

Proviral Integrations of Moloney Virus (PIM) Kinase Inhibitors as Perspective Chemotherapeutic Agents

Mahdi Nohtani¹, Maryam M. Matin^{1, 2, 3}

¹Department of Biology, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran

²Cell and Molecular Biotechnology Research Group, Institute of Biotechnology, Ferdowsi University of Mashhad, Mashhad, Iran

³Stem Cell and Regenerative Medicine Research Group, Iranian Academic Center for Education, Culture and Research (ACECR), Khorassan Razavi Branch, Mashhad, Iran

Abstract

Dysfunctional intercellular signaling cascades mediated by oncogenic kinases to maintain tumor cell growth and survival is main characteristic of tumor cells. In normal cells, the activity of these kinases is fine-tuned by different mechanisms, while their prolonged activation promotes apoptotic resistance and uncontrolled proliferation. PIM kinases are members of serine/threonine kinase family that their activation is frequently cited in human cancers. Phosphorylation of their downstream substrates activate common pathways controlling various physiological processes. PIM kinases activity regulate the balance between cell survival and apoptosis. As a result, these kinases represent promising targets for cancer therapy and they are in the center of intense drug development efforts. Understanding how these kinases control distinct signal transduction pathways is important for designing new drugs and improving their efficacy in the clinic. The PIM kinases are downstream of multiple oncogenic tyrosine kinase receptors, including Janus kinase (JAK) and FMS-like tyrosine kinase 3 (FLT3). The JAK/STAT pathway has an important role in regulating the expression of PIM genes. The PIM family consists of three isoforms that are highly conserved throughout evolution. Since the discovery of PIM kinases, development of PIM inhibitors as perspective anticancer drugs has been a priority in both academic and industrial settings. Majority of PIM kinase inhibitors were designed to target the ATP binding pocket of PIM1. Although the PI3K/Akt pathway inhibitors demonstrated acceptable potential in preclinical and clinical trials, they could not be used effectively due to acquired resistance. Therefore the PIM kinases represent a promising target for anticancer drug discovery and their frequent overexpression in cancer and their association with enhanced tumor growth and chemoresistance imply their major role in cancer progression and metastasis. Combination of PIM inhibitors with PI3K/Akt inhibitors could be an ideal approach to overcome resistance barrier. A growing body of evidence suggests that PIM kinase inhibitors are much more effective when used in combination with other common therapeutic agents for cancer. PIM inhibitors could prevent drug -resistant phenotypes in preclinical models, especially in the context of tumor hypoxia. It remain to be determined whether tumor cells will develop resistance to PIM kinases inhibitors. The combination of PIM kinases and Akt inhibitors appears to be a promising option for cancer therapy. Future research on PIM kinases and their involvement in mechanisms of drug resistance is needed to recognize the full potential of PIM inhibitors as a strategy for cancer therapy.

Keywords: PIM Kinases, Cancer Therapy, Acquired Resistance, Hypoxia, PI3K/Akt Pathway

Corresponding Author: Mahdi Nohtani

Email: mahdi_nohtani@yahoo.com



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