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Role of PD-1/PD-L1 crosstalk on inhibition of T-cell activation and proliferation through blockade of PI3K/Akt/mTOR signaling pathway

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Abstract

Activation, differentiation, and proliferation of T-cells are the major parts of critical defense mechanisms that strengthen immune surveillance. Many crucial underlying mechanisms that act on the initiation of T-cell activation, survival, and proliferation. PI3K/Akt/mTOR signaling pathway is one of the key mechanisms that potentially acts on T-cell activation and growth through numerous pathways. However, PD-1 is the inhibitory receptor, present on the surface of T-cells and other immune cells, that inhibits excessive activation of T-cells to avoid autoimmunity. PD-1/PD-L1 crosstalk strongly inhibits T-cell proliferation through the prevention of the action of PI3K/Akt/mTOR cascade. Additionally, the PD1/PD-L1 axis induces the development of regulatory T-cells (Treg) and downregulates glucose transporter 1 (GLUT1) expression via blockade of PI3K/Akt/mTOR machinery, and leads to cell cycle arrest of T-cell occurs. Therefore, inhibition of PD-1/PD-L1 is the breakthrough to restore the action of the PI3K/Akt/mTOR axis to facilitate T-cell activation and proliferation. In this review, we demonstrate multiple mechanisms of PD-1/PD-L1 crosstalk on inhibition of the PI3K/Akt/mTOR signaling pathway.

Key words PD-1/PD-L1 crosstalk, PI3K/Akt/mTOR, signaling pathway, T-cell activation, T-cell proliferation

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Introduction

T-cell-mediated immune response is one of the crucial defense mechanisms that keep safe body from cancer cells and infections caused by antigens. Several inhibitory mechanisms that suppress excessive activation of T-cells to prevent autoimmunity. PD-1 is an inhibitory receptor, which is present on the surface of T-cells and other hematopoietic cells [1]. After activation of T-cells, PD-1 binds with ligands, PD-L1 and PD-L2, and via distinct mechanisms inhibit activation, differentiation, and proliferation of T-cells [2]. Treg cells are associated with the inhibitory mechanism, and Treg cells are also regulated by the PD-1/PD-L1 signaling pathway [3].

The PD-1/PD-L1-induced blockade of T-cell proliferation and differentiation is responsible for the immune escape of cancer cells [4]. Therefore, to enhance immune surveillance, activation and proliferation of T-cells and inhibition of the PD-1/PD-L1 crosstalk are breakthroughs of cancer research. T-cells and other hematopoietic cells require glucose uptake and metabolism for survival and function. Glucose transporter 1 (GLUT1) is required for glucose uptake in T-cells, thereby higher expression of GLUT1 is very essential for the activation of T-cells [5]. The PI3K/Akt/mTOR is a crucial mechanism by which T-cell proliferation and differentiation occurs through the upregulation of GLUT1 [6], and the PI3K/Akt/mTOR signaling pathway plays a key role in cytokine-regulated GLUT1 trafficking [6]. Additionally, activation of the PI3K/Akt/mTOR pathway acts as a transducer of CD28 signals to enhance glucose uptake [7]. However, there are numerous underlying mechanisms through which the PD-1/PD-L1 axis suppresses T-cell activation via inhibition of PI3K/Akt/mTOR signaling pathway. During T-cell co-receptors CD3 and CD28-mediated stimulation, phosphatase and tension homolog (PTEN) is phosphorylated by casein kinase 2 (CK2), which stabilizes PTEN and suppresses PTEN phosphatase activity, and this mechanism co-stimulates T-cells [8]. The PD-1/PD-L1 crosstalk abrogates PI3K/Akt/mTOR signaling through increasing PTEN phosphatase activity and decreasing stability of PTEN, leading to inhibition of T-cell activation [9]. Treg cell regulates T-cell development and suppresses activation to avoid autoimmunity. PD-1/PD-L1 facilitates Treg cell development through the blockade of PI3K/Akt/mTOR cascade. PD-1/PD-L1-induced FOXP3 transcription accelerates the Treg cell proliferation by preventing PI3K/Akt/mTOR signaling pathway. It has been reported that premature termination of TCR signaling and inhibition of the PI3K/Akt/mTOR axis increase induction of FOXP3 expression and Treg like gene expression [10]. TGF-β is a potent activator of FOXP3 expression, and it synergizes with PD-1 to inhibit PI3K/Akt/mTOR action. Blockade of PD-L1 impairs peripherally induced Treg (iTreg) cell development, and loss of PD-L1 also reduces the expression of TGF-β, which is critical for the function of iTreg cells [11]. Additionally, PI3K/Akt/mTOR signaling pathway induces the cell cycle transition of T-cells and leads to T-cell proliferation, but the PD-1/PD-L1 axis inhibits the cell cycle transition of T-cells via blockade of PI3K/Akt/mTOR signaling and by downregulation of cell cycle checkpoint proteins, and upregulation of cyclin-dependent kinase inhibitors. SKP2 is a transcription factor that initiates the cell cycle transition of the G1 phase, however, PD-1 suppresses SKP2 transcription by reducing the action of PI3K/Akt/mTOR cascade and MEK/ERK pathway [12]. Moreover, the PD-1/PD-L1 axis alters the metabolic reprogramming of T-cells by abrogating the action of PI3K/Akt/mTOR cascade. PD-1/PD-L1 inhibits GLUT1 expression, blocks glucose uptake in T-cells, and induces β-oxidation of fatty acid to release ATP which provides energy to the T-cells. However, the metabolic process of β-oxidation of fatty acid is fatal for the T-cells because the essential component of the cell membrane is phospholipid which breaks down, and leads to inhibition of T-cell proliferation and breakdown of T-cells [13, 14].

Action of PD-1/PD-L1 in T-cell function

PD-1 is a specific inhibitory receptor of PD-L1, after binding PD-1 blocks the activation of T-cells, decreases the secretion of T-cell-mediated cytokines, and enhances the apoptosis of T-cells [15]. When PD-1 binds to PD-L1, one of the phosphorylation sites, the immune-receptor tyrosine-based switch motif (ITSM) phosphorylates to activate a signaling pathway and initiates inhibition of immune systems [16, 17]. Crosstalk of PD-1/PD-L1 is a potent regulator of immunosuppression of T-cells, inhibition of the PD-1/PD-L1 interaction restores T-cell function and initiates anti-tumor action through the activity of cytotoxic T-cells. Inhibitory receptor PD-1 is overexpressed after activation of T-cells and elevated expression is found in tumor-infiltrating T-cells [18]. T-cells need two different signals for the activation, the primary signal is antigen-presenting cell (APC)-mediated and the secondary signal is T-cell receptor (TCR)-mediated, whereas immune-stimulatory molecules presents by APC interacts with TCR, leading to activation of T-cells [19]. PD-1/PD-L1 inhibits TCR-mediated T-cell activation, and reduces T-cell-induced cytokines secretion [20].

The expression of PD-1 in naïve T-cells is tightly regulated but its expression rapidly proliferates when TCR is activated, and it is the protective mechanism to inhibit excessive activation of immune systems [21]. Pro-inflammatory cytokine IFN-γ is secreted by T-cells and natural killer cells (NK) to enhance neo-antigen presentation by major histocompatibility complex (MHC) on tumor cells [22]. PD-L1 is upregulated by IFN-γ, tumor necrosis factor α (TNFα), interleukin-6 (IL-6) and over-expression of PD-L1 by oncogenic pathways allowing cancer cells to escape immunesurveillance and promote their survival and initiates metastasis by abrogating the immune activity of T-cells [23]. IFN-γ has multiple ways to upregulate PD-L1 for attenuating the action of T-cells, and IFN-γ induces PD-L1 via multiple signaling pathways in different types of cancer. IFN-γ induces PD-L1 upregulation via JAK2/STAT1/IFR-1 signaling pathway in gastric cancer [24] [25]. However, IFN-γ-mediated overexpression of PD-L1 occurs via PI3K/Akt and JAK/STAT3 pathways in lung cancer [26]. IFN-α also acts with TCR signal to regulate PD-1 expression and potentially inhibits T-cell-mediated immune response [27]. IL-6 activates JAK1, and JAK1 phosphorylates Tyr112 of PD-L1, which recruits N-glycosyltransferase STT3A to catalyze PD-L1 glycosylation and regulate stability of PD-L1 [23]. Increased expression of IL-6 is associated with higher expression of PD-L1, and IL-6 also induces expression of PD-1 in activated T-cells [28]. IL-6 and IL-12 additionally act to induce PD-1 expression upon TCR activation and enhances PD-1 transcription via STAT3/STAT4 pathway [29]. IL-6/JAK-mediated protein stability enhances T-cell exhaustion through the synergistic action of T-cell immunoglobulin mucin-3 (Tim-3) and PD-1 on tumor-infiltrating leukocytes including CD8+ T-cells (**Figure 1**) [30]. The blockade of T-cell functions is correlated with PD-1 and numerous inhibitory receptors including cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), lymphocytes-activation gene 3 (LAG-3), CD160, and 2B4 [31].

T-cell proliferation through PI3K/Akt/mTOR pathway

Proper regulation of PI3k/Akt is required for T-cell growth, survival, and response. ATP is the energy source, which is required for the T-cell activation, proliferation, and production of cytokine [5]. Upon TCR activation and co-stimulation of CD28, T-cells enhance their ability to uptake glucose through glucose transporter GLUT1 and glycolysis via a mechanism that depends

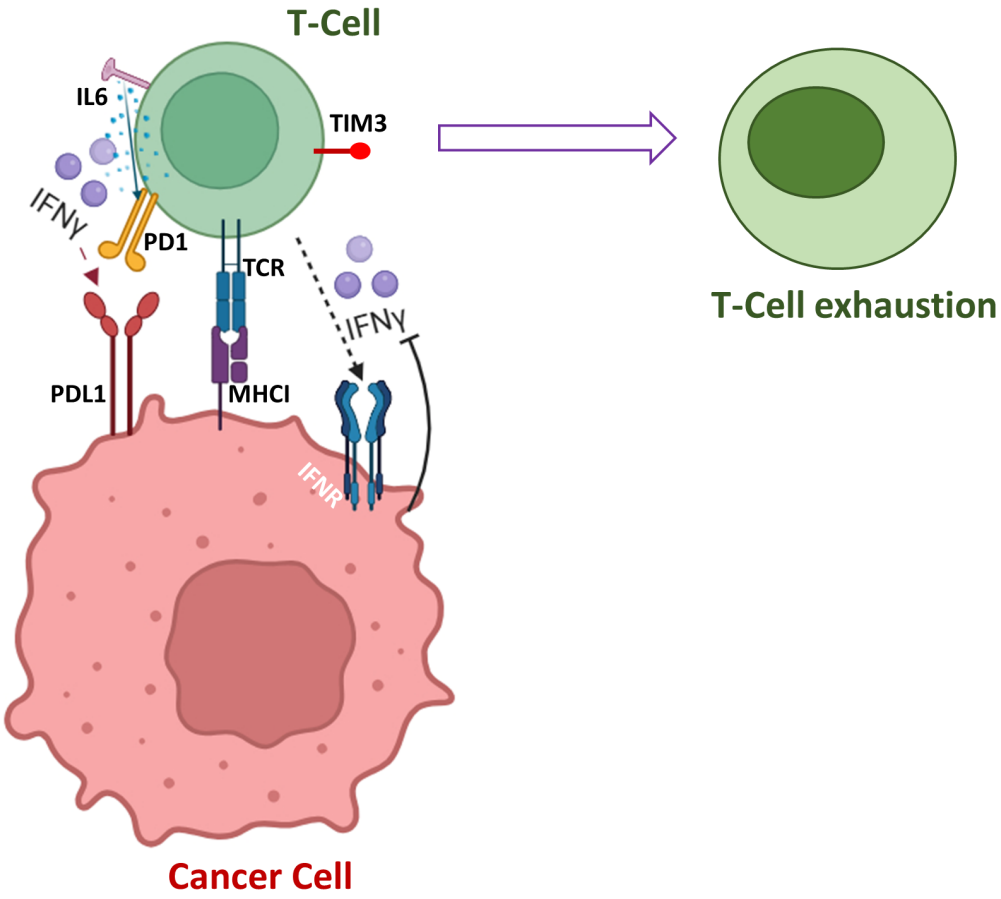

Figure 1. Numerous pathways of T-cell exhaustion.

on the PI3K signaling pathway [32]. In low TCR signal CD28 enhanced GLUT1 expression [32]. T-cell proliferation is inhibited due to the lack of co-stimulation of TCR and CD28, and failure of the activation of PI3K signaling pathway. Akt activation is required for the glycolytic activity to proliferate and activate T-cells. T-cell depends on Akt instead of CD28 for its proliferation if CD28 does not activate T-cells [33]. Activation of Akt diminished the requirement for co-stimulation of CD28 and the higher accumulation of activated T-cells was observed in vivo [32]. In the absence of PI3K-Akt signaling pathway GLUT1 remains intracellular and may degrade by the lysosome and glucose uptake by T-cells is inhibited [6]. Upon activation of the PI3K-Akt signaling pathway, CD28 also enhances the action of CD3, which plays a crucial role in upregulating GLUT1 expression. Akt may also regulate the activity of the GLUT1 transporter through activation of the mammalian target of rapamycin (mTOR). Akt does not require mTOR and regulatory associated protein of mTOR (RAPTOR) to maintain surface GLUT1 levels, but inhibition of mTOR/RAPTOR by rapamycin notably diminished glucose uptake and Akt-stimulated mTOR/RAPTOR may enhance the activity of GLUT1 transporter [6]. Genetic deletion of Tuberous sclerosis complex1 (TSC1) and TSC2, leads to activation of mTORC1 and inhibiting activation of PI3K/Akt signaling [34]. T-regulatory (Treg) cell depends on AMPK, instead of glycolysis and AMPK antagonizes mTOR activation to perform lipid oxidation to meet the energy requirements of Treg. Rapamycin-induced inhibition of mTOR mediates the activity of AMPK and increases lipid oxidation of Treg [35].

PI3K/Akt/mTOR pathway in CD+8 T-cell development

PI3K/Akt pathway significantly contributes to CD+8 T-cell activation and cytokine signaling pathway. Class IA PI3Ks are primarily activated in CD+8 T-cells by TCR, co-stimulatory, and cytokine receptors [36]. PI3K/Akt pathway is activated by TCR, IL-2, and IL-12 receptors. PI3K may regulate T-cell metabolism through the Akt-independent pathway, but Akt signaling is required to develop the effector function of CD+8 T-cells [37]. Activated Akt signaling may control the development and trafficking of CD+8 T-cells by regulating cellular transcriptome. Highly activated Akt downregulates adhesion molecules, chemokine receptor (CCR7), and CD62L and then redirects the trafficking of effector CD+8 T-cells. The proliferation of CD+8 T-cells is manifested by Akt-independent signaling but the development of the effector function of CD+8 T-cells occurs through fully Akt-dependent pathway [38, 39]. mTORC1 has negative regulation in the differentiation of T-cells. TSC1 and TSC2 inhibit mTORC1 by enhancing the conversion of guanosine triphosphate into guanosine diphosphate on the mTORC1 activator Ras homolog enriched in brain (RHEB) [34]. However, mTORC2 controls Akt activation by phosphorylation, promotes CD+8 T-cell differentiation, and enhances the survival of CD+8 T-cells without activating mTORC1 [40].

PI3K/Akt/mTOR pathway in CD+4 T-cell development

PI3K signaling pathway inhibits differentiation of Treg through inactivation of FOXO1 and FOXO3a, leading to activation and differentiation of CD+4 Th-1 and Th2 cells [16]. mTORC2 promotes differentiation of CD+4 Th-1 and Th-2, deletion of scaffold protein, Rictor, disrupts mTORC2, leads to impair Th1 and Th2 cell differentiation [41]. It has been studied that metabolic requirements of CD4+ T-helper (Th) cells differ. Th1, Th2, and Th17 cells all express GLUT1 and need glycolysis for energy requirement, however, Th17 cells uniquely require hypoxia-inducible factor-1α (HIF-1α) for their glycolytic activity and for the expression of HIF-1α in Th17 cells requires activation of mTOR and upon inhibition of mTOR by rapamycin inhibits HIF-1α induction, as well as the expression of glycolytic enzymes in Th17 cells, are blocked [35, 42]. Deletion of mTOR gene in mice, failed differentiation of CD+4 Th-1, Th-2, and Th-17 cells [43].

Inhibition of T-cell activation via blockade of PI3k/Akt/mTOR signaling by PD-1/PD-L1

When ligand PD-L1 binds with the receptor PD-1, intracellular tyrosine is phosphorylated leading to activation. Therefore, PD-1 recruits src homology domain-containing phosphatase 1 (SHP1) and SHP2 to the C-terminal of ITSM which dephosphorylates TCR-mediated signals ZAP70 and CD-3ζ, as a result, blockade of PI3K/Akt signaling pathway and, activation and differentiation of T-cells are inhibited [20]. Inactivation of PI3K/Akt signaling triggers the expression of apoptotic proteins and downregulates the expression of cell survival gene Bcl-xl, thus it stops the secretion of cytokines by T-cells [20].

Downregulation of PI3k/Akt signaling via PD-1-mediated PTEN phosphatase activity

The PTEN gene is a tumor suppressor gene. Impaired PTEN function inhibits PI3K signaling and accumulation of phosphatidylinositol (3, 4, 5)-triphosphate (PIP3), and antagonizes the downstream components of PI3K/Akt signaling, including mTOR [44]. It has been proposed that PD-1 antagonizes PI3K/Akt signaling by upregulation of PTEN. PD-1 inhibits the activation of the PI3K/Akt signaling pathway by regulating PTEN stability and casein kinase 2 (CK2)-mediated phosphorylation of phosphatase [45]. During TCR/CD3 and CD28-mediated stimulation, PTEN is phosphorylated by CK2 in the C-terminal regulatory domain, leading to the stabilization of PTEN, and as a result, enhanced protein abundance and antagonized phosphatase activity. However, PD-1 inhibits phosphorylation in the C-terminal domain of PTEN, thus ubiquitin-induced degradation occurs and decreases the abundance of protein but promotes the phosphatase activity of PTEN. PD-1 inhibits the PI3K/Akt signaling axis by increasing PTEN phosphatase activity [8]. Phosphorylation of PTEN regulates protein stability of PTEN, which controls PI3K/Akt signaling activity, in contrast, phosphatase activity of PTEN antagonizes the PI3K/Akt signaling axis. Phosphorylation of the C-terminal region protects PTEN from ubiquitin-dependent proteasomal degradation and increases PTEN protein stability. In addition, the PD-1-mediated signal suppresses PTEN phosphorylation in the C-terminal domain ser380-Thr382-Thr383 cluster, leading to proteasomal degradation of PTEN and induces phosphatase activity which inhibits the action of PI3K/Akt signaling axis [8, 46].

PD-1/PD-L1-mediated Treg development via downregulation of PI3K/Akt/mTOR axis

Treg cells are very immunosuppressive subpopulation of CD+4 T-cells which is characterized by fork-head box p3 (FOXP3). The crucial role of Treg cells are suppression of over-activated T-cells to avoid autoimmunity [47]. Peripherally induced Treg (iTreg) are generated from peripheral CD+4 FOXP3- naïve T-cells through receiving TCR signal, whereas for the generation of natural/thymic Treg (nTreg), TCR signals are not required [48]. There are multiple mechanisms for the development of Treg. PI3K/Akt signal inhibits thymic Treg development. It was observed that the generation of thymic Treg cells are increased upon attenuation of the PI3K/Akt signal [49]. One of the important mechanisms is PD-1/PD-L1-induced Treg development from naïve CD+4 T-cells through downregulation of the PI3K/Akt/mTOR axis and concurrent upregulation of PTEN. PD-L1 abrogates Akt signaling pathways during conversion of naïve T-cells to Treg cells, via diminishing the phosphorylation of Akt and its downstream substrate mTOR [10, 50].

Upregulation of Foxp3 expression by attenuating PI3k/Akt/mTOR axis in Treg development

Foxp3 has the potential role for the generation of iTreg. TCR signaling via PI3K/Akt/mTOR regulates the expression of Foxp3. Activation of the signal through PI3K/Akt/mTOR reduces the induction of Foxp3. Induction of Foxp3 occurs in response to deprivation of TCR signal, and PI3K/mTOR inhibition [51]. TCR/CD28 activation followed by inhibition of PI3K/mTOR induced Foxp3 in CD+4 T-cells and CD+4 CD8- CD25- thymocytes [10]. PD-1/PD-L1 crosstalk was found to upregulate the expression of Foxp3 and induce signaling molecules which is crucial for the conversion of naïve T-cells to Treg cells by attenuating the PI3K/Akt signal [52]. It was observed that blocking PD-L1 on gastric epithelial cells facilitates the action of CD+4 effector T-cells and inhibits the generation of CD+4 CD25 Foxp3+ Treg cells [53].

PD-1 synergizes TGF-β-induced Foxp3 upregulation in Treg development

In the presence of TGF-β, naïve CD+4 T-cells express Foxp3 and convert into iTreg cells [10]. TGF-β-mediated Treg cells exhibit higher levels of CD25, CTLA-4, and glucocorticoid-induced TNF receptor (GITR) which are required for the activity of Treg cells and the suppression of T effector cells [54]. TGF-β and PD-L1 synergistically upregulate Foxp3 expression, leading to the enhancement of Treg development. It was found that co-culture of PD-L1-lg beads with CD+4 CD62L Foxp3- T-cells significantly increased iTreg development in the presence of TGF-β, and very low amounts of TGF-β were able for the notable conversion of naïve CD+4 T-cells into iTreg cells by PD-L1-lg coated beads [9]. However, PI3K/Akt/mTOR signaling cascade negatively regulates TGF-β towards the conversion of naïve CD+4 T-cells into Treg cells. On the other hand, the PD-1/PD-L1 axis downregulates the PI3K/Akt/mTOR signaling axis to potentiate the action of TGF-β for the development of Treg cells. PD-1-induced transactivation of smad3 via suppression of the PI3K/Akt axis is a crucial mechanism through which PD-1 synergizes TGF-β signaling accelerates suppression of T-cells and regulates T-cells tolerance and immune quiescence [30].

PI3K has four different classes, among them IA and IB classes of PI3K was studied extensively on T-cells [55]. It was revealed that besides the crucial function of thymic development of nTreg and iTreg for the suppression of excessive immune response to avoid autoimmunity, TGF-β also initiates a specific type of immune response by co-activation of some cytokines. TGF-β selectively mediates Akt phosphorylation exclusively at the ser473 domain but not at the Thr308 domain in a class IA PI3K-dependent

manner, leading to the inhibition of Foxo transcription factors and prevention of the differentiation of iTreg cells. TGF-β-induced Akt phosphorylation reduces the differentiation of iTreg, while the elimination of the p85α subunit, class IA PI3K enhances iTreg differentiation [56].

PD-1-induced cell cycle arrest of T-cells via inhibiting PI3K/Akt cascade

SCF (Skp1/Cullin/F-box protein) complex is a ubiquitin ligase drives G1/S cell cycle transition by inhibiting cyclin- dependent kinase (Cdk) inhibitor p27 during S phase [16]. PD-1 blocks cell cycle transition by preventing Skp2 transcription, a component of SCF complex, through inhibition of PI3K/Akt and Ras/MEK/ERK signaling pathways and abrogates T-cell proliferation. TCR-CD3 and CD28-mediated overexpression of Skp2 in response to higher expression of p27 is attenuated by PD-1 signaling. PD-1-mediated blockade of Skp2 through inhibition of PI3K/Akt axis leads to accumulation of p27, suppression of action of cyclin E-Cdk2. Additionally, smad3 transactivation occurs by impaired Cdk2-mediated phosphorylation, as a result, trans-activated smad3 suppresses Cdc25A and facilitates p15 upregulation, a strong Cdk inhibitor and further suppression of Skp2 occurs. Through suppressing PI3K/Akt and Ras signaling pathways, PD-1 potentially activates smad3, a negative regulator of the cell cycle, and the cell cycle transition of T-cells is inhibited [30]. Upregulation of IL-2 restores partial Skp2 expression and MEK-ERK signaling but not Akt signaling [30]. IL-2 prevents inhibitory effects of PD-1 on T-cell proliferation, IL-2 receptor (IL-2R)-induced signals can activate Ras/MEK/ERK and PI3K/Akt pathways via recruitment of Grb2-Sos-Shc complex [57] [58].

PI3k/Akt and IL-7-induced T-cell proliferation, blockade by PD-1/PD-L1 axis

IL-7 exposure is required for the cell cycle transition and proliferation of T-cells, and also IL-7 plays a key role in peripheral T-cells survival and expansion [59] [60]. Upregulation of GLUT1 and glucose uptake are the hallmarks of IL-7-mediated cell cycle entry. The GLUT1 is directly regulated by PI3K and preventing the action of PI3K attenuates IL-7-induced T-cell proliferation [60]. PI3K is a crucial downstream effector of IL-7 stimulation. It has been found that IL-7-induced activation of PI3K acts on the metabolism and proliferation of T-cells via destabilization of cyclin-dependent kinase inhibitor p27 [61] [62]. In response to Akt on IL-7 stimulation, leads to potential upregulation of very late antigen 4 (VLA-4) and chemokine receptor (CXCR4) homing molecules on recent thymic emigrants (RTEs) leads to naïve T-cells migration occurs [63]. IL-7-mediated cell cycle transition is inhibited via PD-1/PD-L1 crosstalk-induced suppression of PI3K, leading to PI3K-regulated GLUT1 expression being reduced. As a result, the metabolic process of T-cells is altered due to the

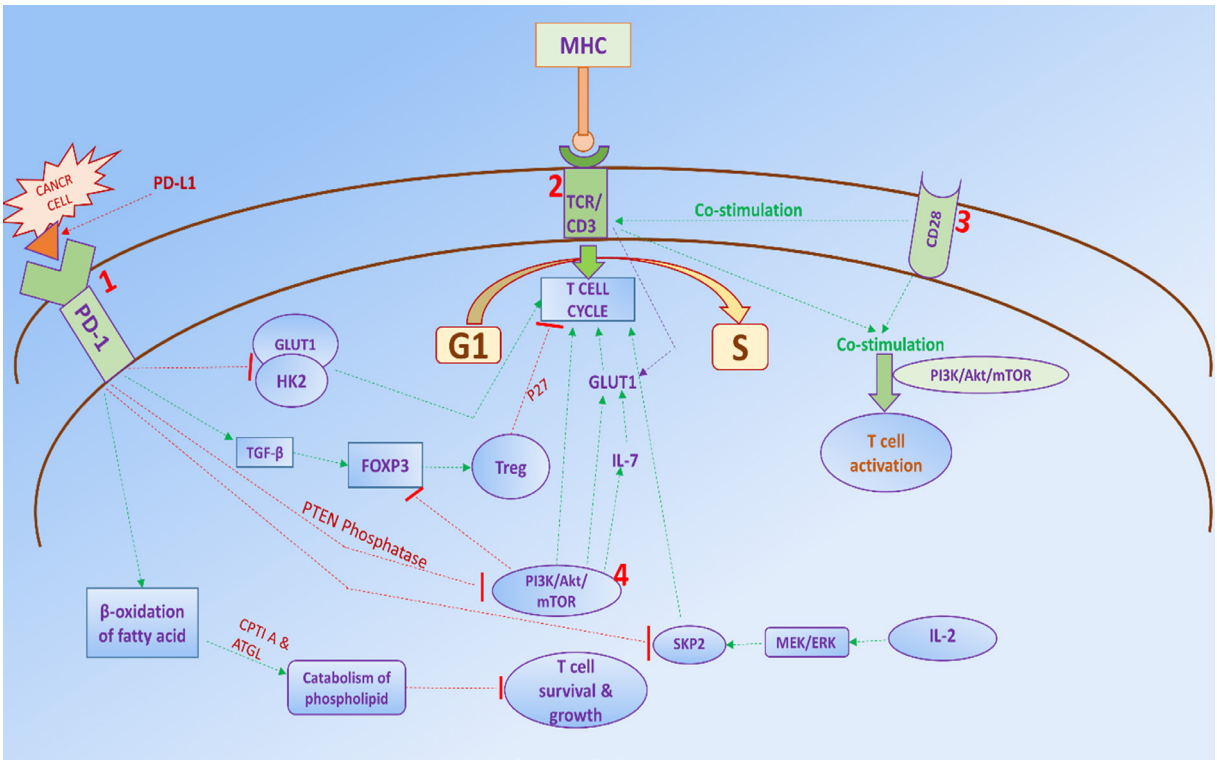

Figure 2. (1) After ligation of the PD-1 receptor with PD-L1 ligand, it inhibits PI3K/Akt/mTOR signaling through numerous mechanisms, such as enhancing the activity of PTEN phosphatase. It also prevents cell cycle transition of T-cells by inducing Treg cells with accelerating the action of TGF-B by reducing SKP2 expression through upregulation of GLUT1 and HK2 and inhibiting PI3K/Akt/mTOR signaling. In addition, Treg induces cell cycle arrest by increasing the expression of CDK inhibitor p27. PD-1/PD-L1 also reduces glucose uptake by T-cells and triggers B-oxidation of fatty acid, and catabolism of phospholipid occurs, leading to a reduction of T-cell survival and growth. (2) After co-stimulation of the TCR/CD3 complex, activates T-cell through the PI3K/Akt/mTOR axis. And increase glucose uptake of T-cell via upregulating GLUT1, thus initiating cell cycle transition of T-cell. (3) CD28 plays a crucial role in stimulating TCR/CD3 complex and activating T-cells via enhancing glucose uptake. (4) PI3K/Akt/mTOR pathway accelerates cell cycle of T-cells via downstream expression of IL-7 and GLUT1; it also reduces Treg development through downregulation FOXP3 expression.

blockade of glucose uptake, and cell cycle arrest occurs.

PD-1/PD-L1-mediated alteration of T-cell metabolic reprogramming by abrogating PI3K/Akt/mTOR pathway

β-oxidation is the process by which fatty acid break down to produce acetyl-CoA, and it is further processed through the citric acid cycle and release ATP. In liver, β-oxidation is determined by the malonyl-CoA-dependent enzyme, carnitine palmitoyltransferase IA (CPT IA) which produces carnitine from long-chain fatty acid. By the action of CPT IA catabolic activities like lipolysis of phospholipid, which is an essential component of the cell membrane, lead to cell growth being inhibited. Glycolysis is the main energy source of T-cells for their proliferation, but when the energy source switches to fatty acid- β-oxidation (FAO), then ultimately proliferation of T-cells is inhibited due to the catabolic activities of phospholipid of the cell membrane. However, PD-1/PD-L1 crosstalk attenuates utilization and transport of glucose by blockade of glucose uptake and glycolysis through inhibition of GLUT1 and hexokinase 2 (HK2), additionally activates FAO by upregulation of CPT IA via suppression of PI3K/Akt pathway and associated TG hydrolase adipose triglyceride lipase (ATGL) also increased which is a key enzyme, catalyzes the action of FAO and CPT IA [13, 14]. It was found that either PI3K/Akt or MEK/ERK alone did not fully upregulated the expression of CPT IA by the action of PD-1, and concomitant inhibition of both cascades enhanced the abundance of CPT IA [14]. PD-1 ligation with PD-L1 accelerates lipolysis through FAO. The abundance of CPT IA expression was increased on T-cells receiving PD-1 signal but was diminished by activation of TCR/CD3 and CD28. Growth factor-induced PI3K/Akt signaling increases in glycolysis and fuel T-cells and other hematopoietic cells, and suppression of either PI3K/Akt or MEK/ERK inhibits glycolysis, as well as OXOPHOS [64] and PI3K-induced activation of mTOR, initiates protein translation, and concurrently inhibits autophagic degradation of proteins which potentiates T-cells proliferation (**Figure 2**) [65]. Moreover, PI3K signaling is very essential for the suppression of lipid catabolism and PI3K/Akt exhibits these actions by preventing the PD-1-mediated CPT IA expression [14].

Conclusion

The PI3K/Akt/mTOR signaling pathway is one of the key regulators of T-cells and not only governs the activation, differentiation, survival, and proliferation of T-cells, but also modulates other cytokines, interleukins and transcription factors which directly or indirectly sharpen the immune mechanism through modulating the action of T-cells. Autoimmunity is the state where the immune system reacts against its own normal components, healthy cells, and tissue, and it could be very harmful when its own normal cells start destroying by the autoimmune response. To avoid autoimmunity, PD-1/PD-L1 axis suppresses activation of T-cells via blockade of the PI3K/Akt/mTOR signaling pathway, which negatively impacts on tight regulation of the immune system, and weakens the immune surveillance. The cancer cells get an advantage of immune escape mechanism by which cancer cells proliferate uncontrolled manner. Thereby, for the activation and growth of T-cells, restoring the action of PI3K/Akt/mTOR cascade through inhibition of PD1/PD-L1 crosstalk is a breakthrough in cancer research.

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Ethics approval

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Data availability

The Data will be available upon request.

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Authors' contribution

JS contributed to the conception, design, writing of this review article and submitted the final version of the manuscript.

Competing interests

None.

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