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Review Article

Roles of Pim-3, a novel survival kinase, in tumorigenesis

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Pim-3 is a member of the Provirus integrating site Moloney murine leukemia virus (Pim) family, which belongs to the Ca^{2+}/calmodulin-dependent protein kinase (CaMK) group and exhibits serine/threonine kinase activity. Similar to other members of the Pim family (i.e. Pim-1 and Pim-2), Pim-3 can prevent apoptosis and promote cell survival and protein translation, thereby enhancing cell proliferation of normal and malignant cells. Pim-3 is expressed in vital organs, such as the heart, lung, and brain. However, minimal phenotypic changes in Pim-3-deficient mice suggest that Pim-3 may be physiologically dispensable. Pim-3 expression is enhanced in several cancer tissues, particularly those of endoderm-derived organs, including the liver, pancreas, colon, and stomach. The development of hepatocellular carcinoma is accelerated in mice expressing the *Pim-3* gene selectively in the liver only when these mice are treated with a hepatocarcinogen, indicating that Pim-3 can act as a promoter but not as an initiator. Moreover, inhibition of Pim-3 expression can retard *in vitro* cell proliferation of hepatocellular, pancreatic, and colon carcinoma cell lines by promoting cell apoptosis. Furthermore, a Pim-3 kinase inhibitor has been reported to inhibit cell proliferation in an *in vivo* xenograft model using a human pancreatic cancer cell line without inducing any major adverse effects. Thus, Pim-3 kinase may be a candidate molecule for the development of molecular targeting drugs against cancer. (*Cancer Sci* 2011; 102: 1437–1442)

Pim-3 was initially identified as a novel gene that is induced by membrane depolarization or forskolin in a rat pheochromocytoma cell line (namely PC12 cells) and was designated as kinase induced by depolarization (KID)-1.[1] However, KID-1 was renamed Pim-3 because it showed high sequence similarity with the proto-oncogene Provirus integrating site Moloney murine leukemia virus (Pim) family proteins.[2] The Pim family is part of the Ca^{2+}/calmodulin-dependent protein kinase (CaMK) group (http://www.kinase.com/human/kinome, accessed May 13, 2011) and was named as such because the gene locus of Pim-1, the prototype Pim kinase, was originally identified as a Proviral Insertion site of Moloney murine leukemia virus.[3] Subsequent studies revealed that Pim-1 and myc can contribute cooperatively to the development of experimental T cell lymphoma.[4] In addition, Pim-2 has been identified as a proviral integration site associated with the rapid development of malignant T cell lymphoma.[5]

Screens using retroviral mutagenesis have uncovered two types of serine/threonine kinases, namely the Akt[6] and Pim[7] kinases, as potent suppressors of myc-induced apoptosis. Moreover, Pim and Akt kinases are critical components of overlapping, but independent, pathways that can promote the growth and survival of non-transformed hematopoietic cells.[8] Because both Pim and Akt kinases can phosphorylate similar sets of substrates that regulate both apoptosis and cellular metabolism, it has been proposed that these kinases are categorized as survival kinases.[9] In various types of tumors, Akt is aberrantly activated and/or phosphatase and tensin homolog (PTEN), an Akt inhibitory molecule, is frequently deleted.[9] Based on these observations, drugs targeting the Akt axis have been developed for the treatment of cancer.[10] Similarly, Pim kinases are aberrantly expressed in a wide variety of tumors[11] and therefore may be a good molecular target in cancer treatment. Here, we discuss mainly the new member of the Pim kinase family (i.e. Pim-3) and its potential roles in tumor development and progression.

Structure of the Pim-3 Protein

Human Pim genes are found at different chromosomal locations in the human genome: Pim-1 is located on chromosome 6p21.2, Pim-2 is located on the X chromosome and Pim-3 is located on chromosome 22q13.[11] The mRNA transcripts for Pim are encoded by six exons with large 5′ and 3′ untranslated regions containing a G/C-rich region and five copies of AUUA destabilizing motifs, respectively. The Pim-1 and Pim-2 genes can generate two and three isoforms, respectively, by using alternative translation initiation sites, although all these isoforms retain their serine/threonine kinase activity.[12,13] In contrast, a single species of Pim-3 mRNA has been detected in various human organs.[14]

The open reading frame of Pim-3 mRNA encodes a protein consisting of 326 amino acids with a calculated molecular weight of 35 861 (Fig. 1).[14] In contrast with most kinases, the Pim-3 protein has no regulatory domains, similar to Pim-1 and Pim-2. Human Pim-3 protein shows a high degree of identity with human Pim-1 (57.1%) and Pim-2 (44.0%) at the amino acid level, even in the kinase domains (Fig. 1), as well as to rat Pim-3 (95.0%), mouse Pim-3 (95.0%), quail Pim (73.9%), and *Xenopus* (Pim-1; 68.7%).[14]

The crystal structure of the Pim-3 protein has not yet been obtained, but several independent groups have reported the crystal structure of Pim-1 and Pim-2 in the presence or absence of their inhibitors.[15–17] The Pim-1 kinase structure adopts a two-lobe kinase fold with a deep, intervening cleft.[15] The N-terminal lobe is composed primarily of β-sheets, whereas the C-terminal lobe is comprised of α-helices. The two domains are connected via the hinge region (residues 121–126; http://www.ncbi.nlm.nih.gov/Structure/mmdb/mmdbsrv.cgi?uid=30738, accessed May 13, 2011). Several residues in the cleft have been identified as the ATP binding site (Fig. 1). Moreover, the ATP binding pocket in Pim-1 is open in either the presence or absence

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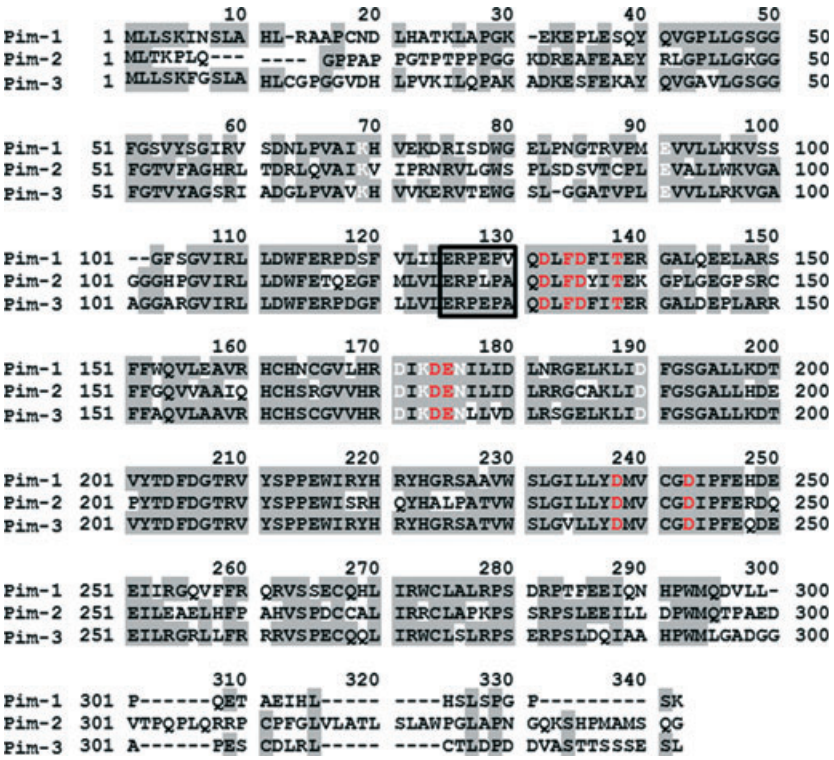

Fig. 1. Amino acid alignment of human Pim family proteins.[14] The amino acid sequence of human Pim family kinases is aligned and the residues identical to human Pim-3 are highlighted. The hinge region is indicated by the box. White and red letters indicate residues important for ATP binding and substrate specificity, respectively.

of ATP,[15] indicating that the Pim-1 kinase active site is maintained in an active conformation. Similar findings have been reported for the structure of Pim-2 kinase.[17] This may account for the association between protein levels of Pim-1 and Pim-2 and overall kinase activity.[11] Given the high sequence similarity between the Pim proteins, it is expected that Pim-3 kinase will have a similar structure to that described for Pim-1 and Pim-2 and that it will also be constitutively active. Furthermore, several residues have been identified as important for determining the specificity of Pim-1 kinase and these residues are conserved between Pim-1, Pim-2, and Pim-3 (Fig. 1).[16]

Expression of Pim-3

The expression of Pim-3 mRNA has been detected in various human tissues, including the heart, brain, lung, kidney, spleen, placenta, skeletal muscle, and peripheral blood leukocytes.[14] However, Pim-3 mRNA has not been found in the colon, thymus, liver, or small intestine.[14] In addition, Pim-3 is expressed in endothelial cells.[18] In the brain, Pim-3 and Pim-1 are induced in the hippocampus in response to stimuli that elicit long-term potentiation.[2] Focal cerebral ischemia enhances Pim-3 mRNA expression in the peri-infarction cortex at early time points.[19] Similarly, ischemia–reperfusion injury enhances intracardiac Pim-3 expression through a p38-mediated signaling pathway.[20] In the mouse embryo, all *Pim* genes are expressed in distinct manners at stages later than embryonic day (E) 14.[21] In mouse embryos, *in situ* hybridization has detected *Pim-3* gene expression in the liver, the periphery of the pancreas, in the secretory epithelium of the stomach, and in the intestinal epithelium.[21] Moreover, Pim-3 has been detected in the kidney, lungs, thymus, and central nervous system of mouse embryos.[21]

A panel of human Ewing's family tumor cell lines has been shown to express Pim-3 mRNA.[22] Moreover, enhanced Pim-3 mRNA expression is observed in nasopharyngeal carcinoma cell lines.[23] Similarly, we revealed that Pim-3 protein is barely detected in normal adult endoderm-derived organs such as the liver, pancreas, colon, and stomach; however, its expression is augmented in premalignant and malignant lesions of these organs (Table 1).[14,24–26] The staining pattern in these tumors is mostly cytoplasmic. In the liver, Pim-3 protein is detected in regenerative nodules and adenomatous hyperplasia, lesions with precancerous potential adjacent to hepatocellular carcinoma (HCC) cells, at a higher frequency than in HCC cells.[14] Similarly, in the colon and stomach, Pim-3 protein is detected in adenoma tissues with a higher incidence than in adenocarcinoma tissues.[25,26] These observations suggest that aberrant Pim-3 expression can occur in the early phase of carcinogenesis.

The Ewing sarcoma breakpoint region-1/E26 transformation-specific (EWS/ETS) fusion proteins are pathognomonic for Ewing's sarcoma tumors and arise from the chromosomal translocations that fuse a portion of the amino-terminal region of EWS to one of five members of the ETS family transcription factors, namely Friend leukemia integration (FLI), v-ets avian erythroblastosis virus E26 oncogene homolog (ERG), fifth Ewing sarcoma variant (FEV), ets variant gene 1 (ETV1), and E1A enhancer binding protein (E1AF).[27] Deneen *et al.*[22] demonstrated that Pim-3 can be upregulated by EWS/ETS fusion proteins, suggesting that ETS protein can regulate Pim-3 gene expression.

To delineate the molecular mechanisms underlying constitutive Pim-3 expression in human pancreatic cancer cells, we characterized the 5′-flanking region of the human *Pim-3* gene. The human *Pim-3* gene contains a canonical TATA box and putative binding sites for several known transcription factors, such as signal transducer and activator of transcription (Stat) 3, Sp1, Ets-1, and nuclear factor (NF)-κB (Fig. 2a).[28] Although Pim-3 expression is enhanced in murine embryonic stem cells by leukemia inhibitory factor/gp130-dependent signaling and the Stat3 transcription factor,[29] the transfection of a dominant negative form of Stat3 failed to inhibit the promoter activity of the *Pim-3* gene in human pancreatic cancer cells.[28]

Using luciferase expression vectors linked to the 5′-flanking deletion mutants of the human *Pim-3* gene, we demonstrated that the region between −264 and −164 bp is essential for

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Table 1. Expression patterns for Pim kinases in various types of malignancies and their biological functions in carcinogenesis

	Pim-1	Pim-2	Pim-3
Expression in			
Prostate adenocarcinoma	+	+	ND
Squamous cell carcinoma of head and neck	+	ND	ND
Nasopharyngeal carcinoma	ND	ND	+
Oral squamous cell carcinoma	+	ND	ND
Gastric cancer	+	ND	+
Colon carcinoma	ND	ND	+
Pancreatic cancer	+	ND	+
Hepatocellular carcinoma	ND	+	+
Ewing's sarcoma	ND	ND	+
Acute myeloid leukemia	ND	+	ND
B Cell chronic lymphocytic leukemia	ND	+	ND
Primary mediastinal large B cell lymphoma	+	ND	ND
Mantle cell lymphoma	+	+	ND
Diffuse large B cell lymphoma	+	+	ND
Biological functions in carcinogenesis			
Inhibition of apoptosis	+	+	+
Phosphorylation and inactivation of Bad	+	+	+
Cell cycle progression	+	+	+
Phosphorylation of Cdc25A	+	ND	ND
Phosphorylation of C-TAK1	+	ND	ND
Phosphorylation of p27	+	+	+
Inactivation of FoxO1a and FoxO3a	+	ND	ND
5′-Cap-dependent protein translation	ND	ND	+
Induction of PGC-1α expression	ND	ND	+
Induction of c-Myc expression	–	–	+
Phosphorylation of c-Myc	+	+	ND
Coactivator of c-Myc	+	+	ND
Phosphorylation of histone H3	+	ND	ND
Endothelial cell tube formation	ND	ND	+

ND, not determined; C-TAK1, Cdc25C-associated kinase 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α.

constitutive *Pim-3* gene expression.[28] This region contains one NF-κB, two Sp1, and two Ets-1 binding sites (Fig. 2a). The mutation in the NF-κB binding site failed to reduce luciferase activity[28] and it is therefore unlikely that NF-κB can contribute to constitutive *Pim-3* gene expression in human pancreatic cancer cells (in contrast with the *Pim-1* gene, which can be induced by CD40-mediated signals in an NF-κB-dependent manner).[12] Further examination has revealed that two Sp1 binding sites and the distal Ets binding site are crucial for constitutive *Pim-3* gene expression in human pancreatic cancer cells (Fig. 2b).[28] The crucial role of Ets-1 in constitutive *Pim-3* gene expression is further supported by our observations that the overexpression of Ets-1 enhances Pim-3 expression, whereas the transfection of a dominant negative form of Ets-1 or Ets-1 siRNA reduces Pim-3 expression in human pancreatic cancer cells.[28] Because the expression of both Ets-1 and Sp1 is enhanced in various types of cancer, including pancreatic cancer,[30,31] it is likely that Ets-1 and Sp1 act cooperatively to induce constitutive *Pim-3* gene expression, as has been seen for their other target genes.[32]

The translation of *Pim-1* mRNA is regulated by several mechanisms, including microRNA.[11] However, it remains unknown whether Pim-3 translation is regulated in a similar manner. Pim-1, and probably Pim-3, can autophosphorylate some of their serine residues.[16] Serine/threonine phosphatase and protein phosphatase 2A dephosphorylate Pim-1 and Pim-3 proteins, eventually decreasing their protein levels.[33]

Roles in Carcinogenesis

We observed that Pim-3 shRNA treatment decreases *in vitro* proliferation of various types of cancer cells by enhancing the apoptosis of these cells (Table 1).[14,24,25] The proapoptotic BH3-only protein Bad is a major regulator of apoptosis. Unphosphorylated Bad binds, and eventually inactivates, antiapoptotic family members, primarily Bcl-X_L, but also Bcl-2, whereas phosphorylation of Bad at Ser^{112}, Ser^{136}, and Ser^{155} impairs its binding to Bcl-X_L and promotes the sequestration of Bad from the surface of the mitochondria to the cytosol by the protein 14-3-3.[34,35] By phosphorylating Bad at Ser^{112}, Pim-1 and Pim-2 inactivate it, eventually inhibiting apoptosis.[36,37] Similarly, enforced expression of Pim-3 increases the amount of Bad phosphorylated at Ser^{112}, whereas Pim-3 shRNA treatment decreases Bad phosphorylation at Ser^{112}.[24,25] Thus, it is likely that Pim-3 inhibits the apoptosis of cancer cells and eventually furthers carcinogenesis (Fig. 3).

Forced expression of Pim-3 can promote anchorage-independent growth and coexpression of a kinase-deficient Pim-3 mutant can attenuate EWS/FLI-mediated NIH 3T3 tumorigenesis in immunodeficient mice.[22] These observations suggest the potential involvement of Pim-3 in this carcinogenesis model.

To delineate the roles of Pim-3 in carcinogenesis in more detail, we prepared mice that express the human *Pim-3* transgene abundantly and selectively in the liver.[38] These mice are born at a Mendelian ratio, are fertile, and do not exhibit any apparent pathological changes in the liver until 1 year after birth. The Pim-3-transgenic mouse-derived hepatocytes exhibit enhanced phosphorylation of Bad^{112}, but contain a similar proportion of

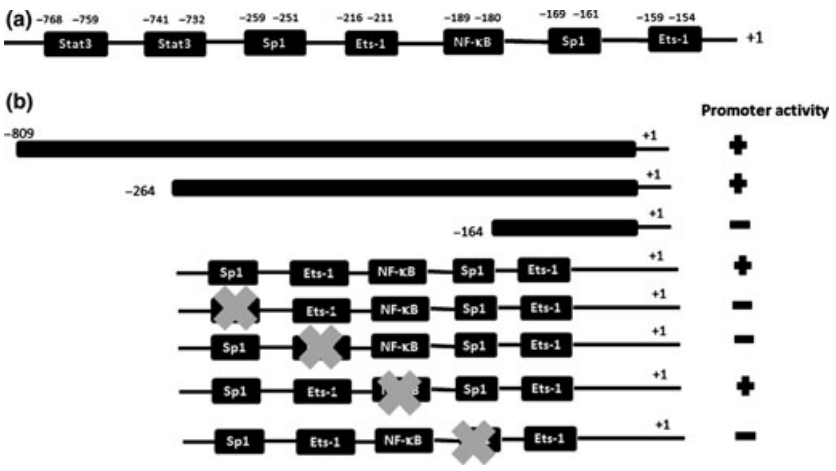

Fig. 2. (a) Structure of the 5′-flanking region of the human *Pim-3* gene with potential binding sites for known transcription factors. (b) Promoter activities driven by the 5′-flanking region of the human *Pim-3* gene, which is either deleted or mutated.[28] The mutation in each binding site is indicated by an ''×''.

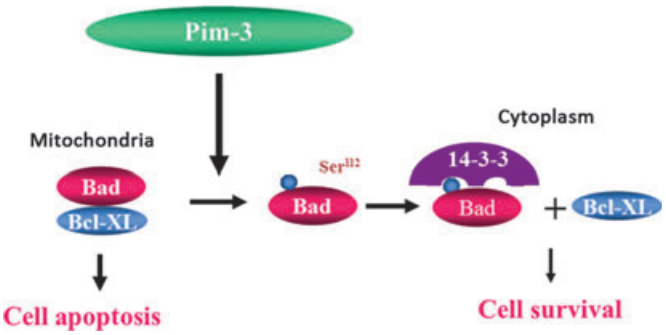

Fig. 3. Presumed mechanisms involved in Pim-3-mediated inhibition of apoptosis.

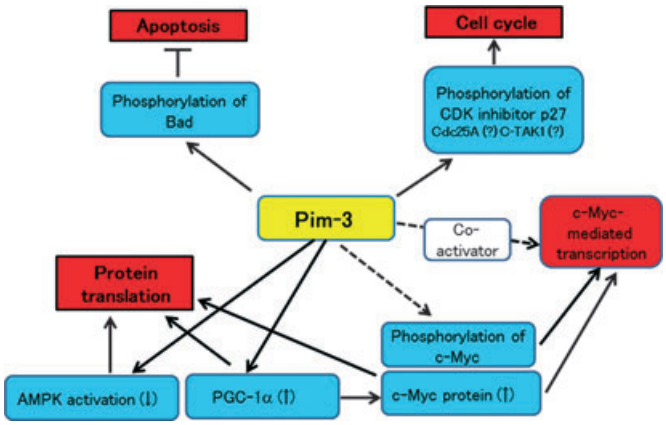

Fig. 4. Presumed roles of Pim-3 in tumorigenesis. Solid and broken lines indicate the functions attributed to Pim-3 and other Pim kinases, respectively. AMPK, AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; C-TAK1, Cdc25C-associated kinase 1.

apoptotic cells compared with wild-type mice. Moreover, Pim-3-transgenic mouse-derived hepatocytes exhibit accelerated cell cycle progression. The administration of diethylnitrosomaine, a potent hepatocarcinogen, induced accelerated proliferation of liver cells in the early phase, as well as lipid droplet accumulation with increased proliferating cell numbers in the later phase, in Pim-3 transgenic mice compared with wild-type mice.[38] Furthermore, the incidence and burden of HCC was greater in Pim-3 transgenic mice than in wild-type mice, and the transgenic mice also had enhanced intratumoral vascular areas.[38] These observations suggest that Pim-3 alone cannot cause HCC, but can accelerate its development (probably by modulating cell cycle progression), in the presence of a hepatocarcinogen.

Information is still sparse as to which molecules are phosphorylated by Pim-3 in addition to Bad. Pim-3 shows a high sequence identity with Pim-1 even in their kinase domains (Fig. 1). Moreover, both Pim-1 and Pim-3 bind to a consensus peptide substrate (AKRRRRHPSGPPTA) with a markedly high affinity, having K_d values in the range 40–60 nM, whereas the affinity for Pim-2 is somewhat weaker (640 nM).[16] These observations suggest that Pim-1 and Pim-3 may phosphorylate a similar set of substrates and therefore the existing observations regarding the biological functions of Pim-1 may provide clues as to the function of Pim-3.

It has been shown that Pim-1 phosphorylates Cdc25A, thereby increasing its phosphatase activity and the activity of cyclin D1-associated kinases, which results in cell cycle progression.[39] The Cdc25C-associated kinase 1 (C-TAK1) is a potent inhibitor of Cdc25C, a protein that actively promotes cell cycle progression at the G_2/M phase. By phosphorylating C-TAK1, Pim-1 inhibits its activity and eventually advances the cell cycle.[40] Furthermore, Pim-1 can phosphorylate p21, another molecule involved in cell cycle progression, at its threonine residues, resulting in its relocation to the cytoplasm and enhanced protein stability.[41,42] These effects are associated with increased cell proliferation.[42] All Pim kinase members can bind to and phosphorylate the CDK inhibitor p27 at its threonine residues and induce the binding of p27 to 14-3-3 protein, resulting in its nuclear export and proteasome-dependent degradation.[43] Moreover, Pim-1 represses *p27* gene transcription via the phosphorylation and inactivation of forkhead transcription factors FoxO1a and FoxO3a.[43] The decreased p27 expression results in cell cycle progression. Thus, it is tempting to speculate that Pim-3 can promote cell cycle progression and thus eventually contributes to carcinogenesis by modulating the function of molecules that regulate cell cycle progression.

Mice deficient for all Pim kinases, designated as triple knockout (TKO) mice, are viable and fertile.[44] However, these TKO mice display reduced body size at birth and throughout postnatal life. The TKO mouse embryonic fibroblasts (MEF) exhibit activated AMP-dependent protein kinase (AMPK), grow slowly in culture, and have decreased rates of protein synthesis, arising from a decreased amount of 5′-cap-dependent translation.[45] Transduction of the *Pim-3* gene alone into TKO MEF can reverse AMPK activation, increase protein synthesis, and drive growth to a similar level as in wild-type MEF.[45] Moreover, Pim-3 expression can markedly increase the amount of c-Myc and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), enzymes capable of regulating glycolysis and mitochondrial biogenesis.[45] Thus, Pim-3 may promote tumorigenesis by augmenting protein synthesis.

Originally, Pim-1 and Pim-2 were implicated in cell survival to suppress myc-induced apoptosis.[5,7] Transgenic mice expressing *Eμ-Pim-1* and *Eμ-Myc* succumb to lymphoma *in utero* or around birth.[4] In contrast, *Eμ-Myc* transgenic mice that are deficient in the *Pim-1* and *Pim-2* genes exhibit delayed lymphoma development.[46] Thus, Myc-driven tumorigenesis depends on physiological levels of Pim-1 and Pim-2. Several mechanisms have been proposed to explain the cooperation between Myc and Pim kinases. For example, it has been suggested that Myc recruits Pim-1 to the E-boxes of Myc target genes, such as *FOSL1* (*Fra-1*) and *ID2*, and that Pim-1 phosphorylates serine 10 of histone H3 on the nucleosome at the Myc-binding sites, acting as a co-activator of Myc.[47] Consistently, expression profile analysis has demonstrated that Pim-1 contributes to the regulation of approximately 20% of Myc-regulated genes.[47] Moreover, Pim-1 and Pim-2 phosphorylate c-Myc protein at its serine and threonine residues.[48] This results in stabilization and subsequent enhancement of the transcription activities of c-Myc protein. Furthermore, Pim-3 can enhance c-Myc mRNA expression via activation of PGC-1α.[45] Thus, Pim kinases can promote tumorigenesis by modulating the activities of c-Myc.[5,7]

Thus, Pim-3 may contribute to tumorigenesis through four main activities similar to those of the Pim family members, namely Pim-1 and Pim-2: (i) the delivery of survival signaling through phosphorylation of Bad; (ii) regulation of cell cycle progression; (iii) regulation of protein synthesis; and (iv) regulation of Myc transcriptional activity (Fig. 4).

Biological Functions in Situations Other Than Tumorigenesis

Both Pim-1 and Pim-3 have an important role maintaining the self-renewal capacity of mouse embryonic stem cells *in vitro*.[29] For example, Pim-3 is concentrated at the cellular lamelipodia

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and is colocalized with focal adhesion kinase in endothelial cells, with Pim-3 shRNA treatment impairing endothelial cell spreading, migration, and proliferation, leading to a reduction in tube-like structure in a Matrigel assay.[18] However, TKO mice did not display any apparent abnormal phenotypes in embryogenesis and vascular development,[44] raising questions as to the physiological relevance of these observations.

The expression of all Pim kinases is induced in the hippocampus in response to stimuli that elicit long-term potentiation (LTP).[2] Mice deficient for Pim-1 fail to consolidate enduring LTP, but they preserve normal synaptic transmission and short-term plasticity.[2] Ischemia or ischemia–reperfusion enhance the expression of Pim-3 in the brain and heart.[19,20] Moreover, the transfection of the *Pim-3* gene into cardiomyocytes attenuates ischemia–reperfusion injury through a p38 MAPK signaling pathway.[20] Similarly, *Pim-3* gene transduction increases Bcl-2 expression, dampens caspase-3 activation, and eventually protects against hepatic failure in D-galactosamine-sensitized rats that are given lipopolysaccharide.[49]

Expression of Pim-3 has been detected in β-cells in the pancreatic islets.[50] Pim-3-deficient mice exhibit increased glucose tolerance and increased insulin sensitivity. Moreover, Pim-3 can negatively regulate insulin secretion by inhibiting the activation of ERK1/2 through an interaction with suppressor of cytokine signaling (SOCS) 6.[50] This contrasts with the effects of the inhibition of another survival kinase, Akt, which can lead to hyperglycemia.[9,10]

Pharmacologic Inhibition of Pim-3 Kinase

The crucial involvement of Pim kinases in several types of cancers indicates that Pim kinase inhibitors may be useful in the treatment of malignant diseases.[51] Indeed, anti-Pim-1 antibody or Pim-1 inhibitory peptide have been shown to inhibit tumor growth in *in vivo* xenograft models using human cancer cell lines.[52,53]

The crystal structure of Pim-1 and Pim-2 reveals the presence of a unique hinge region that connects the two lobes of the protein kinase domain.[15–17] As a result, ATP binds to Pim kinases in fundamentally different ways from how it binds to other protein kinases.[15,16] Thus, it may be feasible to develop a compound that selectively inhibits Pim kinases and not other serine/threonine kinases.[51] Several groups have reported small molecule inhibitors against Pim kinases, including flavonol quercetargetin,[54] imidazole[1,2-*b*]pyridazines,[55,56] bezylindene-thiazolidine-2,4-dione,[57,58] and pyrrolo[2,3-*a*]carbazole.[59] These molecules have been shown to inhibit cell proliferation of human cancer cell lines *in vitro* and/or *in vivo*. Similarly, we have also found that stemonamide synthetic intermediates can inhibit Pim-3, as well as Pim-1 and Pim-2, activity and reduce tumor growth in *in vivo* xenograft models using a human pancreatic cancer cell line without causing any major adverse effects.[60] Given an extraordinarily similar peptide substrate identity between Pim-1 and Pim-3,[16] it may be difficult to obtain an inhibitor specific to either Pim-1 or Pim-3 kinase. Indeed, pyrrolo[2,3-*a*]carbazole potently inhibits Pim-1 and Pim-3 kinase, but only weakly inhibits Pim-2, with IC_{50} values of 0.57 ± 0.04, 0.04 ± 0.01, and >10 μM, respectively.[59] However, it remains to be investigated whether a specific inhibitor against each of the members of the Pim family will provide any advantage over multi-Pim kinase inhibitors.

Future Perspectives

It is known that Pim-3 kinase is constitutively active once it is expressed. Pim-3 kinase is aberrantly expressed in malignant lesions, but not normal tissues, of endoderm-derived organs such as the liver, pancreas, colon, and stomach,[14,24–26] and contributes to tumorigenesis by inhibiting the apoptosis of tumor cells and promoting cell cycle progression. Although Pim-3 is expressed robustly in vital organs such as the heart, brain, and lungs,[14] the roles of Pim-3 under physiological and pathological conditions remain unknown. However, a deficiency of the *Pim-3* gene does not result in apparent changes in phenotype, suggesting that Pim-3 may be physiologically dispensable. Unlike another survival kinase, namely Akt kinase,[9] Pim kinases are not localized downstream of the insulin receptor signaling pathway and therefore inhibition of the Pim kinases has few effects on normal metabolism. Thus, targeting Pim-3 may provide us with novel and safe molecular targeting drugs for solid tumors, in which Pim-3 is aberrantly expressed.

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Disclosure Statement

The authors have no conflict of interests to declare.

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