PI3K/AKT/mTOR and PD-1/CTLA-4/CD28 pathways as key targets of cancer immunotherapy (Review)

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Abstract. T cells play an important role in cancer, and energy metabolism can determine both the proliferation and differentiation of T cells. The inhibition of immune checkpoint molecules programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) are a promising cancer treatment. In recent years, research on CD28 has increased. Although numerous reports involve CD28 and its downstream PI3K/AKT/mTOR signaling mechanisms in T cell metabolism, they have not yet been elucidated. A literature search strategy was used for the databases PubMed, Scopus, Web of Science and Cochrane Library to ensure broad coverage of medical and scientific literature, using a combination of keywords including, but not limited to, 'lung cancer' and 'immunotherapy'. Therefore, the present study reviewed the interaction and clinical application of the PD-1/CTLA-4/CD28 and PI3K/AKT/mTOR pathways in T cells, aiming to provide a theoretical basis for immunotherapy in clinical cancer patients.

Contents

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1. Introduction

Cancer, as a serious health problem, represents one of the main causes of morbidity and mortality worldwide (1). Immunotherapy is a treatment method that utilizes the body's own immune system to combat diseases and has shown potential in cancer treatment. However, despite significant success, immunotherapy still faces multiple challenges (2). Genetic heterogeneity within tumors may lead to inconsistent responses of tumor cells in different regions to immunotherapy, while antigen loss makes it difficult for the immune system to recognize and target all tumor cells (3). Tumor cells may develop resistance to immunotherapy through various mechanisms, such as upregulation or downregulation of programmed death-ligand 1 (PD-L1), changes in the IFNγ signaling pathway and alterations in metabolic pathways (4). For instance, Choi *et al* (4) found that the consumption of developmentally regulated GTP binding protein 2 in melanoma cells not only increases the expression of PD-L1 in tumor cells, but also increases the proportion of IFN-expressing CD8 T cells in tumor-infiltrating immune cells. Immunotherapy may cause immune-related adverse events (irAEs), such as inflammatory reactions in the endocrine system, skin, digestive tract and lungs (5). Therefore, it is important to overcome these adverse factors by developing new therapies (6).

In previous years, immunotherapy has been developed to design effective treatment methods to enhance the specificity and intensity of the immune system towards cancer (7). T cells are cellular effectors and coordinators in cancer, which serve as adaptive immune cells required for immune tolerance,

host defense, immune memory and homeostasis (8). A large amount of data indicates that T cell activation, clone amplification and effector differentiation are closely related to cell energy metabolism (9). Based on studies of immune checkpoint programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), the inhibition of immune checkpoints can more effectively activate T cells and eliminate cancer cells (7) and the immune checkpoint inhibitors may have important therapeutic value (6).

The PI3K/AKT/mTOR pathway represents a primary signaling pathway that regulates processes, including cell metabolism, apoptosis and proliferation (10,11). The activation of PI3K/AKT can strengthen the nutrient intake and energy production of $CD8^+$T cells, whereas mTOR is responsible for participating in regulating both innate and adaptive immune systems and the biological effects of immune cell stimulation (8,12). PI3K/AKT activation can promote PD-L1 expression and co-stimulate CD28, which can enhance T cell activation and metabolism. Therefore, the present article mainly explored the interaction and clinical application of the PD-1/CTLA-4/CD28 and PI3K/AKT/mTOR pathways in T cells.

A literature search strategy was adopted using the PubMed (https://pubmed.ncbi.nlm.nih.gov) database to ensure broad coverage of medical and scientific literature. The present study used a combination of keywords including 'lung cancer', 'PD-1', 'CTLA-4', 'CD28', 'PI3K', 'AKT', 'mTOR', 'T cell' and 'immunotherapy'.

2. Proliferation and differentiation process of Tn/Tm in cancer and changes in energy metabolism

By recognizing and killing tumor cells, T lymphocytes protect the body from cancer (13). According to the functions and phenotypes, T lymphocytes can be mainly classified into immature T cells (Tn) and memory T cells (Tm) (14). To be specific, Tn represents a dormant mature T cell. Through the circulation between the blood and secondary lymphoid organs, Tn exhibits immune surveillance functions (15,16). In addition, Tm is included in maintaining the rapid and long-term immune responses, also known as the memory immune responses (17,18). Situated between Tn and Tcm, Tscm is a significantly different subset (19). Tn and T memory stem cells (Tscm) can self-renew and differentiate into each subset of memory and effector T cells, which are central memory T cells (Tcm), Terminal effector T cells (Tte) and effector memory T cells (Tem) (14). Usually, Tcm cells exist in lymphoid organs and show no direct lytic function (20). Tscm and Tcm go through memory immune responses and quickly clone and proliferate to generate Tem and Tte which particularly kill tumor cells (21).

The energy requirements for T cell proliferation and differentiation are met through the prominent programming of cellular metabolism, and the different phenotypes of T cells can determine their different metabolic modes (22-24). Initial T cells maintain the minimum ATP levels by uptaking basic nutrients via oxidative phosphorylation (OXPHOS) while maintaining basic metabolic needs by relying on fatty acid oxidation (FAO) and glutamine metabolism (8). However, under aerobic conditions, rapidly dividing T cells transition their metabolism from oxidative phosphorylation to aerobic glycolysis and glutamine breakdown (25). Despite the existence of oxygen, glucose can still ferment into lactic acid, which can enter the tricarboxylic acid cycle (the TCA cycle), where the main carbon flux is converted from glucose to glutamine (12,25). After encountering antigens, immature T cells rapidly transform into effector T cells, which exhibit increased nutrient absorption and glycolysis rates and a metabolic activation state, mainly relying on OXPHOS and aerobic glycolysis to maintain T cell adaptability and function (26,27).

Given the 10 enzymatic steps of glycolysis (which converts glucose to pyruvate), some intermediates are generated for the various biosynthetic pathways. That can involve *de novo* fatty acid synthesis, the pentose phosphate pathway, hexosamine biosynthesis and serine biosynthesis, where the pentose phosphate pathway plays an important role in cell growth and offers primary precursors for nucleotide synthesis (28,29). Therefore, glycolysis is not only an energy production pathway in T cells, but also the metabolic foundation for proliferating synthetic organisms (30). Glucose transporter 1 (GLUT1) is a key signaling molecule for T lymphocyte activation and metabolism (31), capturing glucose to convert it into lactic acid, which can be used for oxidative phosphorylation even with sufficient oxygen (32). Glucose is first converted to glucose-6-phosphate (G-6-P), then to fructose-6-phosphate (F-6-P) and further to F-1,6-BP by the key regulatory factor PFK1 in glycolysis (33). Next F-1,6-BP enters the second part of glycolysis, which ultimately produces ATP and pyruvate (34). Therefore, glycolysis contributes much to T cell proliferation and differentiation.

3. Structure and function of the PI3K/AKT/mTOR pathway

According to differences in structure and function, PI3K is classified into categories I, II and III (35). To generate 3,4,5-triphosphate phosphatidylinositol (PIP3), PI3K phosphorylates 4,5-diphosphate phosphatidylinositol. PIP3 co-acts with target proteins [including Akt and phosphoinositol dependent protein kinase (PDK1)] that involve pleckstrin homologous domains on the inner lobe of the plasma membrane (36). Also known as protein kinase B (PKB), there are three subtypes in Akt, which are Akt1/PKBα, Akt2/PKBβ and Akt3/PKBγ (37). To reach complete activation, Akt should be respectively phosphorylated by PDK1 and mTOR complex 2 (mTORC2) (38). MTOR contributes much as the key element of the two multi-subunit proteins that have various functions. The complex is called mTORC1 and mTORC2 (39). In turn, MTORC1 activation can control protein synthesis, metabolism and cell growth. MTOR is fundamentally part of PI3K related kinases (PIKK), and most PIKK members possess conserved domains (40).

The PI3K/Akt/mTOR signaling pathway exists in each of the mammalian cells and exerts a significant impact on different processes, including cell proliferation, metabolism, differentiation and migration. In T cells, PI3Kδ and PI3Kγ subtypes play an important role in development (41). In the process of thymogenesis, absent or inactivated two isomers hinder the CD4 CD8 double negative stage of T cell development. By contrast, PI3Kδ is a subtype that can contribute significantly to PI3K signal transduction in mature T cells (42).

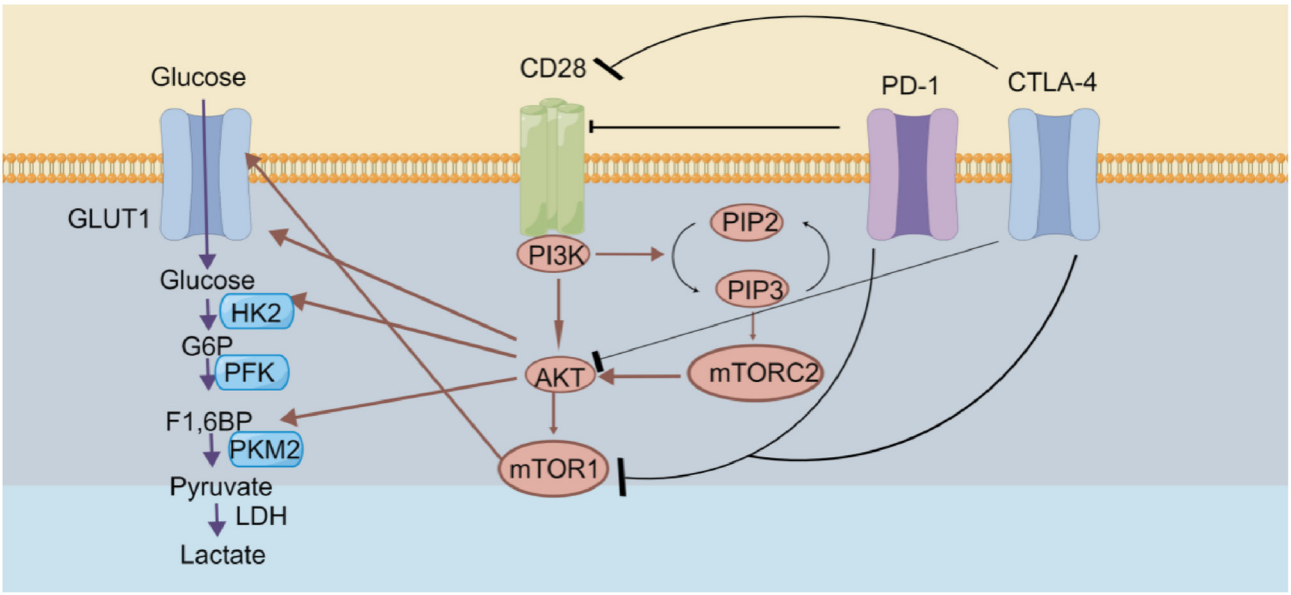

Figure 1. PI3K/AKT/mTOR and PD-1/CTLA-4/CD28 pathways affect the function of T cells and their mechanisms of action in T cells. By Figdraw. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte associated protein 4.

For $CD8^+$T cells, IA type PI3K can be mainly activated by tyrosine kinase-related receptors, including T cell receptors (TCRs), cytokine receptors and co-stimulatory receptors (43). The PI3K/Akt signaling pathway in $CD8^+$T cells is stimulated by the signaling pathways triggered by cytokines IL-12, IL-2, IL-7, IL-15 and IL-21 (44). IL-2 can produce sustained high levels of PIP3, whereas IL-15 can relatively stimulate PI3K weakly, which can cause lower levels of PIP3. Conversely, chemokine receptors and other G protein coupled receptors can activate IB-type PI3K. The mTOR pathway represents an important regulatory factor for cell growth and proliferation and is becoming an attractive target for cancer treatment (45). Apart from the cancer cells, mTOR contributes much to mediating T cell activation and differentiation (46).

4. Interactions between the PD-1/CTLA-4/CD28 and PI3K/AKT/mTOR pathways affect T cell metabolism

PD-1/CTLA-4/CD28 regulates T cell metabolic balance. T cells are activated via antigen recognition through TCRs and co-stimulatory signals including CD28 (47). CD28 is considered a biosensor for T cell metabolism (48). CD28 co-stimulation plays an important role in strengthening T cell activation and metabolism and is antagonized via the inhibitory and checkpoint immunotherapy receptors CTLA-4 and PD-1 (49).

PD-1 is an inhibitory receptor that can inhibit the T-cell immune responses (6). On the contrary, PD-L1 can promote the stimulation of CD28 without triggering the inhibitory signal of PD-1, thereby facilitating the activation of T cells (50). This reflects the intricate regulatory mechanisms among multiple key factors in the immune system.

In addition to revolutionizing cancer treatment, cancer immunotherapy targeting the inhibitory co-receptors PD-1 and CTLA-4 has also shown long-standing clinical benefits for different tumor types (51,52). CTLA-4 inhibits T cell activation while interacting with CD86 or CD80 through transduction of inhibitory signals and/or the inhibition that involves co-stimulatory protein CD28 (53,54). CTLA-4 can also downregulate T cell glycolysis 1, and related studies have shown that CTLA-4 blockade can affect the metabolic adaptability of T cells in tumors related to tumor glycolysis ability (48).

Interaction between PD-1/CTLA-4/CD28 and PI3K/AKT/mTOR pathway affects T cell metabolism. CD28 co-stimulation increases T cell synthesis and metabolism, whereas CD28 family members PD-1 and CTLA-4 can inhibit T cell metabolic reprogramming (55). PD-1 can inhibit glycolysis, promote the FAO of endogenous lipids, and change nucleoside synthesis. In addition, PD-1 negatively regulates T cells through changing mitochondrial cristae formation, which hinders oxidative phosphorylation (56). Besides, CTLA-4 can inhibit Akt/mTORC1 on the CD28 signaling and PI3K/Akt/mTORC1 signaling pathways, which can cause reduced glycolysis and mitochondrial oxidative capacity (57,58). AKT can regulate important enzymes in T cell metabolism, including GLUT1, hexokinase 2 and pyruvate kinase isozymes M1/M2, and mTORC1 can promote the expression of GLUT1, which promotes the process of T cell glycolysis (Fig. 1).

5. Clinical treatment

Blocking treatment of CTLA-4. CTLA-4 is a key negative regulatory molecule recruited to the cell membrane during T-cell activation and can bind to helper molecules of the B7 family expressed by antigen-presenting cells (59,60). Since the binding of CTLA-4 effectively inhibits further activation and proliferation of T cells, the progression of immune response can be controlled and the occurrence of chronic autoimmune inflammation can also be reduced (61). In cancer treatment, the blocking of CTLA-4 can not only relieve the inhibition of

Table I. Clinical use of related inhibitors.

Target points	Drug name	Tumor type
PD-1	Toripalimab	Melanoma, nasopharyngeal carcinoma, epithelial carcinoma of the urinary tract, esophageal cancer, non-squamous non-small cell lung cancer
	Sintilimab	Hodgkin's lymphoma, non-squamous non-small cell lung cancer, lung squamous cell carcinoma, liver cancer, esophageal cancer, gastric or gastroesophageal junction cancer
	Camrelizumab	Hodgkin's lymphoma, liver cancer, EGFR/ALK negative non-small cell lung cancer, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, squamous non-small cell lung cancer
	Tislelizumab	Hodgkin's lymphoma, epithelial carcinoma of the urinary tract, squamous non-small cell lung cancer, EGFR/ALK negative non-small cell lung cancer, liver cancer, non-small cell carcinoma, MSI-H/dMMR advanced solid tumors, nasopharyngeal carcinoma, gastroesophageal junction adenocarcinoma (G/GEJ adenocarcinoma), esophageal squamous cell carcinoma
	Zimberelimab	Hodgkin's lymphoma
	Penpulimab	Hodgkin's lymphoma, squamous non-small cell lung cancer
	Serplulimab	MSI-H advanced solid tumor, non-small cell lung cancer, small cell lung cancer
	pucotenlimab	MSI-H advanced solid tumor
	Pembrolizumab	Melanoma, non-small cell lung cancer, esophageal cancer, squamous cell carcinoma of the head and neck, MSI-H/dMMR advanced colorectal cancer, liver cancer, esophageal cancer/gastroesophageal junction cancer, triple negative breast cancer
	Nivolumab	Non-small cell lung cancer, squamous cell carcinoma of the head and neck, gastric or gastroesophageal junction cancer, gastric cancer, esophageal adeno-carcinoma, epithelial carcinoma of the urinary tract, pleural mesothelioma, esophageal squamous cell carcinoma
PD-L1	Sugemalimab	III Nnon-small cell lung cancer, IV non-small cell lung cancer
	Envafolimab	MSI-H/dMMR advanced solid tumors
	Adebrelimab	Extensive stage small cell lung cancer
	Atezolizumab	Small cell lung cancer, hepatocellular carcinoma, non-small cell lung cancer, non-squamous non-small cell lung cancer
	Durvalumab	Extensive stage small cell lung cancer, unremovable III non-small cell lung cancer
CTLA-4	Ipilimumab	Malignant pleural mesothelioma
PD-1/CTLA-4	Cadonilimab	Cervical carcinoma
mTOR	Temsirolimus	Glioblastoma multiforme, neuroendocrine tumors, soft tissue sarcoma, prostatic cancer, cervical carcinoma
	Sirolimus	Cholangiocarcinoma, liver cancer
	Everolimus	Pancreatic cancer, small cell lung cancer, transitional cell carcinoma, bone and soft tissue sarcoma, epithelial carcinoma of the urinary tract, colorectal cancer
	Ridaforolimus	Bone and soft tissue sarcoma, endometrial cancer

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T lymphocyte associated protein 4.

anti-cancer T cells but also trigger a new immune response. Related studies have shown that ipilimumab is a therapeutic drug with primary clinical significance, especially for patients in advanced stages (62,63). Different from conventional treatment that directly kills cancer cells and rapidly causes tumor volume reduction, it may take several months for ipilimumab to stimulate T cell responses (64). In addition, other applications of ipizumab have also been pursued, especially in combination with other immunotherapies, such as effective immune checkpoint inhibitors, vaccine administration and small molecule tyrosine kinase inhibitors (65).

Blocking therapy of PD-1/PD-L1. The metabolism can affect the functions of the PD-1 pathway. In the cytoplasmic domain in PD-1, there are two tyrosine motifs. Upon binding to ligands, the phosphorylation of tyrosine residues of PD-1 occurs, which can cause the binding to The Src homology 2 and other protein tyrosine phosphatases (PTP) (66). Then, PTP

can phosphorylate kinases and antagonize positive signals that occur via TCR and CD28, which affects the downstream signaling pathways (67), such as Extracellular signal-regulated kinase 1/2 (ERK) (68), PI3K-AKT (69), finally reducing T cell survival, activation and proliferation and altering cytokine production and metabolism.

Given the effectiveness of the PD-1 pathway blockade monotherapy, improved response rates are associated with the infiltration of $CD8^+$T cells at the tumor margin and high levels of PD-L1 expression (70). However, PD-L1 expression is linked to treatment outcomes all the time, as some PD-L1 tumors exhibit poor response to PD-1 pathway blockade while others exhibit a good response. Therefore, multiple biomarkers may play a more effective role in predicting responses of anti-PD-1 monotherapy than PD-L1 expression levels alone (71). In addition, in Renal Cell Carcinoma, certain metabolic signals are linked to treatment failure, which may be caused by the increased metabolic adaptability of tumor cells. Conversely, the immunological markers that involve BACH2 encode transcription factors regulating differentiation and function of effector T cells and memory T cells, as well as CCL3, which can encode chemokines in leukocyte migration, and has a connection to successful RCC treatment of PD-L1 (72,73). In the recent metastatic melanoma data, there is a relationship between mesenchymal and 'inhibitory inflammatory' transcriptional phenotypes and the efficacy of PD-1 inhibitors (74).

mTOR inhibitors. The mTOR pathway is a crucial regulatory factor for innate (including the dendritic cells and macrophages) and adaptive effector (including the T and B lymphocytes) immune cell metabolism, proliferation and anti-inflammatory response (75). Since the mTOR pathway is usually dysregulated in various solid tumors and hematological malignancy types, mTOR inhibitors (mTORi) indicate the immunosuppressive method that can prevent transplant rejection in transplant patients (76) and the anti-tumor therapy, which can be combined with immunotherapy and carefully adjusted for the immunosuppressive dose (77). Using mTORi and reducing the dosage of other immunosuppressive drugs is related to improved overall survival in patients with cancer. research indicates that T cell anergy can be maintained by using mTORi and accompanying immune checkpoint inhibitor therapy. Besides, mTORi stimulates the differentiation of immature T cells into Tregs (78).

Hence, mTORi therapy decreases cancer progression in various malignant tumors and exerts antitumor effects, which is seen to be controversial (79-81). Currently, only a few mTOR inhibitors are employed in clinical practice. All approved mTOR inhibitors belong to the first-generation mTOR inhibitors. Rapamycin is the first mTOR inhibitor approved by the FDA and is currently suitable for preventing organ rejection after organ transplantation. Also, it can be used alone or in combination with calcineurin inhibitors or corticosteroids (82,83) (Table I).

6. Summary and outlook

Cancer immunotherapy is a major breakthrough in the field of oncology (84). Despite significant clinical success, such as the use of immune checkpoint inhibitors to treat melanoma and other solid tumors, there are still several limitations and potential biases that require further research to overcome (85). Not all patients can benefit from immunotherapy, and irAEs, such as endocrine disorders, enteritis and pneumonia may occur, which can have serious effects on patients and sometimes even be fatal (86,87). The predictive value of biomarkers such as tumor mutational burden and PD-L1 expression levels is not consistent and is influenced by tumor heterogeneity (88,89). The use of precision medicine strategies to customize immunotherapy plans based on each patient's specific situation, develop safer immunotherapy strategies and reduce the incidence and severity of irAEs is currently an urgent problem that needs to be solved (90,91). In summary, although cancer immunotherapy has changed the face of oncology, there is still much work to be done to overcome its limitations, reduce bias and ensure its benefits for as many patients as possible.

Despite significant progress in the field of immunotherapy for lung cancer, there are still a number of challenges to be faced. The present article reviewed the components of the PI3K/AKT/mTOR signaling pathway and the interactions between the PD-1/CTLA-4/CD28 and the PI3K/AKT/mTOR pathways in T cells and their impact on T cell metabolism and proliferation ability. CD28 can promote T cell glycolysis through activating the PI3K/Akt/mTOR pathway, while CD28 is inhibited by PD-1 and CTLA4. Therefore, it is necessary to further consider PI3K/AKT/mTOR pathway inhibitors combined with PD-1/PD-L1 inhibition to regulate T cell metabolism and proliferation, which can prevent and treat cancer.

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Authors' contributions

SCW designed the review, prepared the figure, wrote the manuscript and made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. CYL, CXY, YTJ and QC participated in the conception and design of the study. DW, TG and GXH analysed and interpretated the data. WTL, GZ, AQL, YX and YHL were involved in the conception and design of the study and revised the manuscript. JCY revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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