Pharmacological Research 93 (2015) 28–35

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Perspective

Pin1-based diagnostic and therapeutic strategies for breast cancer☆

Jing-Zhang Wang*, Bao-Guo Liu, Yong Zhang

Department of Medical Technology, Affiliated Hospital, College of Medicine, Hebei University of Engineering, Handan 056002, PR China

ARTICLE INFO

Article history:
Received 5 October 2014
Received in revised form
19 December 2014
Accepted 19 December 2014
Available online 30 December 2014

Keywords:
Breast cancer
Pin1
Diagnostic strategy
Therapeutic strategy

ABSTRACT

Pin1 is the only known *cis*-to-*trans* isomerase that recognizes the phosphorylated pThr/pSer-Pro motifs in many signaling molecules, playing unique roles in the pathogenesis of breast cancer. First, Pin1 is prevalently over-expressed in kinds of breast cancer cell lines and tissues, such as MDA-MB-231 cell, MCF-7 cell, Her2+, ERα+, and basal-like breast cancer subtypes. Second, Pin1 amplifies many oncogenic signaling pathways, inhibits multiple tumor suppressors, promotes the angiogenesis and metastasis of breast cancer cells, and enhances the resistance of breast cancer cells to anti-tumor medicines. Third, inhibiting Pin1 blocks most of these detrimental effects in a great number of breast cancer cell lines. These findings suggest Pin1 as a promising diagnostic biomarker as well as an efficient therapeutic target for breast cancer. It is strongly expected that a Pin1-positive subtype of breast cancers should be extremely concerned and that the therapeutic efficacy of Pin1 inhibitors on breast cancer patients should be evaluated as soon as possible. Nonetheless, Pin1-based therapeutic strategies for breast cancer still deserve some debates. Hence, we give the predictions of several important issues, such as application precondition, side effects, and personalized medication, when Pin1 inhibitors are used in the breast cancer therapy. These proposals are meaningful for the further development of Pin1-based diagnostic and therapeutic strategies in order to conquer breast cancer.

Introduction

Breast cancer endangers the health of human beings across the world [1,2]. Screening predictive biomarkers and targeting pathological molecules are very important to prevent breast cancer [3–5]. The reversible phosphorylation of serine or threonine preceding a proline (Ser/Thr-Pro) in proteins is an important signaling switch in diverse human diseases including breast cancer. Several previous reviews have well demonstrated that the peptidyl-prolyl *cis-trans* isomerase Pin1 is the only known isomerase that specifically catalyzes the phosphorylated pThr/pSer-Pro motifs form *cis*-configuration to *trans*-configuration, that Pin1 regulates the transcriptional efficiency, expression levels, function, subcellular localization, stabilization, ubiquitylation, and degradation of many signaling molecules, and that Pin1 plays a vital role in a number of human diseases especially cancers and neurodegenerative disorders [6–9]. Our recent studies revealed the linking role of Pin1 in several chronic human diseases, too [10,11]. In this perspective, we focus on the increasing evidence that uncovers the vital role of Pin1 in the pathogenesis of breast cancer, and we further emphasize the importance of Pin1-based diagnostic and therapeutic strategies for the prevention of breast cancer.

The essential role Pin1 in the pathogenesis of breast cancer

The activation of multiple oncogenes and growth enhancers by Pin1

Pin1 activates more than two dozens of oncogenes and growth enhancers relevant to breast cancer, which is briefly shown in

Abbreviations: Pin1, the peptidyl-prolyl *cis-trans* isomerase; SRC-3/AIB1, steroid receptor coactivator 3; FAK, focal adhesion kinase; Mcl-1, myeloid cell leukemia-1; p70S6K, ribosomal S6 kinase; Stat3, signal transducers and activators of transcription 3; PKB/Akt, serine/threonine protein kinase B; ERα, estrogen receptor-alpha; ErbB2/HER2/neu, human epidermal growth factor receptor 2; Bax, Bcl-2-associated X protein; FOXO4, forkhead box O 4; RUNX3, runt-related transcription factor 3; Daxx, protein death domain-associated protein; RARα, retinoic acid receptor α; ATRA, *all-trans* retinoic acid; SMRT, silencing mediator for retinoic acid and thyroid hormone receptor; SUV39H1, suppressor of variegation 3–9 homologue 1; PML, promyelocytic leukemia protein; AP-1, activator protein-1; VEGF, vascular endothelial growth factor; DAPK1, death-associated protein kinase 1; *PIN1*, the gene encoding Pin1.

☆ Perspective articles contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

* Corresponding author at: Department of Medical Technology, Affiliated Hospital, College of Medicine, Hebei University of Engineering, 81# or 83# Cong Tai Road, Handan 056002, Hebei Province, PR China. Tel.: +86 0310 8575130; fax: +86 0310 8575130.
E-mail addresses: wangjingzhang1981@gmail.com, jingzhangwang@hebeu.edu.cn (J.-Z. Wang).

http://dx.doi.org/10.1016/j.phrs.2014.12.005
1043-6618/

Table 1
Positive effects of Pin1 on multiple oncogenes and growth enhancers relevant to breast cancer.

Oncogenes/growth enhancers	Roles in breast cancer	Binding motifs for Pin1	Function of Pin1	References
AIB1/SRC-3	Activates estrogen receptor and progesterone receptor; Leads to the development and progression of hormone-dependent and -independent breast cancer.	pSer505	Promotes the cooperation of AIB1 and other coactivators.	[7,14,32–34]
Akt/PKB	Associates with disease development, poor prognosis, lower patient survival, and resistance to radiotherapy in breast cancer.	pThr92; pThr450	Increases Akt stability; Protects Akt from degradation.	[26,35]
β-Catenin	Mediates Wnt signaling pathway; Promotes the proliferation, invasion, and metastasis of breast cancer.	pSer246	Inhibits β-catenin degradation; Enhances the nuclear accumulation and stabilization of β-catenin.	[13,27,36,37]
c-Fos	Composes the hetero-dimeric activator protein-1 (AP-1); Facilitates the nuclear import of some oncoproteins in breast cancer cell.	Possibly pThr232; pThr325; pThr331; pSer374	Potentiates the transcriptional response of c-Fos and AP-1 to multiple growth factors.	[15,38,39]
c-Jun	Composes the hetero-dimeric AP-1; Promotes the invasion and migration of breast cancer cell.	pSer63; pSer73	Increases the transcriptional activity of c-Jun toward downstream genes including cycling D1.	[13,16,40]
c-Myc	Promotes the proliferation and invasion of breast cancer cell; Correlates with the poor outcome of breast cancer.	pSer62	Enhances the binding of c-Myc and its coactivators to DNA promotors; Promotes c-Myc to activate the genes involved in cell growth, metabolism, and proliferation.	[17,41,42]
Cyclin D1	Promotes the proliferation, migration, and invasion of breast cancer cell; Serves as a diagnostic biomarker for breast cancer.	pThr286	Up-regulates the expression and the function of cyclin D1 *via* multiple signaling pathways; Increases the nuclear localization of cyclin D1; Stabilizes cyclin D1.	[18,28,43–45]
ERα	Functions as a hormone-regulated transcription factor; Critical for the efficiency of endocrine therapy.	pSer118	Increases ERα levels by inhibiting the proteasome-dependent degradation of it.	[29]
ErbB2(Her2/neu)	Promotes the proliferation and growth of breast cancer cell; Acts as a transcriptional coactivator for Stat3, cyclin D1, *etc.*; Is an independent prognostic factor of poor clinical outcome in MembErbB2+ breast cancer.	–	Attenuates the ubiquitin-mediated degradation of ErbB2; Increases the stability and cellular levels of ErbB2.	[30,46–49]
FAK	Significantly correlates with basal-like/triple negative breast cancer; Critical for the metastasis of breast cancer.	pSer910	Promotes the dephosphorylation of FAK.	[19,50–52]
Mcl-1	Increases the viability of breast cancer cell; Contributes to the proliferation and migration of breast cancer cell; Resist to cell apoptosis; Blocks the chemo-sensitization of breast cancer cell.	pThr92; pThr163	Stabilizes Mcl-1; Up-regulates the cellular levels of Mcl-1.	[20,53,54]
Nanog	Is a transcriptional factor maintaining the pluripotency of breast cancer cell; Promotes the proliferation of breast cancer cell.	pSer52; pSer65	Stabilizes Nanog by suppressing its ubiquitination and degradation.	[31,55]
NF-κB	Up-regulates many genes involved in antiapoptosis, proliferation, angiogenesis, and metastasis of breast cancer cell.	pThr254	Increases the nuclear accumulation and the protein stability of p65, which is a major component of the heterodimeric NF-κB; Enhances the activity ofNF-κB.	[7,13,21]
Notch1	Is over-activated in about 50% of breast cancer; Is a therapeutic target for breast cancer.	pSer2122; pThr2133; pSer2137	Modifies the structure of Notch1; Facilities the generation of the active intracellular domain of Notch1; Enhances the transcriptional activity of Notch1.	[7,22]
p70S6K	Significantly associates with the tamoxifen resistance and the prognosis in ERα+ postmenopausal breast cancer.	pThr389	Enhances the phosphorylation of p70S6K; Activates p70S6K-mediated signaling pathways.	[23,56]
Raf-1	Blocks the drug-sensitivity of breast cancer cell; Contributes to the drug-resistance of breast cancer cell; Enhances the expression of HER-2/Neu and leads to the distant metastases in ERα+ breast cancer.	Possibly pSer642	Hyperphosphorylated Raf-1 is inactive, but Pin1 promotes the dephosphorylation of Raf-1 by PP2A and recycles Raf-1 to its active form.	[24,57–59]
Stat3	Acts as an oncogene and is constitutively activated in various breast cancer cell lines; Associates with the proliferation, migration, drug resistance, and epithelial-mesenchymal transition of breast cancer cell.	pSer727	Promotes the activity of Stat3 and the expression of its target genes.	[25,60,61]