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PIM Kinase Inhibitors and Cancer Treatment

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Abstract

PIM kinases have been pathologically upregulated by different upstream signals in multiple human cancers, including hematological malignancies and solid tumors. PIM kinase inhibitors are a class of drugs that are used primarily for treating various hematologic malignancies, particularly multiple myeloma. Recent developments in this area include new agents designed to enhance their efficacy, reduce their side effects, and overcome resistance to current therapies. Newer PIM inhibitors are developed, and/or are under different phases of clinical trials focusing on their mechanisms of action, combination with other therapies, and personalized medicine approaches.

Keywords: PIM kinase; Hematological malignancies; JAK/STAT; Drug resistance; Drug transporters

Abbreviations: PIM: Proviral insertion in murine malignancies; DLBCL: Diffuse large B cell lymphomas; PDAC: Pancreatic ductal adenocarcinoma

Introduction

The PIM kinases (proviral insertion in murine malignancies) belong to the serine/threonine kinase family [1]. Unlike other kinases, PIM family members are constitutively active and their catalytic activity is not regulated by phosphorylation [2]. The PIM kinase is found in three different isoforms: PIM-1, PIM-2, and PIM-3 [3]. PIM-1/2/3 is encoded by genes located on chromosomes 6p21, Xp11.23, and 22q13, respectively [2]. The three PIM isoforms are characterized by highly conserved structures. The amino acid sequence homology of Pim-1 is 61% and 71%, respectively with PIM-2 and PIM-3. Their tissue distribution varies. PIM-1 and PIM-2 are mainly expressed in hematopoietic cells, whereas PIM-3 is mainly expressed in brain, kidney, and epithelia [4].

Structure of PIM kinases

PIM kinases family members possess serine/threonine bilobal-fold kinase structure consisting of a N-terminal lobe, a C-terminal lobe, and hinge region. The N-terminal lobe contains antiparallel β-sheets, an αC-helix, and a glycine-rich activation loop, whereas the C-terminal lobe contains α-helixes and catalytic residues for transferring phosphate. The ATP binding site is located in the gap between N-terminal and C-terminal lobes [2]. One characteristic feature of Pan-PIM kinase domain is the unique presence of a proline amino acid residue with a tertiary amine in the hinge region. This criterion is exclusive for PIM kinases and is not found in other protein kinases. This structural feature enabled the design of selective Pan-PIM kinase inhibitors that inhibit PIM kinases without affecting the other kinases and are thus devoid of off-target activity present in other kinases [4].

Mechanism of action of PIM kinases

PIM kinases act by phosphorylating particular serine/threonine residues in substrate proteins by transferring the γ-phosphate of ATP. PIM kinases are regulated by calcium/calmodulin [1]. This mechanism is vital for controlling important biological functions such as cell proliferation, differentiation, and apoptosis [1].

PIM kinases in cancer

PIM kinases have an important role in cancer biology. They act as weak oncogene [3]. They are responsible for different types of human cancer when expressed at high levels under pathological conditions [3]. Activation of Pan-PIM kinase by different upstream effectors, such as Janus kinase/signal transducers and activators of transcription (JAK/STAT), phosphatidylinositol 3-kinase/ protein kinase B (PI3k/Akt), or nuclear factor (NF)-κB or suppressor

genes is correlated with the prevention of cellular apoptosis, and subsequent tumorigenesis [4]. Expanding evidence suggests that cancer cells routinely use PIM kinases as a survival mechanism to modify their biology and evade apoptosis [5]. Additionally, PIM kinases are a downstream effector in the VEGFA/Flk1 pathway and play a role in angiogenesis and vasculogenesis [6]. PIM kinases are over-expressed in various types of tumors. PIM-1 and PIM-2 are overexpressed in hematological malignancies such as multiple myeloma, leukemia, lymphoma including diffuse large B cell lymphomas (DLBCL), and in prostate cancer, whereas PIM-3 is overexpressed in hepatocellular, colon, and pancreatic carcinomas [4]. Furthermore, different PIM kinase isoforms have been identified as a clinical biomarker, regulator of expression of drug efflux proteins and potential therapeutic target for personalized treatment of advanced cancer [3]. Currently, the inhibition of Pan-PIM kinase by small-molecule modulators is an attractive target for the development of anti-cancer chemotherapeutic drugs [4]. Some inhibitors have been developed and/or are in different phases of clinical trials [3]. Another option is to directly target PIM kinases through either monoclonal PIM antibody therapy or indirectly by targeting PIM kinase regulators [7].

Classification of Pan-PIM kinase inhibitors

PIM-1/2/3 isoforms have cellular compensatory mechanisms that maintain the functions of each other's. To ensure more effective cancer treatment, the design of inhibitors must emphasize the simultaneous negative modulation of all three isoforms [4]. Clinical trials using first generation Pan-PIM inhibitors have failed to produce significant reduction in disease burden or alleviate chemoresistance in patients. In addition, higher doses of PIM inhibitors may have off-target effects leading to adverse effects, including cardiac events, gastrointestinal side effects, febrile neutropenia, and rash, among others [7]. Newer, highly specific PIM kinase inhibitors can overcome these problems, allowing PIM targeting at lower concentrations [7].

Depending on the interactions of Pan-PIM kinase inhibitors with hinge residues, Pan-PIM kinase inhibitors are classified into two broad types: ATP-mimetic and ATP-competitive inhibitors.

- ATP-mimetics (staurosporine 1 and LY333531 2) form one canonical hydrogen bond (HB) with the backbone CO of the hinge region.

- ATP-competitive inhibitors (SMI-4a 3 and LY294002 4) compensate for the lack of forming canonical HBs with the hinge region by forming other polar contacts inside the ATP-binding site [4]. Summary of clinical trials on several small-molecule inhibitors targeting PIM kinases. The selective PIM-1, PIM-2, and/or PIM-3 isoform inhibitors have shown significant results in patients with advanced stages of cancer including relapsed/refractory cancer [7]. Numerous preclinical studies have demonstrated increased efficacy when PIM inhibitors are part of a dual therapy regimen along with JAK inhibitors [7]. Furthermore, targeting PIM3 kinase and its role in signaling pathways is being investigated as a potential therapeutic strategy to overcome drug resistance in cancer treatment [5].

PIM kinase inhibitors and cancer treatment

The clinical significance of targeting the PIM pathway in lymphoproliferative disorders and solid tumors has been demonstrated by a sheer number of pre-clinical and clinical trials conducted on PIM inhibitors. However, future studies are still needed to delegate the specific roles of individual PIM isoforms, their downstream targets, and how PIM inhibitors are regulated to refine therapeutic options more precisely [7]. Effective strategies to treat leukemia/lymphoma will likely incorporate dual or combination therapy that includes a Pan-PIM inhibitor. PIM kinases are elevated by common protein tyrosine kinase receptors that are deregulated in most lymphoproliferative disorders, therefore targeting PIM and the JAK/STAT pathway is a very interesting option. This would allow reduced dosing of PIM inhibitor and possibly preventing JAK inhibitor resistance [7].

Several PIM inhibitors are currently undergoing clinical trials, such as a phase I clinical trial of Uzanserti for treatment of relapsed DLBCL that has been completed [8]. PIM-1 found on the cell surface of some leukemic cells could be targeted, by monoclonal PIM-1 (mPIM-1) therapy with loss of proliferation, [7]. Dual therapy with Bcl-2 or Mcl-1 antagonists and pan-PIM inhibition may also prove useful, as evidenced by results of preclinical data in ALL with sabutoclax (a pan-Bcl-2 inhibitor) [7]. Multi-inhibitors, PIM-3-CDK4/6-FLT3, ETH-155008, and PIM-FLT3, SEL24/MEN1703 show promise in currently undergoing clinical trials in leukemia [7]. The inhibition of PIM kinases in multiple myeloma is of emerging scientific interest in myeloma treatment. Several PIM kinase inhibitors, such as SGI-1776, AZD1208, and PIM447 (formerly LGH447), are in different phases of clinical trials. The mechanisms by which PIM kinases modulate the immune microenvironment and synergize with the immunomodulatory agents such as lenalidomide have not been deliberately illustrated. Additionally, the effects of combining PIM kinase inhibitors with other targeted agents as a therapeutic target in malignancy are highlighted [9]. The dual PIM- CDK4/6 inhibitor, abemaciclib is investigated for the treatment of HR+/HER2- advanced breast cancer. Pan-PIM inhibitors is paired with inhibitors of the PI3K/AKT/ mTOR pathway, for which PIM kinases show parallel functions in cancer therapy [7].

PIM kinases and resistance to therapy

PIM kinases induce resistance to a variety of chemotherapy and radiotherapy. PIM1 overexpression is associated with a poor response to radiotherapy, and PIM3 overexpression induces resistance to platinum and taxane-based chemotherapy. The role of PIM3 in the chemoresistance of pancreatic ductal adenocarcinoma (PDAC) was shown through either genetic or pharmacological inhibition (i.e., SGI-1776), suggesting that PIM3 inhibition could

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be a potential strategy to sensitize PDAC cells to gemcitabine and improve treatment outcomes in patients with this aggressive cancer [5]. PIM1 and PIM3 have been shown to confer resistance to different types of inhibitors, such as PI3K inhibitors, PI3K/mTOR dual inhibitors, PDH1 inhibitors, Akt inhibitors, and several mTOR inhibitors. Overexpression of PIM-1 results in resistance to anti-HER2/EGFR treatments, immunosuppressive rapamycin, PI3K inhibitors, MET inhibitors, conventional chemotherapy, radiation therapy, and other therapeutic methods [5]. Furthermore, PIM expression seems to be related to the mechanism of acquired resistance in MET inhibitor-resistant clones as the pan-PIM kinase inhibitor AZD1208 inhibits the development of resistant colonies despite having no effect on the growth of cancer cells [5].

PIM inhibitors and drug transporters

PIM may control drug transporters, which may contribute to its ability to resist chemotherapy-induced apoptosis. Treatment with PIM inhibitors sensitizes cells to chemotherapy by regulating ATP-binding cassette (ABC) drug transporters and reduces chemotherapy-induced apoptosis [5].

Conclusion

Current research has focused on the development of a new generation of potent PIM kinase inhibitors reasonable for treatment of human malignancies. Combining therapy of PIM kinase inhibitors and chemotherapy appears to create an additive cytotoxic effect on cancer cells. Currently, ongoing clinical trials focus on the structural and biological characterization of PIM inhibitors, with a particular stress on medicinal chemistry, as well as the design and analysis of persisting challenges aiming to provide valuable insights for future development of PIM inhibitors.

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