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REVIEW

PIM-1 kinase: a potential biomarker of triple-negative breast cancer

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Abstract: Triple-negative breast cancer is associated with a poor prognosis, and effective biomarkers for targeted diagnosis and treatment are lacking. The tumorigenicity of the provirus integration site for Moloney murine leukemia virus 1 (*PIM-1*) gene has been studied for many years. However, its significance in breast cancer remains unclear. In this review we briefly summarized the physiological characteristics and regulation of PIM-1 kinase, and subsequently focused on the role of PIM-1 in tumors, especially breast cancer. Oncogene *PIM-1* was found to be upregulated in breast cancer, especially in triple-negative breast cancer. Moreover, it is involved in tumorigenesis and the development of drug resistance, and linked to poor prognosis. A highly selective probe targeting PIM-1 for imaging has emerged, suggesting that PIM-1 may be a potential biomarker for the accurate diagnosis and targeted therapy of triple-negative breast cancer.

Keywords: triple-negative breast cancer, biomarker, PIM-1

Introduction

Triple-negative breast cancer (TNBC), which is negative for the expression of ER, PR, and HER2, is associated with the poorer prognosis among all types of breast cancer. Since endocrine therapy is ineffective and targeted-therapy is currently unavailable, chemotherapy remains the mainstay of treatment after surgery for TNBC. Therefore, discovering specific biomarkers for the development of early precise diagnosis, effective targeted-therapy, and sensitive assessment of the treatment effect on TNBC is clinically urgent.

The *PIM-1* (*provirus integration site for Moloney murine leukemia virus 1*) gene was identified as an oncogene in mice with leukemia induced by the Moloney murine leukemia virus in the1980s.[1] PIM-1 kinase, encoded by the *PIM-1* gene, is the most studied and important among all three members of the PIM kinase family. The other two members of the PIM kinase family discovered soon afterwards, PIM-2 and PIM-3, exhibit strong homology to PIM-1. Notably, in-vivo and in-vitro experiments suggested that they can be substitutes of PIM-1 to different extent.[2–4] The human PIM-1 kinase shares >90% similarity at the primary structure level with the mouse PIM-1 protein.[5,6] PIM-1 kinase was found to be overexpressed in human hematological malignancies,[7–9] as well as in numerous human solid tumors such as breast cancer,[10] prostate cancer,[10] gastric cancer,[11] and squamous cell carcinoma of the head and neck.[12] The molecular mechanisms of PIM-1-induced tumorigenesis have been studied in great depth. Meanwhile, many different small-molecule inhibitors targeting PIM-1 kinase have been developed. In recent years, increasing

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attention has been paid to the value of PIM-1 in the treatment and diagnosis of tumors. This review aims to explore the potential of PIM-1 kinase as a biomarker of TNBC by briefly summarizing its physiological structure and function, and regulation of the kinase activities of PIM-1. In addition, the association of PIM-1 with tumors and its role in breast cancer are discussed.

Physiological structure and function of PIM-1 kinase

The human *PIM-1* gene is located on chromosome 6p21, and consists of six exons and five introns. It produces a transcript which contains a G/C-rich sequence in the 5′ untranslated region (UTR) and five copies of AUUUA destabilizing motifs in the 3′ UTR.[6,13] The use of alternative translation initiation sites (AUG or CUG) results in the synthesis of different protein isoforms: 34 KD and 44 KD PIM-1 kinase (Figure 1).[14–16] The former isoform is comprised of 313 amino acids, while the latter includes 404 amino acids, both containing the kinase domain.[17–20]

Both PIM-1 protein isoforms exhibit in vitro serine/threonine kinase activities, and mediate their physiological function by phosphorylating a wide range of cellular substrates,[19,20] including: 1) cell cycle regulators, such as cyclin-dependent kinase inhibitor 1A/1B (CDKN1A/1B),[21–24] cell division cycle 25A/C (CDC25A/C),[25,26] checkpoint kinase 1 (CHK1),[27] and forkhead box P3 (FOXP3);[28] 2) transcriptional regulators, such as MYC[29] and MYB,[30] runt-related transcription factor 1/3 (RUNX1/3),[31] and high mobility group box transcription factor 1 (HBP1);[32] 3) signaling intermediates, such as Notch1,[10] suppressor of cytokine signaling 1/3 (SOCS1/3),[33] and mitogen-activated protein kinase kinase kinase 5 (MAP3K5);[34] 4) apoptosis signaling kinase 1 (ASK1)[34] and apoptosis regulators, such as BCL-2-associated agonist of cell death (BAD);[35] 5) protein translation regulators, such as eukaryotic initiation factor 4B (EIF4B);[36] and 6) others, such as breast cancer resistant protein (BCRP),[24] ubiquitin-like with plant homeo domain and RING finger domains 1 (UHRF1),[37] and androgen receptor (AR) (Table 1).[38] Through the phosphorylation of the above substrates, PIM-1 kinase plays a role in cell cycle progression, survival, proliferation, differentiation, apoptosis, and senescence. Xie et al found that 44 KD PIM-1kinase (located primarily on the plasma membrane), instead of the 34 KD isoform (present in both the cytosol and nucleus), phosphorylated BCRP to protect prostate cancer cells from apoptosis induced by chemotherapeutic drugs.[39,40] In addition, Katsube et al suggested that 44 KD PIM-1 kinase protected ATP-binding cassette transporter A1 (ABCA1) from lysosomal degradation in hepatocytes, and thereby regulated the circulating level of high-density lipoprotein.[41] However, thus far, almost all research studies investigating human PIM-1 kinase do not consider the two PIM-1 isoforms independently. Further investigation is warranted to determine whether the two isoforms are involved in a single mechanism of regulation of protein expression, or play different biological roles.

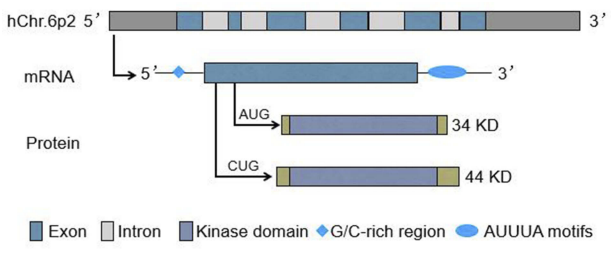

Figure 1 *PIM-1* gene and its transcripts and proteins.

Regulation of PIM-1 kinase activities

Structural analysis revealed that the PIM-1 protein contains a constitutively active kinase conformation that does not require to be phosphorylated for activation.[17] This means that the level of PIM-1 enzymatic activity in a cell is dependent on the absolute amount of protein present. Typically, both *PIM-1* mRNA and protein have a relatively short half-life.[14,39] The regulation of PIM-1 kinase activities largely depends on the induction of transcription and protein degradation, and varies among different cells. Numerous cytokines, growth factors, and mitogens can induce the expression of *PIM-1* in hematological malignancies.[42–44] In solid tumors, the expression of *PIM-1* may also be induced by hypoxia through hypoxia-inducible factor 1α (HIF1α),[45] DNA damage through Krüppel-like factor 5 (KLF5),[46] and estrogen through the estrogen receptor.[47] The majority of these factors transduce their signals through several common signaling pathways, such as the Notch pathway,[10] Janus kinase and signal transducer and activator of transcription (JAK/STAT) pathway,[43,48] and nuclear factor-κB (NF-κB) pathway.[49]

Both 5′ and 3′ UTRs of *PIM-1* mRNA and the alternative translation initiation sites play a vital role in the regulation of *PIM-1* expression.[50] Eukaryotic translation initiation factor 4E (EIF4E) binds to the m^7G cap structure in the 5′ UTR to regulate the expression of *PIM-1*; this process is termed cap-dependent translation.[51] It was reported that miR328 specifically silenced the expression of *PIM-1* through interaction

Table 1 PIM-1 kinase substrates

Cell cycle regulators	Transcriptional regulators	Signaling intermediates	Apoptosis regulators	Protein translation regulators	Others
CDKN1A CDKN1B CDC25A CDC25C CHK1 FOXP3	MYC MYB RUNX1 RUNX3 HBP1	SOCS1 SOCS3 MAP3K5 Notch1	BAD ASK1	EIF4B	UHRF1 BCRP AR

Abbreviations: PIM-1, provirus integration site for Moloney murine leukemia virus 1; CDKN1A, cyclin-dependent kinase inhibitor 1A, also termed p21 and CIP1; CDKN1B, also termed p27KIP1; CDC25A, cell division cycle 25A, also termed MPIP1; CDC25C, also termed MPIP3; FOXP3, forkhead box P3; RUNX1, runt-related transcription factor 1; HBP1, high mobility group box transcription factor 1; SOCS1, suppressor of cytokine signaling 1; BAD, BCL-2-associated agonist of cell death; ASK1, apoptosis signaling kinase 1; EIF4B, eukaryotic initiation factor 4B; UHRF1, ubiquitin-like with plant homeo domain and RING finger domains 1; BCRP, breast cancer-resistant protein; AR, androgen receptor.

with the *PIM-1* mRNA 3′ UTR.[52] Kim et al found that tristetraprolin bound to the adenylate-uridylate-rich element 2 in the 3′ UTR and enhanced the decay of *PIM-1* mRNA in human prostate cancer.[53] Recently, Blanco et al reported that mRNA stability factor HuR (Hu antigen R) interacted with the adenylate-uridylate-rich elements within the 3′ UTR in the context of hypoxia and stabilized the *PIM-1* mRNA, resulting in overexpression of the PIM-1 protein in pancreatic cancer cells.[54]

Ubiquitylation and subsequent proteasomal degradation are the primary post-translational regulation mechanisms of PIM-1 kinase. Research studies showed that heat shock protein 90β (HSP90β) can protect PIM-1 kinase from proteasomal degradation and thus, stabilize the protein level.[55] In contrast, protein phosphatase 2A (PP2A) promotes the ubiquitylation and proteasomal degradation of PIM-1.[56] PIM-1 kinase has been shown to be constitutively active and does not require prior post-translational modifications for activation. However, Iyer et al[57] revealed that, in vitro and in cultured cells, PIM-1 was modified by the small ubiquitin-like modifier (SUMO), and SUMOylation promoted the ubiquitin-mediated degradation of PIM-1 via recruitment of the SUMO-targeted ubiquitin ligase RNF4. Additionally, SUMOylated PIM-1 showed enhanced protein kinase activity in vitro. Hence, SUMOylation may govern PIM1 substrate specificity in certain contexts.[57]

PIM-1 kinase and tumors

Following its identification as an oncogene, the relationship between *PIM-1* and tumors has been the emphasis of research. Firstly, upregulation of PIM-1 has been found in prostate cancer,[10,58,59] squamous cell carcinoma of the head and neck,[12] breast cancer,[24,35] pancreatic cancer,[60–62] gastric cancer,[11,63] oral squamous cell cancer,[64] colorectal cancer,[65] hepatocellular carcinoma,[66] bladder cancer,[67] and non-small cell lung cancer,[68,69] in addition to hematological malignancies. Secondly, dysregulation of PIM-1 has been associated with the invasiveness of cancer cells and patient prognosis. Although earlier studies suggested that upregulation of PIM-1 predicted favorable prognosis in patients with prostate cancer,[58] pancreatic cancer,[61] and non-small cell lung cancer,[69] overexpression of PIM-1 has been linked to increasing invasiveness and/or poor prognosis in a large number of cancers (Table 2). Furthermore, the mechanisms of PIM-1-induced tumorigenesis have been studied in great depth. Eμ-*Pim-1* transgenic mice overexpressing PIM-1 alone developed lymphoma with long latency and low incidence;[70] thus *PIM-1* is considered to be a weak oncogene. However, transgenic mice co-expressing PIM-1 and MYC succumbed to lymphomas *in utero* or around birth.[71] Moreover, MYC has been shown to induce tumorigenesis depending on the expression of PIM-1 kinase in lymphoma, prostate cancer, and breast cancer.[24,70,72,73] In prostate cancer, PIM-1 phosphorylated the serine-62 of c-MYC to induce tumorigenesis,[73] while in breast cancer PIM-1 phosphorylated p27 and BAD, in addition to MYC.[24] Furthermore, PIM-1 was also reported to phosphorylate AKT, facilitating the glycolysis of hepatocellular carcinoma and promoting tumor growth and metastasis.[66] These findings suggest that PIM-1 may be involved in the development, progression, and maintenance of tumors via different mechanisms. This is consistent with the varied regulation of *PIM-1* expression within different types of cells mentioned above. Of note, PIM-1 induced tumorigenesis in a variety of tumors, *PIM-1* knockouts exerted only subtle effects without influence on growth and reproduction,[74] and mice deficient for all members of the *PIM* family (*PIM-1, 2, 3*) are

Table 2 PIM-1 and prognosis of tumors

Tumors	Dysregulation	Prognosis
Lymphoma[7–9]	Up	Correlated to poor prognosis
Prostate cancer[58]	Up	Correlated to favorable prognosis
Prostate cancer[59]	Up	Related to the grade and neoplastic transformation
Pancreatic cancer[60,62]	Up	Correlated to poor prognosis
Pancreatic cancer[61]	Up	Has a positive prognostic impact
Non-small cell lung cancer[68]	Up	Associated with an increase in pathological grade, lymph node metastasis, and advanced clinical stage
Non-small cell lung cancer[69]	Down	Associated with the occurrence of lymph node metastases
Gastric cancer[11,63]	Up	Inversely correlated to the presence of lymphovascular invasion
Squamous cell carcinoma of head and neck[12]	Up	Correlated to poor response to radiation therapy
Oral squamous cell cancer[64]	Up	NR
Breast cancer[24,35]	Up	Associated with a significantly higher risk of recurrence
Colorectal cancer[62]	Up	NR
Hepatocellular carcinoma[65]	Up	Promoted tumor growth and metastasis
Bladder cancer[67]	Up	Plays a role in the initiation and progression of bladder cancer

Abbreviation: NR, not reported.

viable and fertile, displaying only reduced body size and impaired responses to hematopoietic growth factors.[75] Based on this evidence, several research groups have generated structurally different small-molecule inhibitors targeting PIM kinases, with currently ongoing preclinical and clinical trials testing their potency for tumor inhibition.[42]

Roles of PIM-1 kinase in breast cancer

Although research on the expression and function of PIM-1 kinase in breast cancer has not been as extensive as that for other solid tumors (eg, prostate cancer), great progress in determining its roles in this type of cancer has been achieved in recent years. In 2006, Gapter et al demonstrated that the levels of both PIM-1 mRNA and protein were upregulated in breast cancer cells compared with those reported in normal breast epithelial cells.[21] A subsequent study also reported that the expression of *PIM-1* mRNA in human breast cancer was higher than that observed in benign breast tumors. Moreover, elevated *PIM-1* expression was associated with malignancy and a higher tumor grade.[47] Recently, a study performed by Jimenez–Garcia et al and based on several public databases revealed that the expression of PIM-1 was significantly increased in breast cancer compared with normal breast epithelium. Patients with higher *PIM-1* expression were associated with worse prognosis in relapsed and treatment-resistant tumors.[76] This evidence indicates that upregulation of PIM-1 may be a biomarker of breast cancer.

In 2016, Braso–Maristany et al[35] noticed that oncogene *PIM-1* is located on a genomic recurrent amplification region of 6p21-p25 in TNBC. They investigated whether the copy-number status and expression levels of *PIM-*' are increased in TNBC by analyzing three independent published datasets. The results showed that the levels of *PIM-1* mRNA were significantly higher in TNBC compared with those measured in non-TNBC. Furthermore, *PIM-1* gene expression was significantly correlated with its copy number in TNBC.[35] Meanwhile, Horiuchi et al[24] identified nine kinases that were selectively required for the survival of MYC-activated non-immortalized human mammary epithelial cells, among which PIM-1 exhibited the greatest efficacy in maintaining survival. Analysis of four distinct clinical cohorts revealed that *PIM-1* mRNA expression was significantly elevated in TNBC compared with that reported in non-TNBC. In addition, increased *PIM-1* expression was associated with poor prognosis in patients with hormone receptor-negative tumors.[24] These findings, related to the functions of *PIM-1* in TNBC, indicated that *PIM-1* mediated survival, tumor growth, and response to chemotherapy in cooperation with MYC in TNBC. Moreover, small-molecule inhibitors of PIM kinase halted the growth of human TNBC in a mouse model and sensitized TNBC to standard-of-care chemotherapy.[24,35]

Recently, Guo et al generated a highly selective red-emitting fluorescent probe targeting PIM-1 kinase for imaging cancer cells.[77] This probe successfully distinguished breast cancer cells overexpressing PIM-1 kinase from

normal cells in vitro and in vivo. In summary, the aforementioned findings demonstrate that upregulation of PIM-1 may be an important molecular event during the development and progression of TNBC. Thus, PIM-1 may be a reliable biomarker for the diagnosis, treatment, and prognosis of TNBC.

Conclusion and perspectives

After nearly 40 years of research, we have developed a deep understanding of the physiological structure and function of PIM-1. The role of PIM-1 in tumorigenesis has been determined to a certain extent. Exciting results have been obtained from studies involving treatment targeted to PIM-1 in lymphoma[78] and prostate cancer.[79] PIM-1 is overexpressed in TNBC and associated with cell survival, tumor growth, and resistance to chemotherapy in this setting.[24,35] Therefore, PIM-1 may be a reliable biomarker of TNBC. Further studies are warranted to investigate the relationship between PIM-1 and MYC in TNBC, and develop highly selective compounds against PIM-1. Such investigations will provide a new opportunity for the diagnosis and treatment of TNBC.

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Disclosure

The authors report no conflict of interest in this work.

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