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Research progress on the PI3K/AKT signaling pathway in gynecological cancer (Review)

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Abstract. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway is involved in the regulation of multiple cellular physiological processes by activating downstream corresponding effector molecules, which serve an important role in the cell cycle, growth and proliferation. This is a common phenomenon; overactivation of the pathway is present in human malignancies and has been implicated in cancer progression, hence one of the important approaches to the treatment of tumors is rational drug design using molecular targets in the PI3K/AKT signaling pathway. In brief, the present review analyzed the effects of the PI3K/AKT signaling pathway on certain gynecological cancer types.

Contents

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Abbreviations: EGF, epidermal growth factor; RTK, receptor tyrosine kinase; PTEN, phosphatase and tensin homolog; PDK1, 3-phosphoinositol-dependent protein kinase-1; TSC2, TSC complex subunit 2; LKB1, serine/threonine kinase 11; HCCR-1, human cervical cancer oncogene 1

Key words: gynecological cancer, phosphatidylinositol 3-kinase, protein kinase B, mechanistic target of rapamycin kinase

1. Introduction

With the deterioration of the current global environment, particularly in developing countries, three common gynecological tumors (cervical cancer, endometrial cancer and ovarian cancer) have become major threats to women's health (1). Therefore, it is important to actively investigate the underlying molecular mechanisms and potential therapeutic targets associated with such tumors. Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) is one of the signaling pathways proven to serve an important role in regulating cell proliferation, the cell cycle and apoptosis (2). A number of studies suggest that the PI3K/AKT signaling pathway is associated with certain gynecological tumors (3-5), and the rational design of molecular targets for the PI3K/AKT signaling pathway is also an important option for the treatment of tumors. Therefore, the present study reveals the association between the PI3K/AKT signaling pathway and the occurrence and development of certain gynecological tumors by summarizing relevant research and drawing conclusions.

2. Composition and function of the PI3K/AKT signaling pathway

PI3K is a member of the lipid kinases family, which are activated by phosphorylating the 3-hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns) lipids in the plasma membrane (6). PI3K may be divided into three categories according to its preference for lipid substrates and different structures (7). Among them, type I PI3K serves an important role in tumors, and is the subtype that has been studied most thoroughly. The type I PI3K is composed of p110. A heterodimer consisting of a catalytic subunit of p110 and a regulatory subunit p85, wherein there are seven regulatory subunits produced by different genes and gene combinations: p85α, p85β, p55α, p55γ, p50α, p101 and p87. The catalytic subunit (p110) has four subtypes, p110α, p110β, p110γ, and p110δ (7). Typically, the catalytic subunit (p110) binds to the regulatory subunit to stabilize the protein heterodimer and inhibit the activation of PI3K (8). PI3K is normally activated by extracellular signals under physiological conditions, and there are two principal activation pathways, involving interaction with a factor receptor of a phosphorylated tyrosine residue to induce heterodimer conformational changes and activation (9). Various stimuli, including growth factors,

cytokines and hormones, have been reported to activate PI3K. In particular, epidermal growth factor (EGF), platelet-derived growth factor and insulin-like growth factor (10,11) bind to the corresponding transmembrane receptor tyrosine kinase (RTK) region of the N-terminal extracellular domain, resulting in autophosphorylation of tyrosine residues in the cytoplasmic region of the RTK and the linker molecule, followed by p85SH2. The interaction between the domain and the phospho-Tyr residue on the RTK complex recruits PI3K to RTKs, resulting in the allosteric activation of PI3K (8). In addition to RTKs, G-protein coupled receptors are another important class of classical upstream regulators that activate PI3K, the most common being p110β (12). Furthermore, PI3K may be directly or indirectly activated by the catalytic subunit (p110) in combination with small GTPases, including Ras and Ras-related protein Rab-5A (9,12).

According to previous studies, among the four type I catalytic subunits, only phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) is frequently mutated in human cancer (13,14). Although there are numerous mutations in PIK3CA, only two sites have been found to cause an increase in PI3K activity through different mechanisms (15). The ubiquitously expressed PIK3CB is less frequently mutated (16), likely due to the unique regulatory pattern present between the catalytic subunit and the regulatory subunit (17). Mutations in the type I regulatory subunit gene (PIK3R1 or PIK3R2) have been identified in cancer cells and cause an increase in PI3K activity, and it has been demonstrated through cell transformation experiments that PIK3CA serves a key role in the potential carcinogenesis of PIK3R1 mutants (18-20). Moreover, p110α serves an important role in inducing tumor angiogenesis. Studies have demonstrated that after knocking out the p110α gene, embryonic development is slow and fetal vascular formation is defective in the second trimester (21-23). In cancer cells with the wild-type PI3K gene, which causes constitutive signal transduction by PI3K, there is usually carcinogenic damage caused by the upstream tyrosine kinase or Ras (14). Phosphatase and tensin homolog (PTEN) lipid phosphatase or inositol polyphosphate-4-phosphatase type II B deletion is another pathway for elevated PI3K lipid products, but the inactivation of these tumor suppressors is not mutually exclusive with mutations in the PI3K or Ras genes (12,19). Mouse models have also demonstrated that the loss of PTEN and the PIK3CA mutation together may lead to the development of ovarian cancer (24). There are a number of polymerization targets that receive signals generated by the PI3K downstream cascade, but the most important mediator is the serine/threonine kinase AKT (8); AKT serves a dominant role in the signal transduction of the entire PI3K pathway.

There are three subtypes of the serine/threonine kinase AKT in mammals, AKT1, AKT2 and AKT3, which are key molecules in the PI3K signal transduction pathway (25). The amino acid structure of AKT, from the N-terminus to the C-terminus, includes a plekstrin homology (PH) domain, the central catalytic domain and the carboxy-terminal regulatory domain. The PH domain primarily mediates membrane translocation following AKT activation; the catalytic domain contains ATP binding sites. Activation of AKT is dependent on the phosphorylation of its internal Thr308 site; the regulatory domain at the carboxy terminus contains a large amount of proline, containing another phosphorylated Ser473 site required for AKT activation (26-28). In the classical PI3K/AKT activation mode, AKT and the upstream 3-phosphoinositol-dependent protein kinase-1 (PDK1) are recruited into the cell membrane via the interaction of the PH domain with PtdIns (3-5) P3 (PIP3) in PI3K, and phosphorylation of AKT by activation of the Thr308 site in the T-loop by PDK1 (29). The activated phosphorylated AKT is transported from the cell membrane to other regions of the cell to phosphorylate multiple downstream substrates to achieve AKT function (30). Phosphorylation of AKT is considered to be isoform-specific (31). Furthermore, activation and stabilization of AKT is regulated by the phosphorylation of multiple sites, apart from the two major sites, Thr308 and Ser473. AKT1 has 31 potential phosphorylation sites, AKT2 has 22 phosphorylation sites, and AKT3 has 18 phosphorylation sites; with future studies, the number of potential phosphorylation sites for AKT may increase even further.

The PI3K/AKT signaling pathway is frequently in a dysregulated state in tumors, and has now become an important anticancer target (32). The PI3K/AKT signaling pathway itself serves a major role in regulating cell physiology and pathology, including cell proliferation, survival and invasion (Fig. 1). Some of the activating mutations in PI3K/AKT are also common in human tumors, and thus may promote tumor growth (2,33). Additionally, the replacement of E17K by a single amino acid in the PH domain of AKT results in the recruitment of constitutive AKT to the cell membrane (34). Therefore, in recent years, drug targets for PI3K or AKT have been widely developed and clinical trials have been conducted. It follows that the PI3K/AKT signaling pathway is closely associated with tumor development and has garnered much attention.

3. Association between PI3K/AKT and endometrial cancer

Specifically, >80% of endometrial cancer cases have at least one somatic alteration that affects signaling pathways, and the PI3K/AKT signaling pathway is one of the most frequently altered biochemical pathways in endometrial cancer (35). Statistics indicate that ~90% of young endometrial cancer patients have high progesterone receptor expression and exhibit resistance to progesterone therapy (36), and it has also been demonstrated that high activation of the PI3K/AKT/mechanistic target of rapamycin kinase (mTOR) signaling pathway is essential for the progression of endometrial cancer (37). When inhibiting the phosphorylation of mTOR, it has a marked inhibitory effect on the proliferation of endometrial cancer (38). In addition, studies have suggested that the dysregulation of mTOR in primary endometrial cancer may also be associated with the loss of TSC complex subunit 2 (TSC2) and serine/threonine kinase 11 (LKB1) expression (39). Other studies also demonstrated that activation of mTOR complex 2 (mTORC2) and the phosphorylation of AKT are also upregulated in endometrial cancer, suggesting that the rapamycin-insensitive mTORC2 pathway may be involved in the development of endometrial cancer (40). These conclusions suggest that the PI3K/AKT signaling pathway serves a key role in endometrial cancer.

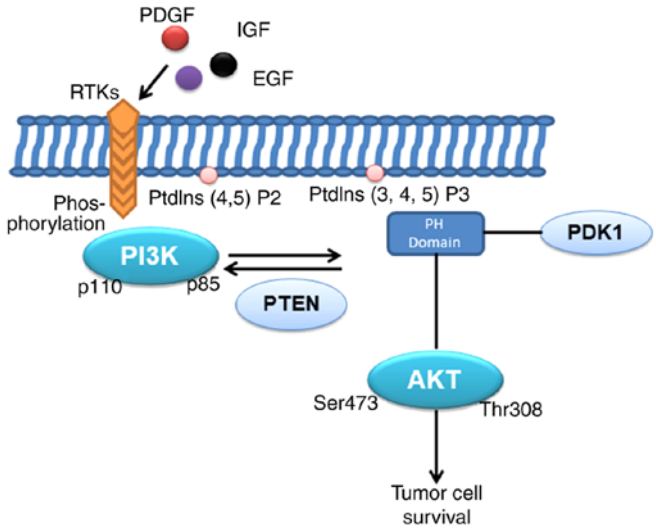

Figure 1. Schematic of the PI3K/AKT signaling pathway. RTK recruits PI3K following activation and phosphorylation, and phosphorylates PtdIns (4,5) P2 to PtdIns (3-5) P3, which activates AKT by recruiting PDK1 to the PH domain of AKT, thereby activating the entire pathway and regulating cell growth. PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; RTK, receptor tyrosine kinase; PtdIns, phosphatidylinositol; PDK1, 3-phosphoinositol-dependent protein kinase-1; PH, plekstrin homology; PTEN, phosphatase and tensin homolog; PDGF, platelet derived growth factor; IGF, insulin-like growth factor; EGF, epidermal growth factor.

According to the molecular spectrum of endometrial cancer reported by The Cancer Genome Atlas in 2013 (41), four major molecular spectra were analyzed and identified in the genome, transcriptome and proteome based on array and sequencing technology: DNA polymerase-ε (POLE; super mutation), microsatellite instability (hypermutation), low copy number (endometrioid) and high copy number (serous). In general, the mutation rates of PI3KCA, PIK3R1, AKT1 and PTEN in endometrial cancer in all cases collected were 59.7, 33, 3.2 and 66%, respectively, and the PIK3R1, AKT1 and PTEN mutation rates in the POLE group were the highest, reaching 94, 71 and 65%, respectively.

An important negative regulator in the PI3K pathway is PTEN, which is located on chromosome 10q23 and encodes a protein with tyrosine kinase functions (42). PTEN has lipid and protein phosphatase activity, which leads to cell cycle arrest at the G2/S checkpoint and inhibits PI3 phosphorylation by dephosphorylation of PIP3 to phosphatidylinositol 4,5-bisphosphate, leading to a decrease in intracellular PtdIns levels and affecting downstream AKT signaling pathways (43); simultaneously, the PTEN-encoded protein phosphatase inhibits cell proliferation and migration, and thus the loss of PTEN activity may result in abnormal cell growth and apoptosis escape. Inactivation of PTEN may be due to gene mutations, promoter methylation or protein degradation, leading to loss of expression or a mild loss of heterozygosity (44-48). However, according to statistics, 20% of cases of endometrial hyperplasia, 55% of precancerous lesions, and 35-80% of endometrial cancer cases have PTEN mutations (49). The molecular mechanisms involved in PTEN mutations may further suggest that the PI3K/AKT signaling pathway is involved in the early events of endometrial cancer and promotes the conversion of precancerous lesions into tumors.

4. Association between PI3K/AKT and cervical cancer

The presence of AKT hyperphosphorylation in cervical cancer specimens suggests a constitutive activation of the PI3K/AKT pathway in cervical cancer (50). The existence of an association between HPV and cervical cancer has long been under consensus, and mTOR inhibitors blocked the phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 and markedly reduced the expression level of human papillomavirus E7 protein in an *in vitro* model, leading to the aggregation of cells in the G1 phase and the induction of apoptosis (51). Moreover, studies have reported that changes in genes related to the PI3K/AKT pathway are associated with an incomplete metabolic response following chemoradiation in cervical cancer, and that PIK3CA-activating mutations are associated with long-term survival post-radiotherapy (52,53). The most common PIK3CA mutation in cervical cancer is in E545K, a tumor-associated mutation site in the helical domain of the p110α catalytic subunit of PI3K, which may lead to constitutive PI3K activation and enhance tumorigenicity (54-56). C420R in PIK3CA may also induce oncogenic conversion by promoting the membrane binding of p110α (57). Activation of the PI3K/AKT pathway is ubiquitous in various cancer types, and the carcinogenic effects of PIK3CA mutations have been widely accepted as evidence for preclinical diagnosis; however, the PIK3CA mutation is not effective as a biomarker in obese patients with cervical cancer, which may be due to obesity-associated factors affecting the transduction of relevant molecules in the PI3K signaling pathway (58,59).

Currently, ~99% of cases of cervical cancer are caused by high-risk HPV (60), and HPV E7 and E6 oncoproteins are essential for promoting cervical cancer. Carcinogenic HPV E6 also rapidly degrades TSC, causing TORC1 and mTOR signaling downstream of PI3K/AKT to be activated (61). Similarly, the tumor suppressor gene LKB1 has been demonstrated to be defective in cervical cancer HeLa cells, and inhibits mTOR by TSC2 stimulation, and the activation of the PI3K/AKT pathway has been observed in cervical cancer cell lines and immunodeficient mouse xenograft models (62). In a Phase I study, PI3K mutations were observed in 15 patients with cervical cancer, 5 of whom experienced significant treatment efficacy with drugs targeting the PI3K/AKT/mTOR pathway. Rashmi *et al* (53) reported that the mutational profile of the PI3K/Akt signaling pathway in cervical cancer tissues is complex; the use of AKT inhibitors to effectively inhibit mTORC1/2 may reduce glucose absorption and glycolysis, and decrease cell viability *in vitro*, thereby increasing the chemosensitivity of cervical cancer. Human cervical cancer oncogene 1 (HCCR-1) is composed of 9 exons and a conserved intron/exon, which is abnormally expressed in cervical cancer cells, contains a TATA box and a CAAT box, and is identified as the putative DNA binding site of TCF/LEF-1 (63). To determine the function of PI3K on the HCCR promoter, a vector containing pCDNA3-PI3K was transfected into NIH/3T3 cells, and the promoter activity in PI3K-transfected cells was 1.72 times that of cells transfected with the vector alone. Additionally, vectors containing wild-type AKT and dominant-negative AKT cDNA were transfected into K562 cells, and the results indicated that wild-type AKT enhanced HCCR-1 promoter activity (64). These data indicated that

alterations in the PI3K/AKT signaling pathway affect HCCR expression, and HCCR is one of the downstream components of the PI3K/AKT pathway, further indicating that the PI3K/AKT signaling pathway affects the development and progression of cervical cancer.

5. Association between PI3K/AKT and ovarian cancer

Ovarian cancer is a type of malignancy that poses a serious threat to female health worldwide, according to recent statistics (65,66). In general, the PI3K/AKT signaling pathway is dysregulated in ovarian cancer, and ~12% of ovarian cancer cases present with mutations in PIK3CA (67,68). High-grade serous ovarian cancer is the most important subtype of ovarian cancer, and ~50% of patients have activations inPIK3CA. In addition, mutations in PI3K also appear to be associated with the histology of ovarian cancer. In cases analyzed previously, 20% had amplifications in PIK3CA, and 5% of the three AKT subtypes presented with PTEN deletion (67,69). Studies in a mouse model have demonstrated that ovarian cancer is triggered by the activation of PIK3CA mutations and a PTEN deletion, and that inhibition of PI3K/mTOR may prolong tumor growth and survival. The expression levels of p-AKT and PIK3CA are associated with ovarian cancer survival, and the activation status of the PI3K/AKT pathway is considered to be an independent prognostic marker in ovarian cancer (as measured by AKT and mTOR phosphorylation levels) (70,71); PIK3CA mutations predict the response to PI3K and mTOR inhibitors (72). A study also reported that alterations in the gene copy number of the catalytic subunits p110α and p110β of PI3K are associated with poor prognosis in ovarian cancer (73).

Polycyclic aromatic hydrocarbons, which are environmental toxins, are known to be reproductive toxins, which cause primary follicle atresia and premature ovarian failure. It has been reported that treatment with the PI3K inhibitor LY294002 may prevent follicular atresia (74). In the face of toxic follicle destruction, follicles attempt to induce cell survival by upregulating the PI3K/AKT/mTOR pathway, which in turn leads to increased follicle proliferation, consuming reserves of primitive ovarian follicles (75). Therefore, the PI3K/AKT/mTOR pathway in ovarian cancer may be used as a predictor of damage to primordial follicles during normal oocyte maturation (75). The function of the PI3K/AKT pathway in ovarian cancer is very complex, with two major alterations: Various alterations in the PI3K/AKT pathway itself, and different effects on the PI3K/AKT pathway. Through these modifications, PI3K/AKT has been demonstrated to serve a key role in ovarian cancer development, progression and chemoresistance. This complexity, which begins with PI3K/AKT dysregulation, may be due to overactivation and mutations in the catalytic domain and regulatory domain mutations, or the modification of downstream targets of PI3K (76). In the development and progression of ovarian cancer, it is clear that the PI3K/AKT pathway serves an important role in the complex phenotype of ovarian cancer in unique ways, many of which may be highly invasive. In serous carcinoma or low-grade endometrial ovarian cancer, mutations in the pathway may contribute to cell proliferation, invasion and migration by modifying cell cycle inhibitors and matrix metalloproteinases (77).

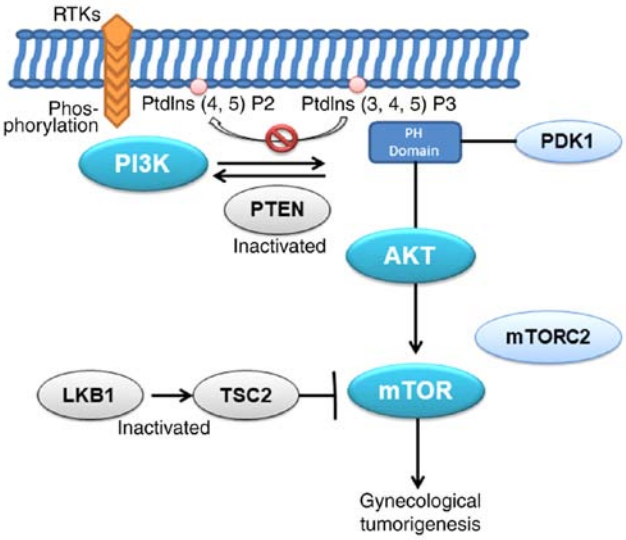

Figure 2. Effect of the PI3K/AKT signaling pathway on gynecological tumors. By inactivating PTEN, LKB1 and other regulatory factors, the phosphorylation levels of associated molecules in the PI3K/AKT pathway are altered, and the activity of downstream mTOR is further changed, thereby triggering the occurrence of gynecological cancer. PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; RTK, receptor tyrosine kinase; PtdIns, phosphatidylinositol; PDK1, 3-phosphoinositol-dependent protein kinase-1; PH, plekstrin homology; PTEN, phosphatase and tensin homolog; LKB1, serine/threonine kinase 11; TSC2, TSC complex subunit 2; mTOR, mechanistic target of rapamycin kinase; mTORC, mTOR complex 2.

6. Current status of treatment for the PI3K/AKT signaling pathway

To date, various PI3K-associated inhibitors with isomeric properties have been tested in various tumors, although a number of these drugs have not yet been used in clinical practice, including GDC0941, XL147, BKM120, NVP-BYL719 (p110α specificity), SAR260301 (P110β specificity) and TGR-1202 (p110β specificity) (12,78). PI3K and mTOR are structurally similar, and there are currently many studies in progress on dual inhibitors of PI3K and mTOR, such as NVP-BEZ235, GDC-0980 and XL765, which may be able to overcome the limitations of single kinase inhibition via the feedback loop (12,78-80). In addition, different AKT subtypes mediate different pathophysiological changes in tumors, including AKT1, which primarily mediates tumorigenesis and early development, whereas AKT2 appears to primarily promote tumor metastasis (81,82). Thus the investigation of specific inhibitors of AKT isoforms is also a promising strategy for the treatment of tumors. Up to now, the standard drugs targeting the PI3K/AKT pathway, widely used in clinical practice, have been downstream mTOR blockers, including temsirolimus and everolimus. Comprehensive clinical studies have demonstrated that the overall efficiency of mTOR blockers varies from 4-24% (83). In clinical trials of ovarian cancer, it was reported in five cases that sirolimus may be more effective in the treatment of clear cell ovarian cancer (84). The second generation of mTOR blockers is also under development. It is reported that second-generation mTOR blockers contain two protein complexes, TORC1 and TORC2, which simultaneously inhibit mTORC1 and mTORC2, thereby reducing the influence of negative feedback AKT phosphorylation; with this, the therapeutic effect is likely to be better, and less resistance will

occur (85). With ongoing research, the prospect of drug targets for the PI3K/AKT pathway is becoming a focus for tumor treatment.

With the development of new knowledge, in addition to the aforementioned more classical mTOR inhibitors, the targeted treatment of PI3K/AKT has been gradually enriched. Previous studies have identified multiple genetic alterations in gynecological tumors, including PTEN loss, ARID1A mutations, ERBB2 overexpression, and the mutation of PI3K/AKT (86). Excessive activation of PI3K/AKT may produce resistance to tumors, including endometrial cancer, targeting RTK inhibitors of EGFR and VEGF, thus drug sensitivity increases markedly following targeted reduction of this resistance (87-89). Targeted inhibitors of PI3K, BKM120 and MK-2206, have demonstrated antitumor activity, while MK-2260 exhibits limited single-agent activity in wild-type and mutant PIK3CA, and this positive role is undoubtedly encouraging (90). In addition, comprehensive genomic analysis of metastatic cervical cancer has produced important findings for the identification of novel therapeutic targets and the targeted treatment of cervical cancer; studies have demonstrated that the use of FGFR tyrosine kinase inhibitors in patients with FGFR3-TACC3 fusion expression has achieved good results and it has been suggested that FGFR3-TACC3 gene fusion activation is associated with the HPV-induced carcinogenesis-related FGFR pathway, and these molecular alterations involve the PI3K/AKT/mTOR and RAF proto-oncogene/MEK pathways (91,92). Since 2012, CRISPR has been an active part of cancer research as a powerful gene editing technique, used for cutting target DNA. Studies have demonstrated that in PTEN wild-type endometrial cancer cells, the use of CRISPR/Cas9 to cut PTEN, as a negative regulator of PI3K/AKT, may enhance the inhibition of cells by a combination of PARP/PI3K (93); this reveals that CRISPR/Cas9 may be a useful technology in cancer therapy.

7. Conclusion

PI3K/AKT is one of most important signal transduction pathways, which is involved in cell proliferation, cell cycle regulation, apoptosis and other relevant pathophysiological processes, and serves a key role in the occurrence and development of tumors (Fig. 2). Therefore, it is feasible that relevant drug molecules may be used to block or inhibit the PI3K/AKT signaling pathway to facilitate the identification of anti-tumor targets. The specific function of each molecular site and domain of the pathway in different tumors remains obscure and requires investigation in future research; however, targeted drugs for each subunit and site have gained further development and verification. With the deepening elucidation of the underlying mechanism by numerous studies, it is considered that drug targets for the PI3K/AKT signaling pathway will become effective clinical therapeutic approaches in cancer prevention and treatment.

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Authors' contributions

XZ and DT designed the theme of the review. JW, YL and CC retrieved the relevant literature. XS wrote and reviewed the article.

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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