PTEN gene and AKT/mTOR pathway in gynecological cancers and cancer immune escape

Xi Zeng¹,², Ming-Rong Xi¹,², Hong-Wei Ma¹,²,*

¹Department of Gynecology and Obstetrics, The West China Second University Hospital, Sichuan University, 610000 Chengdu, Sichuan, China
²Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, 610000 Chengdu, Sichuan, China

*Correspondence
mahongwei1024@foxmail.com
(Hong-Wei Ma)

Abstract

Gynecological cancers (GCs) include cervical, uterine, ovarian, vulvar and vaginal cancer. For women in China, 2 of the 10 most common cancers are GCs (8th: cervical cancer, incidence rate: 3.96%; 10th: ovarian cancer, incidence rate: 2.91%). These cancers can lead to enormous psychological and economic burdens. Phosphatase and tensin homolog (PTEN) gene and protein kinase B (Akt) and mammalian target of rapamycin (mTOR) pathway are widely involved in the development of GCs, and an imbalance in regulatory T cells (Treg) in the cancer micro-environment mediated by PTEN and Akt/mTOR pathway was shown to lead to cancer cell immune escape, growth and metastasis. Considering that the pathogenesis of PTEN and Akt/mTOR pathway in GCs and cancer immune escape remains unclear, this review article intends to provide an update in this field. We made a comprehensive search of several databases, including Web of Science, MEDLINE, Ovid and Cochrane Database of Systematic Reviews, was conducted from inception to March 2022. The search strategy included the combinations of the following medical terms: gynecological cancers, cervical cancer, uterine cancer, ovarian cancer, vulvar cancer, vaginal cancer, PTEN gene, AKT/mTOR pathway, and cancer immune escape. We found that currently the mechanism of the PTEN gene and Akt/mTOR pathway in GCs is not fully clear. However, the activation of the Akt/mTOR signaling pathway and imbalance of Treg cell in the micro-environment caused by the function loss of PTEN is involved in the occurrence and development of GCs, and related to the prognosis of patients. This review article presented the latest research progress on the PTEN gene and AKT/mTOR pathway in GCs and cancer cell immune escape.

Keywords
PTEN/AKT-mTOR pathway; Malignant gynecological cancers; Tumor microenvironment; Immune escape; Signaling pathways

1. General introduction of gynecological cancers

In recent years, cancer has become the leading cause of death among city residents and the second cause of death among rural residents, making it a stark public health issue in China [1]. As the most populous country in the world, China has more than 700 million females, accounting for approximately one-fifth of women worldwide [2]. Gynecological cancers (GCs) include cancers of the cervix, uterus, ovaries, vulva and vagina. For women in China, 2 of the 10 most common cancers are GCs (8th: cervical cancer, incidence rate: 3.96%; 10th: ovarian cancer, incidence rate: 2.91%) [1,3]. These cancers contribute to enormous psychological and economic burdens worldwide. Presently, the main treatment method for most GCs is surgery. However, surgical treatment may not be possible for patients unfit for surgery, those with desire for fertility preservation, or patients with advanced-stage disease. Simultaneously, other treatments such as chemotherapy and hormonal therapy have their potential limitations. Therefore, studying the mechanism of tumorigenesis could help identify potential bio-therapeutic targets for improving the treatments of GCs.

Cancer occurrence involves the interaction among genetic factors, micro-environment and inflammatory cells [4]. Cancer cells are equipped with abilities to allow immortal proliferation, active energy metabolism, tissue infiltration and metastasis [5]. The phosphatase and tensin homolog (PTEN) and the AKT/mTOR pathway are among the most important immuno-suppressive signal axes for regulating cancer growth and immune tolerance [6]. In various malignant cancers, the inactivation or lack of expression of PTEN was shown to activate the AKT/mTOR pathway, enhance cancer cell proliferation, and promote cancer immune escape [7]. Thus, mechanisms relating to cancer proliferation and immune escape may provide new methods for immuno-target therapy. Therefore, this review provides an update on PTEN and the AKT/mTOR pathway; Malignant gynecological cancers; Tumor microenvironment; Immune escape; Signaling pathways
2. Introduction of PTEN gene and AKT/mTOR pathway

The PTEN gene was first discovered in 1997 [8]. It is located at 10q23.3, with a full length of 200 kb, containing 9 exons and 8 introns [9]. The PTEN protein comprises 403 amino acids encoded by 1209 nucleotides, with protein phosphatase and lipid phosphatase activities. The phosphatase domain is located at the N-terminus, accounting for 1/2 of the entire molecule [8], and has the ability to (1) inhibit cell growth, colonization and inducing cell apoptosis, (2) participate in cell adhesion, migration and diffusion, (3) inhibit angiogenesis, (4) participate in endoderm and the differentiation of germ layer and ectoderm, and (5) regulate metabolism and aging [10].

The protein kinase B (PKB), also known as AKT, is a serine/threonine-protein kinase with a molecular weight of 57 kDa. The AKT acting methods can be divided into phosphoinositide 3-kinase (PI3K) dependent and independent ways. The dependent way requires the activation of PI3K to phosphorylate AKT, while the non-dependent way is regulated by the binding of AKT through calmodulin [11]. The activated AKT can phosphorylate a series of substrates, affecting cell physiological processes such as cell proliferation, differentiation, apoptosis, metabolism, angiogenesis, cell cycle, etc. [12]. Previous studies have shown that the AKT gene may be mutated, activated or amplified in ovarian, colon, stomach, breast and lung cancers and malignant glioma [13].

The mammalian target of rapamycin (mTOR) was first discovered in 1994 and is classified as a phosphatidylinositol kinase-related kinase (PIKK) family member [14]. It is one of the important substrates of AKT and has a serine/threonine kinase containing 2549 amino acids with a molecular weight of 289 kDa [14]. The PIKK family members are widely involved in cell growth, cycle regulation and other processes. The mTOR can accept a variety of signals, including growth factors, nutrition and energy and is a key regulator of cell growth and proliferation [15,16]. There are at least two mTOR complexes in cells: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Raptor is the main regulatory protein of mTORC1 and can be controlled by signals such as energy and nutrition, and is sensitive to rapamycin. Independent companion of mTOR complex 2 (RICTOR) is the main regulatory protein of mTORC2 and is insensitive to rapamycin [15]. Although there is no clear consensus on the biological role of the two regulatory proteins, the basic viewpoint is that both are involved in cancer growth regulation [17]. mTORC1 can promote mRNA translation, protein synthesis and degradation, lipid synthesis, energy metabolism, and participate in cell autophagy to maintain micro-homeostasis [18]. mTORC2 can activate AKT by phosphorylating the serine 473 site of AKT to promote the growth of cancer cells [19].

3. The signal mechanism of PTEN gene and AKT/mTOR pathway in cancers

At present, it is believed that there are four main signal mechanisms for PTEN’s anticancer effects, including the AKT/mTOR pathway, the mitogen-activated protein kinase (MAPK) pathway, the focal adhesion kinase (FAK) pathway and the cyclin pathway [20].

In the PTEN and AKT/mTOR pathway, AKT is a proto-oncogene negatively regulated by PTEN [21]. PTEN can dephosphorylate the phosphoinositol of 3-hydroxyinositol and block the AKT/mTOR signaling pathway. Activation of the PI3K/AKT pathway either by PTEN-loss mutation or AKT-activating mutation might be sufficient to initiate tumorigenesis [22]. The main enzyme in the PI3K/AKT pathway is PI3K. It can convert phosphatidylinositol (4,5) bisphosphate (PIP2) into phosphatidylinositol (3,4,5) bisphosphate (PIP3), which in turn activates AKT. Conversely, a loss of function in PTEN may accelerate cell proliferation and inhibit cell apoptosis [23]. Thus, PTEN and AKT/mTOR pathway play a critical role in embryonic development, cell migration, cell apoptosis, signal transduction and other physiological processes [24]. It was reported that in cancer cell lines when AKT is activated, mTOR can be activated by the phosphorylation or inhibition of tuberous sclerosis complex 1 (TSC1) or tuberous sclerosis complex 2 (TSC2) dimer [25]. Then, the AKT protein can be regulated by the RICTOR/mTOR to promote cancer cell growth [26].

Moreover, PTEN protein is equipped with tyrosine phosphatase activity and lipid phosphatase activity, which can inhibit FAK by antagonizing the activity of tyrosine kinase and other phospholipases, reduce FAK phosphorylation, mediate cell transfer and growth, restrain growth factor receptor-bound protein 2 (GRB2) and activate the protein kinase of MAPK. The increased phosphorylation of FAK and MAPK can further promote metastasis [27]. Therefore, the PTEN and AKT/mTOR pathway can regulate cancer cell adhesion, infiltration, migration, differentiation, development, survival, and proliferation (Fig. 1).

4. Abnormal expression of PTEN/AKT/mTOR in gynecological cancers

Abnormal expressions of PTEN/AKT/mTOR have been found in GCs, which are hypothesized to be the pathway involved in cancer occurrence, leading to out-of-control cell proliferation and metabolism and resistance to apoptosis [20]. Some clinical trials investigating the role of different mTOR inhibitors also indicated that targeting mTOR alone could lead to unsatisfactory outcomes in GC [28].

Cancer of the corpus uteri, commonly called endometrial cancer, is the second most common cancer of the female genital system in China [1]. The mutation rate of the PTEN gene is about 20% in patients with endometrial atypical hyperplasia and about 83% in endometrial cancer, but it is seldom mutated in the normal population, suggesting that loss of PTEN function may be an early event in endometrial cancer [29, 30]. The degree of mutation is closely related to the stage
PI3K activation may occur via RAS mutation by loss of PTEN. Activation of the PTEN/AKT/mTOR pathway can increase mTOR secretion, modulating cell survival, migration, growth, progression, and metabolism. (GPCR: G protein-coupled receptor; RAS: rat sarcoma; BAD: Bcl-2associated death promoter; NFκB: nuclear factor kappa-B; GSK3: Glycogen synthase kinase-3; FOXO: factor forkhead box O; SGK: Serum and Glucocorticoid Induced Kinase; PKC: protein kinase C; eIF4: eukaryotic initiation factor 4; Bim: BCL2-Like 1)

of carcinogenesis [31]. A statistically significant decrease and difference in the expression of the PTEN gene was observed from normal endometrium and endometrial hyperplasia to endometrial cancer tissues [32]. Zheng et al. [30] showed that miR-206 could exert a carcinostatic effect on endometrial cancer by targeting histone deacetylase 6 (HDAC6) via the PTEN/AKT/mTOR pathway. In animal research experiments, mice with heterozygous deletion of PTEN (PTEN+/−) were shown to develop endometrial atypical hyperplasia, which could progress to well-differentiated endometrial cancer [33]. By using the Cre-LoxP system to knock out the PTEN gene in mouse endometrium, endometrial cancer was successfully generated after one month and invaded the myometrium within three months [34]. In addition, mice with knocked out PTEN gene were more sensitive to mTOR inhibitors [35], which could significantly delay the development of endometrial cancer [36].

In ovarian cancer, PTEN mutations and deletions were found to be mainly related to ovarian endometrioid carcinoma and epithelioid carcinoma; and the levels of PTEN are significantly lower than in normal or benign cancer tissues [37, 38]. In later clinical stages, lower expressions of PTEN were detected, and PTEN expressions were positively correlated with the degree of differentiation of ovarian cancer [39]. It was also found that loss of PTEN expression mostly occurs in advanced-stage ovarian cancer and could be used as a prognostic marker for ovarian cancer [40].

In cervical cancer, the change of PI3K/AKT/mTOR pathway molecules in cervical cancer lesions showed that the p-PI3K, p-AKT and mTOR protein levels in cervical cancer lesion tissues were significantly higher than in adjacent lesion tissues and cervical intraepithelial neoplasia tissues [40]. In normoxic cells, activated mTORC1 signaling could regulate the senescence efficacy of experimental E6/E7 inhibition [41]. Under hypoxia, human papillomavirus (HPV) positive cancer cells could evade senescence due to hypoxic impairment through the mTORC1 signaling. Hypoxic repression of E6/E7 is mediated by the AKT kinase, which is ac-
In vulvar cancer, the downstream component of the AKT cascade, mTOR was found to be widely expressed in most vulvar cancer samples in immunohistochemical staining [28]. In vitro experiments showed that mTOR inhibitors of rapamycin, everolimus and AZD2014 could significantly inhibit the proliferation of vulva cancer cell lines of celsalssorus-39 (CAL-39) and SW-954 [44]. Therefore, the inhibition of the PTEN/AKT/mTOR pathway could be a promising therapeutic strategy in managing vulvar cancer patients.

5. Abnormal expression of PTEN/AKT/mTOR in cancer immune escape

5.1 Brief introduction to cancer microenvironment

The cancer microenvironment, where the cancer is located during the developmental process, consists of cancer cells, infiltrating immune cells, new blood vessels, endothelial cells, tissue fluid and cancer-related fibroblasts [45]. The immune cells and inflammatory factors in cancer stroma can maintain the balance of the cancer host microenvironment [46]. When carcinogens stimulate the stromal cells in the cancer microenvironment, the expressions of cadherin and regulatory cells in cancer are reduced, making the cancer cells easier to invade surrounding tissues. Based on the interaction between cancer cells and stromal cells, the primary cancer can continue to proliferate, invade and metastasize [47].

5.2 PTEN/AKT/mTOR pathway and Treg in immune escape

CD4+ T cells are important components in the induction and maintenance of peripheral immune tolerance. According to their surface markers, CD4+ T cells can be divided into two subtypes: T helper type 1 (Th1) cells, which are mainly involved in cellular immunity and secrete interleukin-12 (IL-12), interferon-β (IFN-β), IFN-γ, etc., and T helper type 2 (Th2) cells, which are mainly involved in humoral immunity and secrete IL-4, IL-5, IL-6, IL-19, IL-13, etc. [48]. In the cancer microenvironment, cancers can significantly inhibit the cancer-associated antigen (TAA) specific immune responses through CD4+ T cells, allowing them to escape immune surveillance and continue to develop [49].

At present, regulatory T cells (Treg) are recognized as the most representative cell group with negative immune regulation function among CD4+ T cells, which can promote cancer growth and immune escape [48].

The precise suppressive mechanisms of Tregs in the tumor immunity are not fully defined. In vitro and in vivo studies on the functions of Treg cells indicated that Tregs might use multiple mechanisms to target various immune cells, including the effector T cells, natural killer cells and dendritic cells [50]. Treg can regulate immune escape by (1) regulating inhibitory cytokines such as IL-10, IL-35, and transforming growth factor β (TGF-β), (2) regulating perforin and granzyme to lyse cells, (3) introducing the inhibitory second messenger cyclic adenylic acid (cAMP) into target cells through the intercellular space, acting adenosine A2a receptor on the surface of effector T cells and destroying cell metabolism, and (4) regulating the molecular interaction between cell surface molecules and the surface of antigen-presenting cells, reducing the number of activated T cells and exerting immunosuppression effects [51, 52].

In research involving human endometrial cancer specimens, the proportion of Treg cells in the peripheral blood and cancer-infiltrating lymphocytes was found to be significantly increased and related to cancer stages [53]. In the endometrial cancer tissues, the levels of CD4+ T cells and transcription factor forhead box p3 (FOXP3) were negatively correlated with the prognosis of the patients [54]. However, unlike autoimmune diseases, the inhibitory effects of Treg cells on TAA-specific immune response were due to the decrease in the number of T cells rather than simply the enhancement of T cell inhibitory ability [54].

Studies on other GCs also confirmed a significant increase in the proportion of Treg cells in the peripheral blood of patients, suggesting that these elevated Treg cells could inhibit TAA-specific immune responses in cancer patients [55]. In the human chimeric model of severe combined immunodeficiency (SCID), the number of Treg cells in the micro-environment of ovarian cancers was shown to be increased, which could promote cancer growth by inhibiting TAA-specific responses [56] and was significantly related to poor prognosis [57]. Treg cells were found to be significantly up-regulated with high expressions of AKT/mTOR pathway molecules [49]. The integrity of the PTEN gene function plays an important role in maintaining the homeostasis of CD4+ T cells [57]. CD4+ T cell proliferation and serum autoantibodies were found to be increased in nude mice lymphoma models with specific T cell PTEN gene mutations and had enhanced lymphoma cell migration and proliferation ability [58]. It was also reported that cancer could enhance the ability to resist apoptosis, increase autoantibodies and produce hypergammaglobulinemia [59], suggesting that the PTEN gene played an indispensable role in the growth and homeostasis regulation of CD4+ T cells [57].

The above studies indicate that the PTEN/AKT/mTOR pathway can participate in the regulation of Treg cells in the cancer microenvironment. The absence of PTEN can cause serious defects in T cells, reduce the number of Treg cells, disrupt the body’s immune tolerance state, and break the body’s anticancer immune response ability [57, 60].

6. Conclusion

The occurrence and development of cancer occur through complex processes. The activation of the AKT/mTOR signaling pathway and imbalance of Treg cells in the micro-environment
caused by the loss of function of PTEN is involved in the occurrence and development of GCs and affects the prognosis of the patients. Thus, the inhibition of the PTEN/AKT/mTOR signaling pathway in GCs and maintaining the balance of Treg cells in the microenvironment are worthy of further research as new strategies for the immunotherapy of GCs.

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XZ—Project development, Literature Collection, Manuscript writing, Funding obtaining; MRX—Literature Collection, Critical revision of the manuscript, Supervision, Funding obtaining; HWM—Project development, Literature Collection, Critical revision of the manuscript, Supervision. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
Not applicable.

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CONFLICT OF INTEREST
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