

Review Article

The role of Pim kinase in immunomodulation

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Received July 26, 2020; Accepted November 2, 2020; Epub December 1, 2020; Published December 15, 2020

Abstract: Pim kinase, which has three isozymes (Pim-1, Pim-2 and Pim-3), is a serine/threonine kinase abnormally expressed in many cancers. High Pim kinase expression has been recognized to be associated with disease progression and prognosis. It is well accepted that Pim kinase is considered a clinical biomarker and potential therapeutic target for tumor cell. In recent years, researches verified the role of Pim kinase in immunomodulation. The mechanisms by which Pim kinase modulates the immune microenvironment and regulates immune cells, as well as the effects of Pim kinase inhibitors on immunity, have not been systematically described. This review comprehensively focuses on the current research status of Pim kinase pathways and the immune regulation.

Keywords: Pim kinase, immune, cancer, PI3K/Akt/mTOR, inhibitors

Pim kinase

Pim kinase is a newly identified constitutively active serine/threonine kinase that plays a key role in the control of cell proliferation, apoptosis and migration. Pim kinase is expressed as three different isozymes, Pim-1, Pim-2 and Pim-3 [1, 2], which are overexpressed in many cancers, especially in hematologic malignancies [3]. Pim-1, Pim-2 and Pim-3 share a high degree of amino acid sequence homology. The similarity between Pim-1 and Pim-2 is 61%, while that between Pim-1 and Pim-3 is 71% [4].

Pim-1 is a proto-oncogene located on chromosome 6, comprising 6 exons and 5 introns within its 5 kb of genomic DNA [5]. The mouse Pim-1 gene produces two isoforms of Pim-1, a 33 kDa protein and a 44 kDa protein; the latter is the extension of the amino terminus of the former, which is synthesized by alternating translational initiation at the upstream CUG codon [6]. The 33-kDa protein product is highly expressed in the liver and spleen but only poorly expressed in mature granulocytes in adulthood [7]. Pim-1 has been found in hematopoietic lymphocytes, prostate cells, vascular smooth muscle cells [8], myocardial cells [9] and breast tissue [10]. Pim-2 is located on the X chromosome [11]. Two Pim-2 transcripts were identified at the RNA level: the first was repre-

sented by a band with a size of 2.2 kb and was highly expressed in hematopoietic tissues, the testis, the small intestine and the colon; the second transcript was represented by a band of 5.0 kb and was detected in the small intestine, colon, spleen, and thymus [4]. Pim-2 is highly expressed in lymphoid and brain tissues, in solid tumors such as liver cancer and prostate cancer, and in hematologic malignancies. Pim-3 is located on chromosome 22 [11], and the cloned 2392 bp human Pim-3 cDNA encodes a predictive open reading box consisting of 326 amino acids [12, 13]. Pim-3 is highly expressed in breast, kidney, brain and liver cancers [14].

The Pim kinase pathway

Pim kinase can regulate the malignant migration of tumors and their growth, proliferation, and metabolism through signaling pathways such as the phosphatidylinositol (PI) 3-kinase (PI3K)/AKT, JAK-STAT, and FLT3-ITD signaling pathways, which are induced by multiple cytokines, including SCF, G-CSF, interferon- γ (IFN- γ), interleukin-12 (IL-12), IL-15, GM-CSF, IL-2, IL-3, IL-6, IL-7 and prolactin [15-17].

Inhibition of Pim kinase caused AKT activation through ROS led to apoptosis and anti-proliferation [18]. However, Pim-3 is the least-studied kinase in the Pim family and appears to not play

an important role in normal biological functions; in addition, the expression level of Pim-3 has been considered an important indicator to assess the importance of its role in tumorigenesis and metastasis [19]. The SSRP1/ETS-1/Pim-3 signaling pathway is closely related to the proliferation, apoptosis, autophagy, invasion and colony formation of nasopharyngeal carcinoma cells [20].

Apoptosis and cell proliferation pathways

BAD/Bcl-2: Bad selectively dimerized with Bcl-xL and Bcl-2 to promote cell death [21]. When the IL-3 level is reduced, mitochondrial dysfunction occurs in FDCP1 cells, and the 33 kD Pim-1 kinase can improve cell survival by synergizing with bcl-2 and regulating it by phosphorylating Bad, while the 44 kD Pim-1 kinase blocks apoptosis via a Bcl-2-independent method [22, 23]. Similarly, Pim-2 kinase phosphorylates BAD on Ser112 and suppresses apoptosis [24].

c-Myc: c-Myc consists of three exons including coding the Myc proteins [25]. Pim-2 directly phosphorylates c-Myc on Ser329 to stabilize it. Pim-1 is more effective in mediating the reduction in c-Myc Thr58 phosphorylation and the increase in c-Myc Ser62 phosphorylation than the increase in c-Myc Ser329 phosphorylation. Thus, Pim-1/Pim-2 kinases enhance the transcriptional activity of c-Myc to regulate cell proliferation [26], but also inhibit the induction of c-Myc expression by Pim-3, and the individual Pim subtypes may regulate each other directly or through substrate competition [27]. Akt-dependent-phosphorylation of serine 400 (Ser-400) near its carboxyl terminal end by Akt and Pim-2 kinase activates NF- κ B, leading to increased activity of I κ B kinase and synergistically promoting cell proliferation independent of growth factor expression via Myc [28-30].

JAK/STAT: Pim-1 plays a role in BCR-ABL-mediated cellular transformation. BCR-ABL activates leukemia cells via signal transducer and activator of transcription (STAT5) and upregulates the expression of Pim-1 [31]. Pim-1 inhibits the activation of the JAK/STAT pathway by interacting with suppressor of cytokine signaling 1 (SOCS1) and SOCS3 and enhancing the inhibition of STAT5 [32]. However, the high expression of Pim-1 is significantly correlated with the activation of STAT3 and STAT5, CXCR4 phosphorylation on S339, P-glycoprotein ex-

pression, and cell proliferation in diffuse large B cell lymphoma (DLBCL) [33]. Both CXCL12-CXCR4 and EGF-EGFR signaling can activate the JAK-STAT signaling pathway to regulate the expression of Pim-1 [34]. The interaction between CXCL12 and CXCR4 also promotes the homing and migration of stem cells, thus supporting the survival of hematopoietic progenitor cells [35].

FIT3-ITD: FIT3-ITD specifically activates the serine/threonine kinase RSK1/2 by activating the MEK/ERK pathway and PDK1. RSK1 promotes proliferation and survival by activating the mTORC1/S6K/4EBP1 pathway and eIF4B cooperation with Pim by phosphorylating S6RP on S235/S236, TSC2 on S1798, and eIF4B on S422 and, also in cooperation with Pim, on S406 [36]. Pim-1 regulates mTOR activity by phosphorylating PRAS40, while an increase in mTOR activity may regulate cell growth [37]. mTORC1 can positively regulate FLT3-ITD, which may inhibit the mTORC1 pathway through STAT5 [38].

Other ways

In addition, Pim-1 interacts with heterochromatin-associated protein 1beta (HP1beta) and the cytoplasmic proteins dynein and dynactin by forming a complex with NuMA to promote apoptosis [39].

Pim-1 phosphorylates p100, which participates in downstream signaling of Ras, and forms a stable complex with it to stimulate the transcriptional activity of c-myc in a p100-dependent manner and participate in cytokine-regulated growth, survival and metabolic protein synthesis of cells [40, 41]. Pim-1 induces phosphorylation of eNOS on Ser633, increasing eNOS activity and mediating angiogenesis [42].

Cell cycle regulation

Pim-1 phosphorylation significantly reduced the activity of C-TAK1 kinase, especially its ability to phosphorylate and inactivate Cdc25C, a protein that can actively promote cell cycle progression through the G2/M checkpoint [43]. Effective phosphorylation of p21 by Pim-1 on Thr145 or Ser146, located in the nucleoplasm, affects cell stability and promotes cell proliferation to accelerate tumorigenesis [44]. Pim-2 overexpression caused upregulation of E2F-1,

resulting in upregulation of p73, activation of p57 expression, and G1 arrest via CDK2 inhibition. Pim-1 and Pim-2 directly regulate CHK1, whose phosphorylation on Ser280 promotes cell cycle progression and resistance of CHK1 in leukemia cells [45]. Pim kinases promote cell cycle progression and tumorigenesis by knocking down the expression of p27 (Kip1) at the transcriptional and translational levels [46].

Cell migration

Pim-1 regulates the HGF-MET signaling pathway and cell migration, and Pim-1 phosphorylates the eukaryotic translation initiation factor eIF4B, which is required for MET translation, at S406 [47]. Pim-1 phosphorylates glycogen synthase kinase-3 (GSK3B) and FOXP3, leading to increased adhesion, cell migration and invasion via regulation of Prostaglandin endoperoxide synthase 2 (PTGS2), which is an inflammatory factor that catalyzes the synthesis of prostaglandin E(2) (PGE2) [48, 49]. Phosphorylation-dependent stimulation of Notch1, a signaling molecule that is also a Pim substrate, promotes the migration of prostate cancer cells and balances glycometabolism in breast cancer cells [50].

Energy metabolism

Pim-1 is upregulated by hypoxia in liver cancer and promotes tumor growth and metastasis by promoting glycolysis in cancer cells [50]. Pim-2 can directly phosphorylate pyruvate kinase M2 (PKM2) on Thr454 residues, resulting in increasing protein levels of PKM2, to promote the role of glycolysis and energy production as well as reduced sensitivity to apoptosis, glucose utilization and cell proliferation while reducing mitochondrial respiration [51, 52]; in addition, inhibition of mTORC1 activity can reverse Pim-2-mediated aerobic glycolysis [52]. Expression of Pim-3 significantly increases expression of c-Myc and the protein level of peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α), as well as the level of ATP, and inhibits AMPK activation, which demonstrates that Pim kinase mediates the control of energy metabolism [27].

Transcription and splicing

Heterochromatin 1 (HP1 γ) phosphorylation as a phosphorylation target by Pim-1 kinase affects the structure or silencing of chromatin [53].

And Phosphatidic acid phosphatase (PAP1), which is involved in transcription and splicing regulation, is another target protein of Pim-1 [54] (**Figure 1**).

Regulation of immune cells by Pim kinase

T lymphocytes

Pim kinase positively regulates glycolysis in T cells, which plays a multipotent role in coordinating tumor immune escape and supporting the survival of Reed-Sternberg (RS) cells in classical Hodgkin lymphoma (cHL) [55]. Socs-1 regulated the stability by Pim kinase to inhibit JAK-STAT signaling and T cell development [56]. Pim kinase inhibition in T cells leads to increased Foxo1 activity, which promotes differentiation into the T central memory (TCM; CD44⁺CD62L⁺) phenotype to enhance antitumor ability [57]. The basal level of Pim-1 expression can be increased by stimulating α/β T cells and γ/δ T cells with phorbol myristate acetate (PMA) and ionomycin, but Pim-1 expression cannot be induced in B cells [58]. Overexpression of Pim-1 results in impaired functional rearrangement of TCR β , leading to the production of a large number of CD4⁺CD8⁺ cells, which can also affect cell cycle progression in selected CD4-CD8- precursors but does not affect the expression of cell cycle machinery components, except for the G1-specific phosphatase Cdc25A, upon antigen receptor stimulation [59]. In addition, β selection may require the hyperactivation of c-myc by Pim-1. Pim-1 enables T progenitor cells to bypass the initial TCR checkpoint, allowing the CD4⁺CD8⁺ population in the thymic lumen to slowly expand to almost normal size [60-62]. Pim-1 can enhance NFATc activity and IL-2 production, promoting the proliferation and/or survival of IL-2-dependent lymphocytes by acting as a downstream effector of Ras [63]. IL-7 promotes the expression of HXKII and Pim-1 genes through JunD/ap-1 JNK activation, thus partially promoting T cell metabolism and growth, as well as pim-induced JunD can control the expression of proteins involved in signal transduction, metabolism and cell survival [64]. Lymphoproliferation can be strongly accelerated by Pim-1 through inhibition of apoptosis [65]. Pim-1 enhance cytokine-dependent cell survival and superantigen-induced T cell activation, strongly inhibit the immunosuppressive effect of rapamycin and help to regulate lym-

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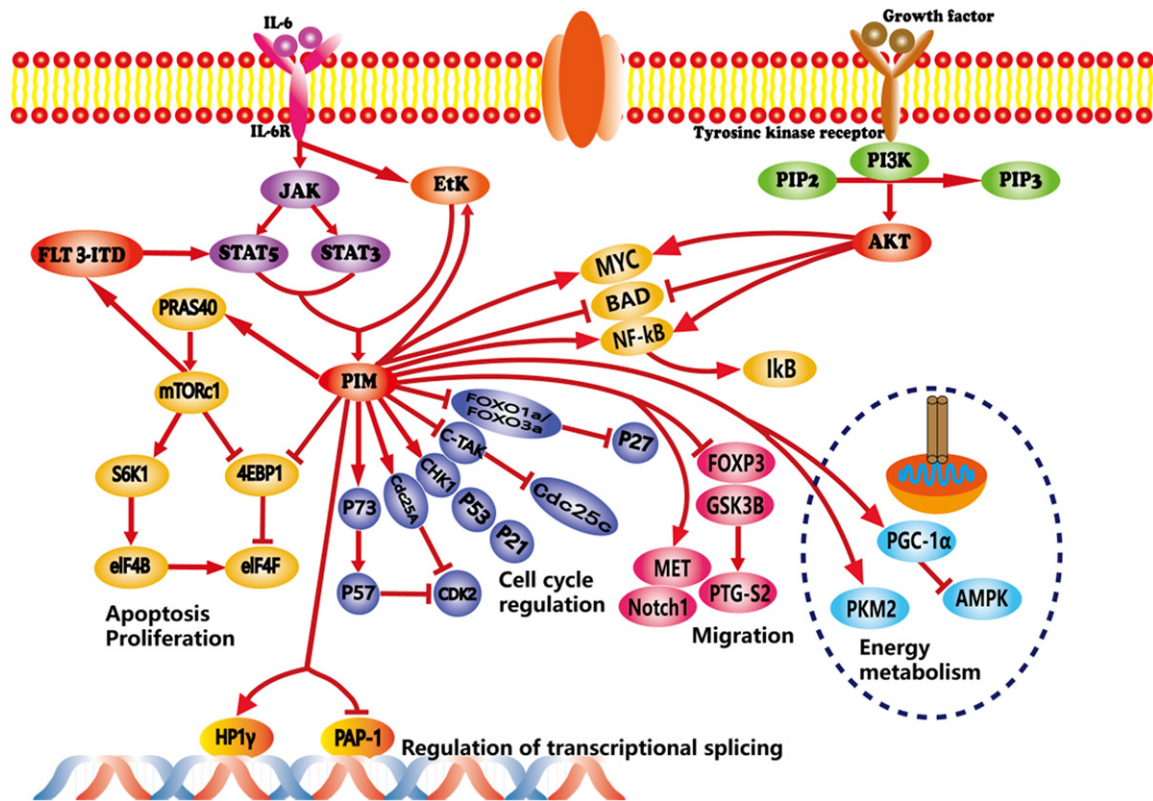


Figure 1. Pim kinase signaling. Pim kinase is involved in apoptosis and proliferation, cell cycle regulation, migration, energy metabolism, transcription and splicing.

phocyte growth and proliferation [66]. Pim-1 or Pim-2 is required for v-Abl-mediated tumorigenesis, especially Pim-1, which plays a key role in v-Abl transformation, possibly by participating in the modulation of SOCS-1 and regulating apoptotic signaling [67]. Pim-1 is involved in T cell amplification and T progenitor cell differentiation. In T cells lacking Pim-2, SOCS-1 and p73 are downregulated and IL-9R is upregulated to promote cell survival and proliferation and the production of proinflammatory cytokines [68]. MiR-26b-5p enhances T cell responses by negatively targeting Pim-2 in HCC by contributing to the secretion of cytokines, e.g., tumor necrosis factor α (TNF- α), IFN- γ , IL-6 and IL-2 in CD4⁺ and CD8⁺ cells [69]. Therefore, Pim-2 negatively regulates the T cell-mediated immune response, while Pim-1 and Pim-3 play a positive regulatory role.

CD4⁺ cells

Pim-1/3 promote the proliferation of CD4⁺ T cells by regulating G0/G1 cell cycle arrest without affecting cell survival, leading to decreased

p27kip1 expression and cell cycle progression following TCR stimulation [70]. P27Kip1 may affect the T cell response by regulating Smad3 phosphorylation because it regulates transcriptional mechanisms independent of its function in the cell cycle [71]. In addition, γ c cytokines have a prosurvival effect that is essential for T cell development, but Pim-1 can promote thymocyte development and T cell development and survival in the absence of γ c [72]. The proliferative effect of IL-27 on naive CD4⁺ T cells is dependent on IL-27-induced c-MYC and Pim-1 and is related to cyclin D2, cyclin D3, and CDK4 in a c-Myc and Pim-1-dependent manner [73]. Knockdown of Pim-3 and overexpression of TLR7 can promote the proliferation and activation of CD4⁺ T cells [74].

Th1/Th2 cells

IL-12 and IFN- α control the differentiation of Th1 cells, while IL-4 promotes Th2 cell differentiation. CD4⁺ cells are induced to differentiate into Th1 or Th2 cells, and this process is modulated by upregulating or downregulating the

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mRNA expression of Pim-1 and Pim-2 [75]. Pim kinase regulates the early IL-12/STAT4 signaling pathway in Th1 cells, which potentially regulates the transcription of the downstream effector IFN through IL12R [76]. Pim-1 kinase is upregulated and Runx3 is downregulated to promote the differentiation of Th2 and Th17 cells, while Th1 cells are unaffected [77]. T cells lacking Pim-2 exhibit differentiation into Th1 cells, exacerbating graft-versus-host disease (GVHD) [68]. Pim-2 kinase negatively regulates the T-cell-mediated GVH and graft-versus-leukemia (GVL) responses [78]. Decreasing Pim-3 the balance of Th1 and Th2 cytokines to skew the immune response toward a Th1 phenotype, which contributes to the antitumor immune response [74, 79]. Strongly downregulating Pim gene expression to induce differentiation into Th2 cells can prevent stabilization of SOCS protein family members, which can also prevent negative feedback regulation of IL-4-induced STAT6 activation [75].

Treg cells

The Foxp3 transcription factor is considered the main regulator of CD4⁺ CD25⁺Foxp3⁺ regulatory T (Treg) cell development and function and is negatively regulated by the PI-3K/Akt/mTOR axis [80]. Pim-2 kinase is another target gene of Foxp3 and regulates their activation and survival through mTOR-independent pathways [66, 81], as well as phosphorylating Foxp3, leading to decreasing inhibition of Treg cell development [82]. Constitutive expression of Pim-2 in Tregs affects the response to rapamycin in a manner dependent on Foxp3. In the presence of rapamycin, Tregs are preferentially expanded, and their expansion is positively correlated with the expression of Foxp3; in addition, the inhibitory activity of Tregs is positively correlated with TGF- β 1 and Pim-2 mRNA expression but not with Foxp3 mRNA expression [81, 83]. The combination of rapamycin and high-dose IL-2 does not affect the antigen presentation by B cells to Tregs, effectively promoting the proliferation of Tregs, enhancing their inhibitory activity in vitro and stimulating immune tolerance [83].

CD8⁺ T cells

Pim-1 is a target gene of CD27 and promotes the proliferation and survival of CD8⁺ T cells via a mechanism independent of mTOR and

IL-2 [84]. The NF κ B-Pim-1-Eomesodermin axis maintains the quality of CD8⁺ T-cell memory [85]. Knockdown of Pim-3 and overexpression of TLR7 can promote the proliferation and activation of CD8⁺ T cells [74, 79].

B cells

Pim-1 deficiency does not significantly affect early lymphoid/B cell development through the pre-pro-B cell stage, resulting in a significant decrease in IgM⁺ B cell precursors; in addition, overexpression of Pim-1 has a developmental stage-specific effect on B lymphocyte generation [86]. Coexpression of Pim-1 and Myc inhibits apoptosis and leads to IL-7-independent proliferation of the transduced pre-B cells while preventing them from differentiating into IgM⁺ immature cells, although the mature B cell pools are unaffected; thus, the promotive effect of Pim-1 and Myc overexpression on B cell proliferation seems to be limited to the period of B cell development from pre-B1 to immature B cells [87]. The increased expression of Pim-1, cyclin D2 and Bcl-x(L) as well as STAT5 directly affect the proliferation and survival of pro-B cells and restore the differentiation of B cells in IL7R^{-/-} mice [99]. Inhibition of Pim-1 inhibits IL-27 effect on proliferation of naive CD4(+) T cells and B cells and cyclin induction [74]. Increased phosphorylation of Pim-1 substrates (e.g., p100, c-myc, and HP1) synergistically affects c-Myc and c-Myb to promote the proliferation and survival of B cells [88]. EBNA3C enhances Pim-1-mediated phosphorylation of p21 on Thr145 and promotes the nuclear localization of Pim-1 by modulating the regulation of Pim-1-mediated p21/WAF1 (the cell cycle inhibitor) activity; therefore, EBNA3C significantly induces Pim-1-mediated degradation of the p21 protein to promote B cell survival [89]. In v-Abl-transformed pre-B cells, Pim-1 and Pim-2 interact with SOCS-1 but overcome the negative regulatory effect of SOCS-1 [67]. Pim-2 exerts antiproliferative effects that prevent the transition of pre-B cells harboring RAG double-strand breaks (DSBs) from G1 to S phase, during which these DNA breaks could be aberrantly repaired to promote the survival and limit the proliferation of pre-B cells [90]. B lymphocyte stimulator (BLyS)/BAFF, a TNF superfamily ligand that promotes B cell survival via the Akt/mTOR and Pim-2 pathways, is necessary for the maintenance of B cells in a normal steady state

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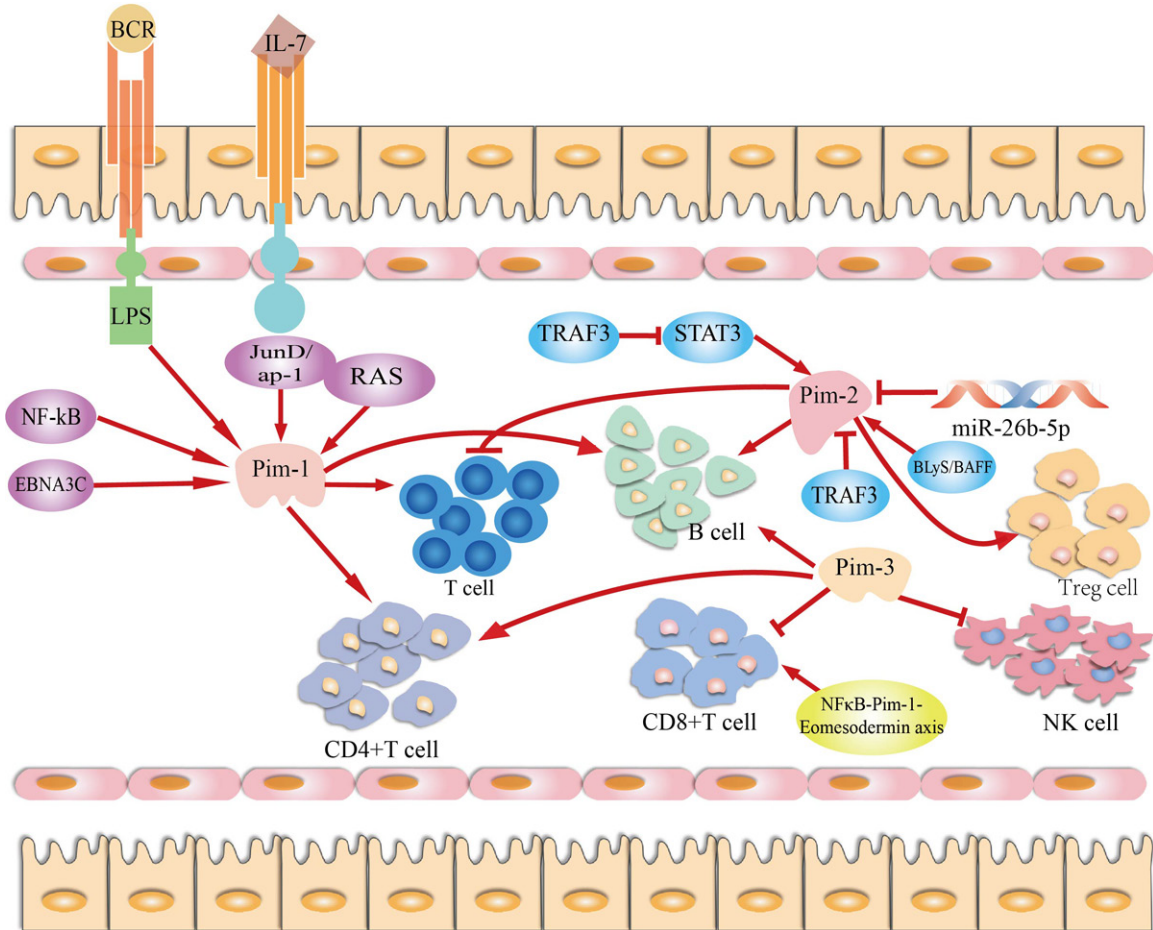


Figure 2. Regulation of immune cells by Pim kinase.

[91]. Loss of TRAF3 increases STAT3 phosphorylation and Pim-2 protein production, resulting in stabilization of the c-Myc protein to promote the survival of B cells without altering their proliferation [92]. The direct Myc target Pim-3 cooperates with other Pim kinases to support the viability of Myc-induced B cell lymphomas [93].

Natural killer (NK) cells

Knockdown of Pim-3 and overexpression of TLR7 can induce the apoptosis of tumor cells and reduce their proliferation, also inducing the expression of NKG2D and the production of IFN- γ while reducing the expression of NKG2A and PD-1 to promote the activation of NK cells [74, 79] (Figure 2).

Pim kinase inhibitors

Pim kinase has become an important target of antitumor drugs, which are mainly classified as benzofurans, indoles, oxadiazoles, pyrazines,

pyrimidines, pyrroles, quinolines, thiazolidines, triazoles and their derivatives [94] (Table 1). To overcome the problems of drug resistance and treatment refractoriness, a combination of Pim inhibitors (Pim-Inh), PI3K/AKT/mTOR pathway inhibitors, FLT3 pathway inhibitors and other inhibitors has been gradually developed to improve tumor control [95-97]. However, the current research on Pim kinase inhibitors focuses mainly on the mechanisms of tumor cell proliferation and apoptosis, but the effects on immune regulation and the immune microenvironment have not been further studied.

Pim inhibitors suppress LPS-induced macrophage activation and skew T cell differentiation toward the Treg phenotype [98]. T cells incubated with RS cells treated with a Pim kinase inhibitor (SEL24-B489) had higher expression levels of activation markers than T cells incubated with control RS cells, and these increased expression levels not only reduced the activity of RS cells but also coordinated tumor immune escape [55]. The Pim-1-specific inhibi-

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Table 1. Pim kinase inhibitors

Name of inhibitors	Class	IC50 or Ki	types
ETP-45299	imidazopyridine derivative	Pim-1: 30 nM, Pim-2: 1049 nM, Pim-3: 81 nM	non-small cell lung cancer
K00135	imidazo[1,2-b]pyridazines	Pim-1: 0.12 µM, Pim-2: 1.8 µM	gastric cancer
K00486	imidazo[1,2-b]pyridazines	Pim-1: 0.04 µM, Pim-2: 2.5 µM	
SGL-1776	imidazo[1,2-b]pyridazines	Pim-1: 7 nM, Pim-2: 363 nM, Pim-3: 69 nM	MM, AML, salivary gland adenoid cystic carcinoma
SMI-4a	benzylidene-thiazolidene-2,4-dione	Pim-1: 21 nM, Pim-2: 100 nM	endometrial cancer, non-small cell lung cancer, B-ALL, breast cancer
compound 14j	3H-benzo[4,5]thieno[3,2-d]pyrimidin-4-ones	Pim-1: 2 nM, Pim-2: 3 nM, Pim-3: 0.5 nM	B-Cell Lymphoma
AZD1897	benzylidene-1,3-thiazolidine-2,4-diones	Pim-1: 3 nM, Pim-2: 3 nM, Pim-3: 3 nM	AML
AZD1208	benzylidene-1,3-thiazolidine-2,4-diones	Pim-1: 0.4 nM, Pim-2: 5 nM, Pim-3: 1.9 nM	AML, neuroblastoma
SEL24-B58	Benzoimidazol	Pim-1: 31 nM, Pim-2: 154 nM, Pim-3: 15208 nM	
Tricyclic Benzo[CD]azulenes	Tricyclic Benzo[CD]azulenes		CML
LGB321	3-(S)-amino-piperidine pyridyl carboxamide	Pim-1: 0.001 nM, Pim-2: 0.002 nM, Pim-3: 0.0008 nM	MM
LGH447	3-S-amino-piperidine pyridyl carboxamide	Pim-1: 5.8 pM, Pim-2: 18 pM, Pim-3: 9.3 pM	MM
INCB053914 3914	(N-((R)-4-((3R,4R,5S)-3-amino-4-hydroxy-5-methylpiperidin-1-yl)-7-hydroxy-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)-6-(2,6-difluorophenyl)-5-fluoropicolinamide phosphate)	Pim-1: 0.24 nM, Pim-2: 30 nM, Pim-3: 0.12 nM	
DHPCC-9	1,10-dihydropyrrolo[2,3-a]carbazole-3-carbaldehyde	Pim-1: 12 nM, Pim-2: 51 nM, Pim-3: 10 nM	Prostate Cancer
CX - 6258	3-(5-((2-oxindolin-3-ylidene)methyl)furan-2-yl)amides	Pim-1: 0.005 µM, Pim-2: 0.025 µM	Prostate Cance
LY333'531	inhibitor of the beta isoform of protein kinase	Pim-1: 0.2 µM, Pim-2: >20 µM	AML
IBL-202	inhibitor of the PI3 kinases		CLL
SEL24-B489	FLT3-ITD inhibitor		AML, CLL, Hodgkin lymphoma
LY294002	phosphatidylinositol 3-kinase inhibitor	Pim-1: 4 µM	colon cancer, Cervical Squamous Cell Carcinoma, Malignant Glioma Cells
P9	mAb	Pim-1: 2.5-5 µg/ml	
HJ-PI01			triple-negative human breast cancer

tor mAb P9 was shown to significantly inhibit the powerful immune response to H-2d alloantigens both in vitro and in vivo, with an IC50 of 2.5-5 µg/ml; therefore, P9 could act as a Pim-1 antagonist and be a potential agent for immunosuppressive therapy [99, 100].

We have identified the influence of Pim kinase on immunity, which can improve the survival of B cells, induce the differentiation and enhance the proliferation of T cells, activate NK cells, etc. These observations suggest that we should devote more attention to the influence of Pim inhibitors on immune regulation, which may serve as the future basis for the selection of antitumor drugs.

Conclusion

Pim kinase plays a crucial role in cellular pathways. It phosphorylates p21waf1 and p27kip and activates CDC25A/CDC25C, which control cell cycle progression. It regulates cellular apoptosis and proliferation by regulating BAD, BIM, IκB-NFκB, and MYC; mediates energy metabolism via PKM2 and AMPK; phosphorylates GSK3B and FOXp3; and regulates PTG-S2-mediated cell migration to promote tumor invasion. Pim kinase not only participates in tumor occurrence and development through multiple mechanisms but also regulates immune cells. For example, Pim kinase promotes the survival of B cells and T cells, induces the differentiation and proliferation of T cells, and activates NK cells to further induce the immune response via production of cytokines, e.g., IL-6, IL-2, IL-3, IL-15, TNF-α, IFN-γ, and IL-12, and activation of the NF-κB, MYC, and mTOR pathways.

However, we still know little about the mechanism by which Pim kinase participates in immune regulation, and more in-depth research is needed. Pim kinase not only can affect the proliferation and apoptosis of tumor cells and regulate their cell cycle but also can regulate immune cells and coordinate their antitumor activities. In HL, Pim kinase inhibitors can induce RS cell apoptosis and activate T cells to enhance their immunity and cytotoxic effects on tumor cells [55]. Collectively, these studies indicate that Pim kinase inhibition plays a vital role in cancer and immune cells. However, several aspects need further investigation: 1. the effects of different Pim kinase subtype inhibi-

tors on immune cell function and mechanisms to regulate immunity; 2. whether immune exhaustion can be reversed by using a Pim kinase inhibitor; 3. whether the combination of Pim kinase inhibitors and other immunomodulatory drugs such as immune checkpoint (PD-1/PDL-1) inhibitors, etc. can greatly enhance the antitumor ability of immune cells. As our understanding of Pim kinase evolves, more Pim kinase inhibitors will be identified to regulate cell survival and immunity.

Acknowledgements

The present study was supported by the National Natural Science Foundation of China (grant nos. 81400085 and 81900131), the Tianjin Municipal Natural Science Foundation (grant nos. 16ZXMJSY00180 and 18JCQNJC-80400), and the Tianjin Education Commission Research Project (grant nos. 2018KJ045 and 2018KJ043).

Disclosure of conflict of interest

None.

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