances.

Inhibition of Daxx and promyelocytic protein (PML) contributes to the suppressive role of Pin1 in cancer cell apoptosis. Pin1 binds phosphorylated Daxx and PML and facilitates their ubiquitin-proteasome-dependent degradation, which impairs induction of apoptosis [6,29,30]. It binds to Daxx through the pSer178-Pro motif and binds to PML through phosphorylation at Ser403, Ser505, Ser518, and Ser527 in the C-terminal half of PML [29,30].

It also binds directly to and regulates the activities of Bcl-2 family members. For example, it supports the anti-apoptotic role of Bcl-2 by associating with phosphorylated Bcl-2 during paclitaxel-induced arrest in the M phase in the mitochondria, where it induces a conformational change in Bcl-2 [31]. In addition, Erk and Pin1 cooperatively regulate Mcl-1 stability [32]. Pin1 binds to and increases the stability of Mcl-1, which leads to the inhibition of apoptosis [32]. It also has potent anti-apoptotic activity by means of its ability to amplify the oncogenic properties of mutant p53 forms and Notch [33,34]. In this way, it leads to aberrant activation of mitochondrial anti-apoptotic genes such as Mcl-1 and survivin, which in turn inhibit Bax-induced apoptosis. Furthermore, it inhibits apoptosis by binding phosphorylated survivin on Thr34, supporting its anti-apoptotic activity [35]. Thus, Pin1 promotes cancer cell survival by suppressing the function of pro-apoptotic proteins or enhancing that of anti-apoptotic proteins.

Role of Pin1 in Cancer Metabolism

Notch signaling is critical for sustaining cell metabolism via activation of the PI3K-AKT signal. Notch and PI3K-AKT pathways are intertwined. Notch ligand bound to the extracellular domain of Notch induces proteolytic cleavage and release of the intracellular domain, which enters the nucleus to modify gene expression involved in cell–cell communication for processes such as cell

proliferation, development, and angiogenesis. Notch signaling is dysregulated in many cancers, and faulty Notch signaling is implicated in many diseases including T-cell acute lymphoblastic leukemia. Pin1 can induce Notch1 activation in cancer by triggering Notch1 cleavage by γ-secretase, leading to an increased release of the intracellular domain and ultimately enhancing Notch1 transcriptional and tumorigenic activity [34]. There is a strong correlation between Pin1 overexpression and Notch1 activation [34].

Glucocorticoids are involved in the regulation of metabolism and inflammation. They act by binding to the ubiquitously expressed glucocorticoid receptor (GR) that regulates energy metabolism. Upon activation by glucocorticoids, GR translocates to the nucleus where it stimulates or inhibits gene expression. Pin1 acts through N-terminal phospho-serine residues to regulate GR recruitment to its target sites in the genome, indicating that Pin1 can promote cancer cell metabolism by enhancing GR transactivation [36].

NF-kB, another regulator of cancer metabolism, regulates energy homeostasis and metabolic adaptation by controlling the balance between the utilization of glycolysis and mitochondrial respiration. The metabolic reorganization resulting from NF-kB inhibition can cause oncogenic transformation and impaired metabolic adaptation in cancer even in the absence of tumor suppressor mutations [37]. The NF-kB function is regulated by Pin1-mediated prolyl isomerization. Upon cytokine treatment, Pin1 binds to the pThr254-Pro motif in p65 and inhibits p65 binding to inhibitor of kB-α (IkB), resulting in increased nuclear accumulation and protein stability of p65 and enhanced NF-kB activity [38].

The role of Pin1 in cancer cell metabolism includes the regulation of lipid biosynthesis. For example, in breast cancer cells stimulated with epidermal growth factor (EGF), it enhances the promoter activity of sterol regulatory element-binding protein 1 (SREBP1), resulting in the increased expression of fatty acid synthase and thus an increase in intracellular fatty acid synthesis [39].

PIN1 INHIBITORS

Numerous reports have suggested the potential utility of Pin1 inhibitors for cancer therapy, and several groups have developed potent antagonists including small-molecule-based drugs and peptide drugs to inhibit Pin1 function [40-43]. Pin1 has three domains: the N-terminal WW domain (responsible for binding to pSer/Thr-Pro motifs in its specific substrate), the C-terminal catalytic PPIase domain (which isomerizes specific pSer/Thr-Pro motifs), and a flexible linker. The first two have been targeted for inhibitor development. These inhibitors have been tested in growth inhibition assays in cancer cells to evaluate their potential.

PPIase Domain Inhibitors: Peptide Drugs

Liu et al. [44] screened cyclic peptide libraries and identified a potent derivative peptide (IC$_{50}$ = 32 μM) that enhanced cell permeability and inhibited the proliferation of breast cancer

cells. BT474 peptide-treated breast cancer cells showed increased levels of α-PML and α-SMRT proteins, and decreased intracellular levels of Pin1 [44]. Etzkorn et al. designed a substrate-derived peptide that blocked the PPIase activity of Pin1 (IC_{50} = 1.5 μM) and the proliferation of A2870 ovarian carcinoma cells (GI_{50} = 8 μM) [45,46].

PPIase Domain Inhibitors: Small-Molecule-Based Drugs

Juglone, a molecule produced by walnut trees and used widely as a Pin1-inhibiting compound, inhibits cell growth in prostate cancer [47-50]. Using protease-coupled enzymatic assays to screen compounds, Uchida *et al.* identified dipentamethylene thiauram monosulfide (IC_{50} = 4 μM) and TME-001 (IC_{50} = 6.1 μM), which prevent the growth of colon cancer cells (HCT116) and cervical cancer cells (HeLa), respectively [51,52]. Pfizer and Vernalis identified small molecules as Pin1 PPIase domain inhibitors derived via structure-based drug design (PPIase domain inhibitors). Pfizer screened a million compounds using both fluorescence-polarization binding and enzymatic assays to find Pin1 inhibitors, and synthesized a potent Pin1 inhibitor with single digit IC_{50} (IC_{50} = 6 nM) [53]. Unfortunately, the compound lacked activity in cell-based assays because the phosphate group of the compound conferred poor permeability [53]. The Vernalis group utilized the NMR-based fragment screen system with a 900-fragment library and the protease-coupled functional assay to identify Pin1 inhibitors. An elaborate compound with high potency (IC_{50} = 830 nM) was synthesized. Treatment with the compound decreased cyclin D1 expression in PC3 prostate cancer cells [54].

More recently, Lu's group identified all-trans retinoic acid (ATRA), a therapeutic for acute promyelocytic leukemia (APL), by employing applied mechanism-based high-throughput screening for compounds that target active Pin1 [41]. ATRA binds to Pin1 and inhibits PPIase activity (IC_{50} = 820 nM), and eventually degrades active Pin1. ATRA-induced Pin1 ablation degrades the PML-RARA protein encoded by the fusion oncogene in APL cells and animal models, as well as tissues from human patients. In addition, ATRA inhibits the growth of MDA-MB-231 triple-negative breast cancer cells. In animal models, ATRA acts on multiple Pin1 substrate oncogenes such as cyclin D1, AKT, PKM2, and NF-kB/p65 and tumor suppressors including SMAD and SMRT [41].

WW Domain Inhibitors

Pin1 is inactivated by phosphorylation of Ser16, which prevents the WW domain from recruiting the Pin1 protein to its substrates. This mechanism suggests that inhibitors that compete with Pin1 substrates for WW binding might be effective inhibitors in cells [10,55]. Déprez et al. synthesized a putative WW domain ligand that showed 15 μM K_d activity and found that this lead molecule suppressed the expression of cyclin D1 in SH-SY5Y neuroblastoma cells [56]. Urusova and colleagues discovered the Pin1 inhibitor EGCG, a cancer chemo-preventative compound that is the major flavonoid in green tea. X-ray crystal co-structures showed that EGCG binds to both the WW and PPIase domains of Pin1 [42]. It suppressed Pin1 activity in a protease-coupled assay

(IC_{50} = 20 μM) and inhibited cyclin D1, the JNK signal, and Bcl-xL expression in ErbB2-transformed murine embryonic fibroblasts (MEFs) [42]. Tolerable doses of EGCG also reduced the growth of ErbB2-transformed MEF xenografts in immune-deficient mice.

PERSPECTIVES AND CONCLUSIONS

Pin1 inhibitors that act as PPIase inhibitors and/or WW domain inhibitors may act on multiple cancer-driving pathways to block their signals and tumorigenesis (Figure 2). Thus, Pin1 might be a useful therapeutic target for cancer treatment.
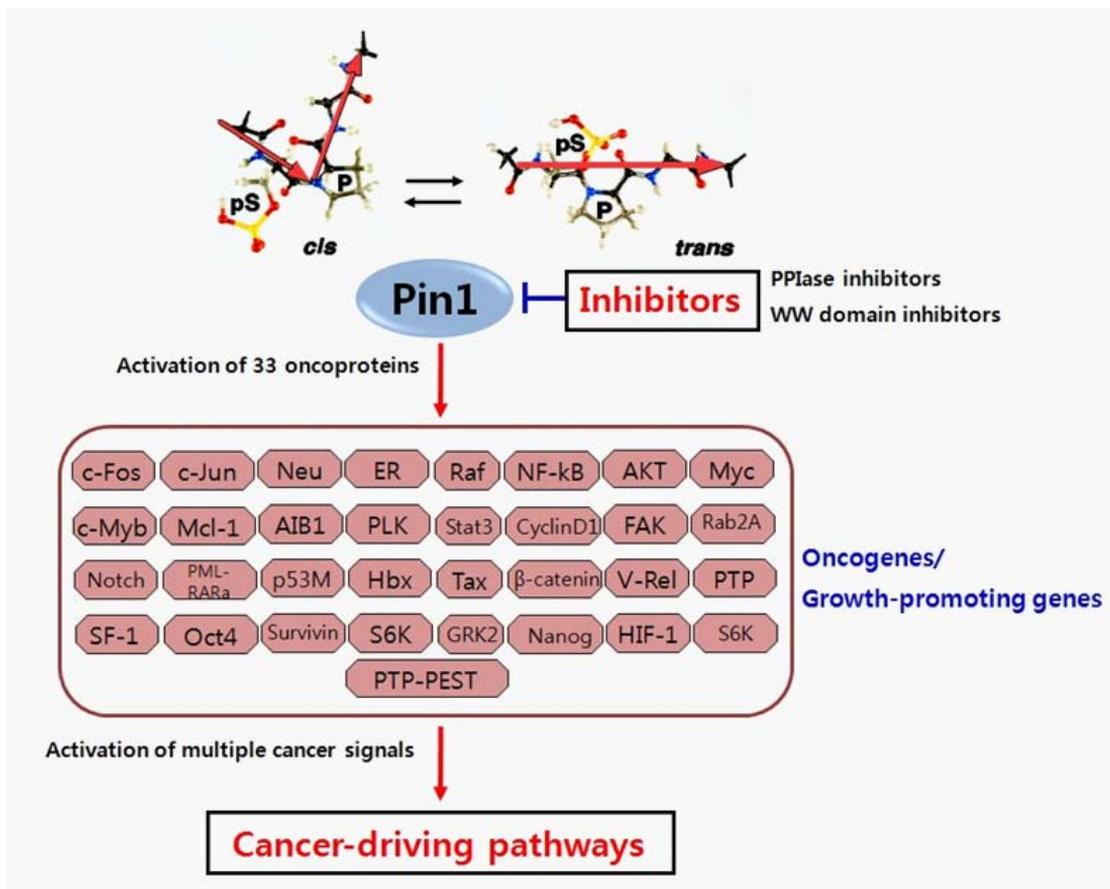

Figure 2: Pin1 inhibitors inactivate multiple cancer-driving pathways. Pin1 activates a variety of oncoproteins and growth-promoting proteins. Pharmacological Pin1 inhibitors have been developed to suppress the catalytic activity (PPIase inhibitors) and/or binding activity (WW domain inhibitors) of Pin1. These pharmacological Pin1 inhibitors might disrupt Pin1-mediated cancer-driving pathways.

ACKNOWLEDGMENTS

References

1. Lu KP, Zhou XZ. The prolyl isomerase PIN1: a pivotal new twist in phosphorylation signalling and disease. Nat Rev Mol Cell Biol. 2007; 8: 904-916.

2. Wulf G, Finn G, Suizu F, Lu KP. Phosphorylation-specific prolyl isomerization: Is there an underlying theme? Nature Cell Biol. 2005; 7: 435-441.

3. Lee, TH, Pastorino L, Lu KP. Peptidyl-prolyl cis-trans isomerase Pin1 in ageing, cancer and Alzheimer disease. Expert Rev Mol Med. 2011; 13: e21.

4. Blume-Jensen P, Hunter T. Oncogenic kinase signalling. Nature. 2001; 411: 355-365.

5. Lu KP, Hanes SD, Hunter T. A human peptidyl-prolyl isomerase essential for regulation of mitosis. Nature. 1996; 380: 544-547.

6. Lu Z, Hunter T. Prolyl isomerase Pin1 in cancer. In Cell Res. 2014; 24: 1033-1049.

7. Ranganathan R, Lu KP, Hunter T, Noel JP. Structural and functional analysis of the mitotic peptidyl-prolyl isomerase Pin1 suggests that substrate recognition is phosphorylation dependent. Cell. 1997; 89: 875-886.

8. Fischer G, Aumuller T. Regulation of peptide bond cis/transisomerization by enzyme catalysis and its implication in physiological processes. Rev Physiol Biochem Pharmacol. 2003; 148: 105–150.

9. Pastorino L, Sun A, Lu PJ, Zhou XZ, Balastik M, Finn G, et al. The prolyl isomerase Pin1 regulates amyloid precursor protein processing and amyloid-beta production. . Nature. 2006; 440: 528-534.

10. Lu PJ, Zhou XZ, Shen M, Lu KP. Function of WW domains as phosphoserine- or phosphothreonine-binding modules. Science. 1999; 283: 1325-1328.

11. Luo ML, Gong C, Chen CH, Hu H, Huang P, Zheng M, et al. The Rab2A GTPase Promotes Breast Cancer Stem Cells and Tumorigenesis via Erk Signaling Activation. Cell Rep. 2015; 11: 111-124.

12. Shi M, Chen L, Ji J, Cai Q, Yu Y, Liu B, et al. Pin1 is Overexpressed and Correlates with Poor Prognosis in Gastric Cancer. Cell Biochem Biophys. 2015; 71: 857-864.

13. Xu GG, Etzkorn FA. Pin1 as an Anticancer Drug Target. Drug News Perspect. 2009; 22: 399-407.

14. Wulf GM, Ryo A, Wulf GG, Lee SW, Niu T, Petkova V, et al. Pin1 is overexpressed in breast cancer and potentiates the transcriptional activity of phosphorylated c-Jun towards the cyclin D1 gene. EMBO J. 2001; 20: 3459-3472.

15. Ayala G, Wang D, Wulf G, Frolov A, Li R, Sowadski J, et al. Pin1 is a novel prognostic marker in prostate cancer. Cancer research. 2003; 63: 6244-6251.

16. Bao L, Kimzey A, Sauter G, Sowadski JM, Lu KP, Wang DG. Prevalent overexpression of prolyl isomerase Pin1 in human cancers. Am J Pathol. 2004; 164: 1727-1737.

17. Ryo A, Nakamura M, Wulf G, Liou YC, Lu KP. Pin1 regulates turnover and subcellular localization of beta-catenin by inhibiting its interaction with APC. Nature Cell Biol. 2001; 3: 793-801.

18. Suizu F, Ryo A, Wulf G, Lim J, Lu KP. Pin1 regulates centrosome duplication and its overexpression induces centrosome amplification, chromosome instability and oncogenesis. Mol Cell Biol. 2006; 26: 1463-1479.

19. Xu YX, Manley JL. The prolyl isomerase pin1 functions in mitotic chromosome condensation. Mol Cell. 2007; 26: 287-300.

20. Wulf G, Garg P, Liou YC, Iglehart D, Lu KP. Modeling breast cancer in vivo and ex vivo reveals an essential role of Pin1 in tumorigenesis. EMBO J. 2004; 23: 3397-3407.

21. Welcker M, Orian A, Jin J, Grim JE, Harper JW, Eisenman RN. The Fbw7 tumor suppressor regulates glycogen synthase kinase 3 phosphorylation-dependent c-Myc protein degradation. Proc Natl Acad Sci U S A. 2004; 101: 9085-9090.

22. Dougherty MK, Müller J, Ritt DA, Zhou M, Zhou XZ, Copeland TD. Regulation of Raf-1 by direct feedback phosphorylation. Mol Cell. 2005; 17: 215-224.

23. Liou YC, Ryo A, Huang HK, Lu PJ, Bronson R, Fujimori F, et al. Loss of Pin1 function in the mouse causes phenotypes resembling cyclin D1-null phenotypes. Proc. Natl Acad Sci USA. 2002; 99: 1335-1340.

24. Ryo A, Liou YC, Lu KP, Wulf G. Prolyl isomerase Pin1: a catalyst for oncogenesis and a potential therapeutic target in cancer. J Cell Sci. 2003; 116: 773-783.

25. Shen M, Stukenberg PT, Kirschner MW, Lu KP. The essential mitotic peptidyl-prolyl isomerase Pin1 binds and regulates mitosis-specific phosphoproteins. Genes Dev. 1998; 12: 706-720.

26. Crenshaw DG, Yang J, Means AR, Kornbluth S. The mitotic peptidyl-prolyl isomerase, Pin1, interacts with Cdc25 and Plx1. The EMBO journal. 1998; 17: 1315-1327.

27. Stukenberg PT, Kirschner MW. Pin1 acts catalytically to promote a conformational change in Cdc25. Mol Cell. 2001; 7: 1071-1083.

28. Zacchi P, Gostissa M, Uchida T, Salvagno C, Avolio F, Volinia S, et al. The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults. Nature. 2002; 419: 853-857.

29. Ryo A, Hirai A, Nishi M, Liou YC, Perrem K, Lin SC, et al. A suppressive role of the prolyl isomerase Pin1 in cellular apoptosis mediated by the death-associated protein Daxx. J Biol Chem. 2007; 282: 36671-36681.

30. Reineke EL, Lam M, Liu Q, Liu Y, Stanya KJ, Chang KS, et al. Degradation of the tumor suppressor PML by Pin1 contributes to the cancer phenotype of breast cancer MDA-MB-231 cells. Molecular and cellular biology. 2008; 28: 997-1006.

31. Pathan N, Aime-Sempe C, Kitada S, Basu A, Haldar S, Reed JC. Microtubule-targeting drugs induce Bcl-2 phosphorylation and association with Pin1. Neoplasia. 2001; 3: 70-79.

32. Ding Q, Huo L, Yang JY, Xia W, Wei Y, Liao Y, et al. Down-regulation of myeloid cell leukemia-1 through inhibiting Erk/Pin 1 pathway by sorafenib facilitates chemosensitization in breast cancer. Cancer res. 2008; 68: 6109-6117.

33. Girardini JE, Napoli M, Piazza S, Rustighi A, Marotta C, Radaelli E, et al. A Pin1/Mutant p53 Axis Promotes Aggressiveness in Breast Cancer. Cancer Cell. 20: 79-91.

34. Rustighi A, Tiberi L, Soldano A, Napoli M, Nuciforo P, Rosato A, et al. The prolyl-isomerase Pin1 is a Notch1 target that enhances Notch1 activation in cancer. Nat cell biol. 2009; 11: 133-142.

35. Cheng CW, Chow AK, Pang R, Fok EW, Kwong YL, Tse E. PIN1 inhibits apoptosis in hepatocellular carcinoma through modulation of the antiapoptotic function of survivin. Am J pathol. 2013; 182: 765-775.

36. Poolman TM, Farrow SN, Matthews L, Loudon AS, Ray DW. Pin1 promotes GR transactivation by enhancing recruitment to target genes. Nucleic acids res. 2013; 41: 8515-8525.

37. Mauro C, Leow SC, Anso E, Rocha S, Thotakura AK, Tornatore L, et al. NF-kappa B controls energy homeostasis and metabolic adaptation by upregulating mitochondrial respiration. Nat Cell Biol. 2011; 13: 1272-U234.

38. Ryo A, Suizu F, Yoshida Y, Perrem K, Liou YC, Wulf G, et al. Regulation of NF-kappaB signaling by Pin1-dependent prolyl isomerization and ubiquitin-mediated proteolysis of p65/RelA. Mol Cell. 2003; 12: 1413-1426.

39. Yun HJ, Kim JY, Kim G, Choi HS. Prolyl-isomerase Pin1 impairs trastuzumab sensitivity by up-regulating fatty acid synthase expression. Anticancer res. 2014; 34: 1409-1416.

40. Moore JD, Potter A. Pin1 inhibitors: Pitfalls, progress and cellular pharmacology. Bioorg Med Chem Lett. 2013; 23: 4283-4291.

41. Wei S, Kozono S, Kats L, Nechama M, Li W, Guarnerio J, et al. Active Pin1 is a key target of all-trans retinoic acid in acute promyelocytic leukemia and breast cancer. Nat Med. 2015; 21: 457-U230.

42. Urusova DV, Shim JH, Kim DJ, Jung SK, Zykova TA, Carper A, et al. Epigallocatechin-gallate Suppresses Tumorigenesis by Directly Targeting Pin1. Cancer Prev Res. 2011; 4: 1366-1377.

43. Uchida T, Takamiya M, Takahashi M, Miyashita H, Ikeda H, Terada T, et al. Pin1 and Par14 peptidyl prolyl isomerase inhibitors block cell proliferation. Chem Biol. 2003; 10: 15-24.

44. Liu T, Liu Y, Kao HY, Pei D. Membrane permeable cyclic peptidyl inhibitors against human Peptidylprolyl Isomerase Pin1. J med chem. 2010; 53: 2494-2501.

45. Etzkorn FA. Pin1 flips Alzheimer's switch. ACS chem biol. 2006; 1: 214-216.

46. Wang XJ1, Xu B, Mullins AB, Neiler FK, Etzkorn FA. Conformationally locked isostere of phosphoSer-cis-Pro inhibits Pin1 23-fold better than phosphoSer-trans-Pro isostere. Journal of the American Chemical Society. 2004; 126: 15533-15542.

47. Chao SH, Greenleaf AL, Price DH. Juglone, an inhibitor of the peptidyl-prolyl isomerase Pin1, also directly blocks transcription. Nucleic acids res. 2001; 29: 767-773.

48. Esnault S, Rosenthal LA, Shen ZJ, Sedgwick JB, Szakaly RJ, Sorkness RL, et al. critical role for Pin1 in allergic pulmonary eosinophilia in rats. J Allergy Clin Immunol. 2007; 120: 1082-1088.

49. Fan G, Fan Y, Gupta N, Matsuura I, Liu F, Zhou XZ, et al. Peptidyl-prolyl isomerase Pin1 markedly enhances the oncogenic activity of the rel proteins in the nuclear factor-kappaB family. Cancer res. 2009; 69: 4589-4597.

50. Kesavapany S, Patel V, Zheng YL, Pareek TK, Bjelogrlic M, Albers W, et al. Inhibition of Pin1 reduces glutamate-induced perikaryal accumulation of phosphorylated neurofilament-H in neurons. Mol Biol Cell. 2007; 18: 3645-3655.

51. Mori T, Hidaka M, Lin YC, Yoshizawa I, Okabe T, Egashira S, et al. A dual inhibitor against prolyl isomerase Pin1 and cyclophilin discovered by a novel real-time fluorescence detection method. Biochemical and biophysical research communications 2011; 406: 439-443.

52. Tatara Y, Lin YC, Bamba Y, Mori T, Uchida T. Dipentamethylene thiuram monosulfide is a novel inhibitor of Pin1. Biochem Biophys Res Commun. 2009; 384: 394-398.

53. Dong L, Marakovits J, Hou X, Guo C, Greasley S, Dagostino E. Structure-based design of novel human Pin1 inhibitors (II). Bioorg Med Chem Lett. 2010; 20: 2210-2214.

54. Potter A, Oldfield V, Nunns C, Fromont C, Ray S, Northfield CJ, et al. Discovery of cell-active phenyl-imidazole Pin1 inhibitors by structure-guided fragment evolution. Bioorganic & medicinal chemistry letters. 2010; 20: 6483-6488.

55. Lu PJ, Zhou XZ, Liou YC, Noel JP, Lu KP. Critical role of WW domain phosphorylation in regulating its phosphoserine-binding activity and the Pin1 function. J Biol Chem. 2002; 277: 2381-2384.

56. Smet C, Duckert JF, Wieruszeski JM, Landrieu I, Buée L, Lippens G, et al. Control of protein-protein interactions: Structure-based discovery of low molecular weight inhibitors of the interactions between Pin1 WW domain and phosphopeptides. J Med Chem. 2005; 48: 4815-4823.