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Research Progress on the Effects of PI3K/Akt Pathway on Immune Escape

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Abstract: The PI3K/Akt pathway can promote immune escape in tumors, making cancer cells more difficult for the immune system to attack. It is usually possible to regulate the number and function of immune cells by inhibiting apoptosis and T cell activation, and generate immune escape mutations to make cancer cells more resistant to immune monitoring. In-depth understanding of the role of PI3K/Akt pathway in immune escape will help to reveal the mechanism of tumor development, improve the effectiveness of cancer treatment. development, improve the effectiveness of cancer treatment, and restore the immune system's monitoring and attack on cancer cells by inhibiting the activity of PI3K/Akt. In this review, we review the research progress on the effects of G protein-coupled receptor-activated PI3K/Akt pathway on immune escape. This review aims to summarize domestic and international studies that reveal how the PI3K/Akt pathway plays a key role in immune escape, and through in-depth understanding of the role of the PI3K/Akt pathway in immune escape. This review aims to summarize domestic and international studies that reveal how the PI3K/Akt pathway plays a key role in immune escape, and through in-depth understanding of the molecular mechanism, new therapeutic targets can be identified. Scientists from abroad have explored various cancer forms, such as lung, ovarian, and endometrial cancers, etc., so as to provide targeted treatment strategies and increase the applicability of immunotherapy for different cancers; By studying the role of PI3K/Akt pathway, we can explore the potential application of PI3K/Akt pathway for different cancers. By studying the role of PI3K/Akt pathway, we can explore the potential application of existing drugs or new drugs in immunotherapy, so as to improve the diversity of treatment. techniques are combined with clinical data to discover associations between the PI3K/Akt pathway and treatment response in patients to support personalized medicine. Current studies have found that the PI3K/Akt pathway is a key mechanism for immune monitoring of tumor cell escape, and in-depth study of its role is expected to improve the quality of treatment. Current studies have found that the PI3K/Akt pathway is a key mechanism for immune monitoring of tumor cell escape, and in-depth study of its role is expected to improve current immunotherapy strategies and improve patient survival. In the future, whether there are new therapeutic opportunities for PI3K/Akt pathway in immune escape studies, so as to help optimize cancer treatment strategies, improve the efficacy of immunotherapy in future, whether there are new therapeutic opportunities for PI3K/Akt pathway in immune escape studies, so as to help optimize cancer treatment strategies, improve the efficacy of immunotherapy, and improve patient treatment outcomes.

Keywords: PI3K/Akt Pathway; Immune Escape; Cell Apoptosis; T Cell Activation; Cancer Treatment.

1. Introduction

Phosphatidylinositol-3-kinase (PI3K) is an important intracellular bifocal enzyme with both Activity of phosphatidylinositol kinase and the activity of serine/threonin (Ser/Thr) kinase. In the intracellular milieu, PI3K participates in a complex signaling network by catalyzing the phosphorylation of phosphatidylinositol molecules and regulating cell survival, growth, and metabolic responses[1]. Conversely, serine/threonine protein kinase (Akt) is a core belonging to the serine/threonine-specific family of protein kinases, which plays an integral role in numerous fundamental cellular physiological processes. Akt regulates cellular activities at multiple levels, including, but not limited to, critical regulation of glucose metabolism processes, inhibitory effects on apoptotic programs, effects on cell proliferation and differentiation processes, and active participation in transcriptional regulation and cell migration mechanisms. Consequently, the aberrant function of Akt kinase is frequently associated with the pathogenesis of diverse diseases, particularly in the domains of tumor biology and metabolic disorders. Both PI3K and Akt belong to the category of proto-oncogenes. Immune evasion represents a pivotal reason why the immune system is unable to control the growth of tumors. This pathway plays a pivotal role in the immune evasion of cancer cells[2].

2. Generation of the PI3K/Akt Pathway

G protein-coupled receptors play a pivotal role in the regulation of the PI3K/Akt signaling pathway. Upon interaction with a specific exogenous signaling molecule, a G protein-coupled receptor undergoes a conformational change that effectively activates the G protein to which it is coupled.

The activation of PI3K is mediated by activated G proteins, which stimulate PI3K and activate its catalytic activity, thereby catalyzing the conversion of phosphatidylinositol diphosphate (PIP2) to phosphatidylinositol trisphosphate (PIP3) on the cell membrane. At the same time, the presence of a phosphatase called PTEN, a tumor suppressor gene, can reverse catalyze this process, inhibiting the downstream signaling of the PI3K pathway through dephosphorylation of PIP3. As a key second messenger molecule, PIP3 can recruit and anchor Akt and its upstream activator PDK1 on the cell membrane after its production[3].

This process directs the transfer of Akt to the plasma membrane and initiates its partial activation state. Once fully

activated, Akt efficiently transmits survival and proliferation signals to various intracellular pathways by phosphorylating a series of substrate proteins. Consequently, the activation of Akt strongly promotes cell survival, proliferation rate, and growth. It is also deeply engaged in diverse cellular physiological activities, inclusive of the regulation of glucose metabolism and cell cycle progression. In conclusion, G protein-coupled receptors exert a profound influence on numerous physiological and biochemical responses of cells by initiating the pathway involving PI3K/Akt signaling. This pathway holds a crucial position in maintaining normal physiological homeostasis and in regulating various pathological conditions[4].

3. PI3K/Akt Pathway and Apoptosis

The activation of Akt kinase plays a pivotal role in cell biology, enhancing the viability of tumor cells by inhibiting the process of programmed cell death, or apoptosis. This process essentially enables cancer cells to circumvent the natural clearance mechanism of the body's immune system, which is responsible for destroying abnormal cells through its own apoptotic pathway. In recent years, it has been demonstrated that this signaling pathway is frequently aberrantly activated in a multitude of cancer types. This abnormality is typically attributable to a multitude of factors, including, but not limited to, the amplification of the PI3K catalytic subunit gene, which results in elevated PI3K activity, or the over-activation of Akt itself due to a range of contributing factors. Additionally, the mutation or loss of function of negative regulators of the pathway, such as PTEN, represents another significant contributing factor to the persistent activation of Akt.

Recent studies have demonstrated the efficacy of the PI3K/Akt pathway in inhibiting apoptosis and promoting cancer cell survival through a multitude of mechanisms. The aforementioned mechanisms include the following: The pathway directly affects the phosphorylation of apoptosis-associated proteins and alters their activity status to block apoptosis. It also plays a central role in regulating cell survival and death decisions by directly affecting or indirectly regulating a series of key transcription factors. The pathway also regulates cell cycle progression, ensuring that cancer cells are not subject to normal cell cycle checkpoints and thus maintaining rapid and uncontrolled proliferation. Additionally, it maintains mitochondrial homeostasis, preventing mitochondria from releasing intrinsic factors that trigger apoptosis, thereby protecting cancer cells from the initiation and execution of the internal apoptotic pathway. Abnormal activation of this pathway represents a central strategy employed by tumor cells to evade apoptosis, acquire drug resistance, and promote tumor progression. This provides a theoretical rationale for the development of anticancer drugs targeting this pathway[5].

Programmed cell death ligand 1 (PD-L1), an immune checkpoint molecule, is closely associated with bidirectional regulation during epithelial-mesenchymal transition (EMT). In a variety of tumor types, including lung cancer and breast cancer, there is a positive or negative relationship between PD-L1 expression and the levels of EMT markers, indicating that PD-L1 plays a pivotal role in the dynamics of EMT. The mechanism of upregulation of PD-L1 expression during EMT involves a multitude of pathways, including the activation of the PI3K/Akt pathway[6]. Consequently, the upregulation of PD-L1 in tumor cells facilitates immune evasion[7].

4. PI3K/Akt Pathway and T Cell Activation

It has been demonstrated that the PI3K/Akt signaling pathway reduces the likelihood that tumor cells will be effectively recognized and attacked by the immune system. This occurs through its inhibitory effect on T cell activation. Additionally, the pathway promotes an increase in the population of regulatory T cells (Tregs), which in turn weakens the overall strength of the body's immune response to tumors. It is of interest to note that experimental data have revealed that inhibitors of this pathway selectively inhibit the function and proliferative activity of regulatory T cells (Tregs), with relatively little effect on conventional T cells[8].

A series of research studies clearly demonstrate that under in vitro experimental conditions, different Akt and PI3K inhibitors exhibit significant selective inhibitory effects on the activation and proliferation of Tregs, which are more precisely targeted compared to normal T cells. Such PI3K/Akt inhibitors possess significant therapeutic anti-tumor potential and their efficacy has been shown to be directly correlated with the reduction in the number and activity of Tregs. In this context, existing studies have specifically highlighted PI3K/Akt signaling pathway inhibitors as an effective pharmacological tool for selective depletion of inhibitory Tregs. Such inhibitors are capable of effectively enhancing the anti-tumor immune response in the host body upon application, thereby providing a compelling rationale for further optimization of tumor immunotherapy strategies[9].

Activation of the PI3K/Akt pathway can affect antigen presentation and major histocompatibility complex (MHC) molecule expression in tumor cells in multiple ways. Previous studies have focused on the potential of PI3K and Akt inhibitors to improve tumor immunotherapy outcomes. Inhibition of this pathway theoretically allows for the restoration or enhancement of tumor cell immunogenicity, increased MHC molecule expression, and reduced immunosuppressive molecule production, thus facilitating more effective tumor cell recognition and attack by immune cells. Some PI3K and Akt inhibitors have demonstrated synergistic effects in combination with immune checkpoint inhibitors in clinical trials, which can enhance the efficacy of immunotherapy. Akt can be involved in regulating the production of MHC molecules along with various proteins associated with antigen processing and presentation through the downstream effector regulation of factors involved in transcription, like the nuclear factor κB (NF-κB) alongside signal transducer and activator of transcription 3 (STAT3). When Akt is hyperactive, it may result in a reduction in the expression of MHC-I and MHC-II-like molecules on the surface of tumor cells. This, in turn, impairs the effective presentation of tumor antigens to CD8+ killer T cells and CD4+ helper T cells. Consequently, the anti-tumor function of CD8+ T cells is diminished, recognition and clearance of tumor cells by the immune system is impaired, and immune escape is promoted[10]. Casein kinase II (CK2) is involved in the promotion of important processes such as cell proliferation, invasion, migration, apoptosis, and tumor growth through this pathway. Additionally, CK2 has been found to promote tumor growth by regulating tumor-associated macrophages (TAMs) in the tumor microenvironment to an M2 phenotype and reducing effector CD8+ T cells, thereby promoting tumor immune escape[10].

As specialized lymphocytes, CD8+ T cells are highly adept

at recognizing and eliminating tumor cells and intracellular pathogens, playing a pivotal role in anti-cancer and anti-infection immunity. Strong Akt signaling prompts CD8+ T cells to migrate to inflammatory sites for immediate response, whereas moderate inhibition of Akt leads to the differentiation of CD8+ T cells into memory T cells, which are capable of remaining latent for extended periods and rapidly responding to reinfection, maintaining long-term immune memory. This finding establishes the central role of Akt signaling in the functional differentiation of CD8+ T cells as a regulatory "switch" for the balance between immediate and persistent immune responses. In recent years, studies have shown that PI3K inhibitors can enhance the sensitivity of tumor cells to CD8+ T cells, and by interfering with tumor metabolism, it is expected that this will break through the immune escape mechanism[12]. Based on this, in-depth understanding of the molecular mechanism of PI3K/Akt pathway can promote the development of drugs that accurately regulate the formation and the preservation of CD8+T cell memory, optimize the temporal and spatial distribution of immune response through fine regulation of Akt signal, improve the efficacy of vaccines, and enhance the sustainability and efficiency of tumor immunotherapy. It also provides new therapeutic strategies for a variety of immune diseases[13].

Recent studies have demonstrated that Akt kinase exhibits heightened activity in immunoresistant tumors, particularly in cases resistant to conventional immunotherapy. This evidence underscores the pivotal role of Akt kinase in promoting tumor immune escape. Local injection of Akt inhibitors into immunoresistant tumors significantly enhances the efficacy of vaccines or CD8+ T-cell therapies targeting specific antigens. This counteracts immunosuppression of the tumor microenvironment by intensifying immune responses against tumor antigens. Atypical triggering of the PI3K/Akt signaling route leads to more than just tumor growth, survival, and invasion, but also promotes immune escape as a key mechanism in immunoresistant tumors. Studying and intervening in this pathway is not only essential for comprehending the intricate mechanism of immune evasion, but also offers a theoretical foundation and practical guidancefor the creation of a new immunotherapy tactics for refractory tumors[14].

In their activated state, CD4+ thymocytes and peripheral T cells are able to regain the ability to express a key transcription factor (Foxp3) for Tregs function in a pathway independent of transforming growth factor-β (TGF-β). This pathway is none other than the PI3K/Akt/mTOR signaling pathway, which is a core pathway for Tregs activation and function. Previous studies have shown that this pathway promotes radiation resistance. The pdk1-driven radioresistance in hepatocellular carcinoma is associated with the activation of the PI3K pathway. In addition, this pathway is usually activated, leading to radiation resistance in glioblastoma cells[15]. Inhibition of this signaling network was able to induce the re-expression of Foxp3 and its associated characteristic Treg cell mRNAs, implicating a critical role for this pathway in maintaining the Treg cell phenotype. In contrast, the efficiency of Foxp3 induction was reduced in PTEN-deficient T cells due to persistent activation of this pathway. Therefore, the efficient induction of Foxp3 can be restored by inhibiting PI3K, which is valuable for an in-depth understanding of the mechanism of Tregs generation and the design of intervention strategies to maintain immune homeostasis[16].

The pathway involving PI3K/Akt/mTOR signaling holds a crucial regulatory position in numerous cell physiological activities, encompassing a broad spectrum of cell proliferation and metabolism. In particular, activation of PI3K plays a key role in T cells. It not only contributes to the cell survival and proliferation process, but also profoundly affects T cell differentiation and is essential for determining the phenotype of effector and memory T cells. Consequently, inhibitors of this pathway can effectively intervene in the activation state and functional manifestation of T cells. PI3K inhibitors have demonstrated considerable potential in the treatment of T cell-mediated diseases. This class of drugs is particularly important in the field of allogeneic hematopoietic stem cells transplantation, where they can be used to target the regulation of T cell function and possible antileukemic effects. The administration of PI3K inhibitors represents an efficacious approach to intervene in this pathway. By interfering with this pathway, PI3K inhibitors can modulate inappropriate immune responses and enhance the ability to clear residual leukemia cells after transplantation. This, in turn, improves patient prognosis and quality of life[17].

Recent studies have demonstrated that in low-dose photodynamic therapy (PDT) of LLC cells, precise regulation of the PI3K/Akt signaling pathway results in elevated levels of HIF-1α protein, which enhances the cell's immune escape ability. Although this treatment is relatively mild, it may have the unintended consequence of impairing the body's immune clearance of tumor cells. Activation of this pathway not only supports the stability and activity of HIF-1α, but also indirectly affects immune cells. This has become a new strategy for tumor cells to evade immune surveillance using low-dose PDT[18].

In B cells, PI3K deficiency has a profound impact on development and antigen response. In contrast, T cell development, immune function, and migration dynamics are regulated by PI3K, which is also involved in regulatory T cell homeostasis. These findings suggest that the PI3K signaling pathway is the pathway is complex and not a single activation mechanism. T cell autoimmune responses in the PI3K-deficient mouse model suggest that PI3K signaling is essential for maintaining immune system homeostasis and proper response, emphasizing the need for balanced regulation of this pathway[19].

5. PI3K/Akt Pathway and Cancer Treatment

The level of activity of the PI3K/Akt signaling pathway exhibits considerable variability across different cancer types. The pathway is frequently demonstrated to be hyperactivated in a multitude of cancer types, including ovarian, endometrial, breast, gastric, and gliomas. This hyperactivation may be caused by a variety of genetic and epigenetic changes, including, but not limited to, mutations in the PI3K catalytic subunit genes, amplification of the Akt gene, or inactivation of the PTEN oncogene. These differences reflect the heterogeneity of tumorigenesis and may also determine the different propensities of different tumors for growth, invasion, metastasis, and resistance to apoptosis.

In ovarian cancer research, phosphorylated forms of Akt and mTOR, both of which play key roles in the proliferation of ovarian cancer cells, have been frequently observed. This serves as a potential target for intervening in the growth of ovarian tumors. Akt, an important cell survival signaling

mediator that is often hyperactivated in primary ovarian cancer cases, plays a central role in the maintenance of ovarian cancer cells to escape programmed cell death, which is also known as apoptosis. Consequently, pharmacological strategies aimed at blocking the Akt signaling pathway could theoretically preferentially target ovarian cancer cells that are highly dependent on Akt activity to maintain their survival status. In contrast, normal non-cancerous cells do not rely heavily on the continuous activation of Akt to maintain their survival. Such pharmacological intervention is anticipated to result in the selective elimination of ovarian cancer cells, an improvement in therapeutic efficacy, and a reduction in adverse effects on normal tissues[8].

In the field of endometrial cancer research, indoleamine 2,3-dioxygenase (IDO) plays a pivotal role in the complex process of tumor immune escape. The activity of this enzyme is particularly closely related to its interaction with the pathway involving PI3K/Akt signaling. Further researches have indicated that the expression level of IDO can be indirectly affected by regulating the activity status of cyclooxygenase-2 (COX-2) in the tumor microenvironment. Consequently, the interaction between tumor immune escape strategies and the PI3K/Akt signaling pathway, which together drive powerful adaptations for tumor survival and development in vivo, appears particularly prominent[20].

In breast cancer research, vimofenib inhibits the expression of the breast cancer immune escape biomarker BCL2A1 by targeting the PI3K/Akt signaling pathway and inhibiting breast cancer cell growth[21].

Mutations in the pathway involving PI3K/Akt/mTOR signaling have been identified as predictors of immune cell infiltration and immunotherapy response in gastric adenocarcinoma studies[22].

In gastric cancer research, it has been demonstrated that IL-8, which is induced by H. pylori infection, can create a microenvironment conducive to immune escape in gastric cancer cells by activating the PI3K/Akt signaling pathway. This, in turn, up-regulates the expression of PD-L1. The PI3K/Akt/PD-L1 signaling axis is the mechanism through which IL-8 exerts its immune-suppressive effects on gastric cancer cells. This effectively inhibits the recognition and killing efficacy of killer T cells on gastric cancer cells[23].

In glioma research, it has been demonstrated that the loss of the PTEN gene can lead to the dysregulated activation of the pathway involving PI3K/Akt signaling. This aberrant activation process is not only accompanied by an overproduction of pro-inflammatory cytokines, but also significantly impairs the effective infiltration and activation of CD8+ cytotoxic T-cells into tumor tissues in melanoma patients. In contrast, inositol polyphosphate 4-phosphatase type II (INPP4B), a negative regulator, inhibits tumor cell proliferation and overcomes immune escape in gliomas by inhibiting this pathway[24].

The immune checkpoint CD276 interacts with the PI3K/Akt signaling pathway, affecting tumor energy metabolism, suppressing immune responses, promoting tumor angiogenesis, and accelerating immune escape and metastatic processes[25]. The study demonstrated that the PI3K/Akt signaling pathway interacts with tumor energy metabolism, inhibiting immune responses, promoting tumor angiogenesis, and accelerating immune escape and metastasis. A number of studies have demonstrated that abnormalities in this pathway are prevalent in a wide range of malignant tumors. Akt, as a key molecular switch regulating cell proliferation, cycling, survival, migration, and neovascularization, is central to the integration of oncogenic signals and is an important target for cancer therapy. Consequently, intervention strategies targeting this pathway are expected to develop more precise anti-cancer therapies[26].

Activation of the PI3K/Akt pathway can modulate the immune escape mechanism of tumor cells. On the one hand, Akt-mediated signaling can affect the antigenicity of tumor cells, resulting in the inefficient expression of mutant antigens that would otherwise be recognized by the immune system. Conversely, Akt can also affect the expression of immunosuppressive molecules such as PD-L1. By up-regulating the binding of these ligands to the PD-1 receptor on T cells, Akt can achieve the suppression of the immune response of T cells and further promote the immune escape of tumor cells.

6. Conclusion

This review provides an in-depth analysis of the mechanisms by which the PI3K/Akt signaling pathway promotes immune escape in a variety of cancer types. It reveals that the pathway helps cancer cells evade host immune surveillance by inhibiting apoptosis, decreasing T-cell activation, modulating immune cell function, and up-regulating immune-suppressive molecules such as PD-L1 expression. Studies have demonstrated that intervention strategies targeting this pathway effectively inhibits biomarkers related to immune escape, suggesting that our pathway is an important target for immunotherapy. Furthermore, abnormalities in the PI3K/Akt pathway were closely associated with immune cell infiltration and treatment response in gastric adenocarcinoma, ovarian cancer, and endometrial cancer, emphasizing its value as a predictor and indicator of therapeutic efficacy assessment.

However, there are several limitations to the current study. Firstly, although the PI3K/Akt pathway is known to play a key role in a variety of cancers, there may be differences in its mechanism of action and sensitivity in each cancer type and each patient's molecular subtype. This necessitates more precise molecular typing and individualized studies. Although some progress has been made in the development of drugs targeting this pathway, the challenges of drug resistance and side effects remain, and further optimization of drug design and combination therapy strategies is needed. Furthermore, although the combination of bioinformatics and clinical data has helped to identify the link between therapeutic response and the status of this pathway, more validation of how to translate these findings into effective therapeutic regimens in clinical practice is still needed.

Future research should concentrate on several key areas. Firstly, there is a need to deepen the understanding of the mechanism of action of the PI3K/Akt pathway in different cancers and immune microenvironments. Secondly, there is a need to discover and validate new targets and small-molecule inhibitors against the PI3K/Akt pathway. This can be achieved by using high-throughput screening technologies and artificial intelligence algorithms. Thirdly, there is a need for more interdisciplinary collaborations. Collaborations should be established to combine genomics, proteomics, immunology, and other multi-omics data in order to promote the development of precision medicine and realize patient-specific therapeutic strategies. Furthermore, the design and implementation of clinical trials should be strengthened in

order to evaluate the safety and efficacy of PI3K/Akt inhibitors in combination with other immunotherapies or targeted therapies. Through efforts, more innovative treatment opportunities will be opened up in the future studies on PI3K/Akt pathway and immune escape, which will significantly improve the accuracy and success rate of cancer treatment.

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