

MINI-REVIEW

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

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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 in GCs.

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 downstream molecule of the *PTEN* gene. Mature 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 phosphorylases, 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

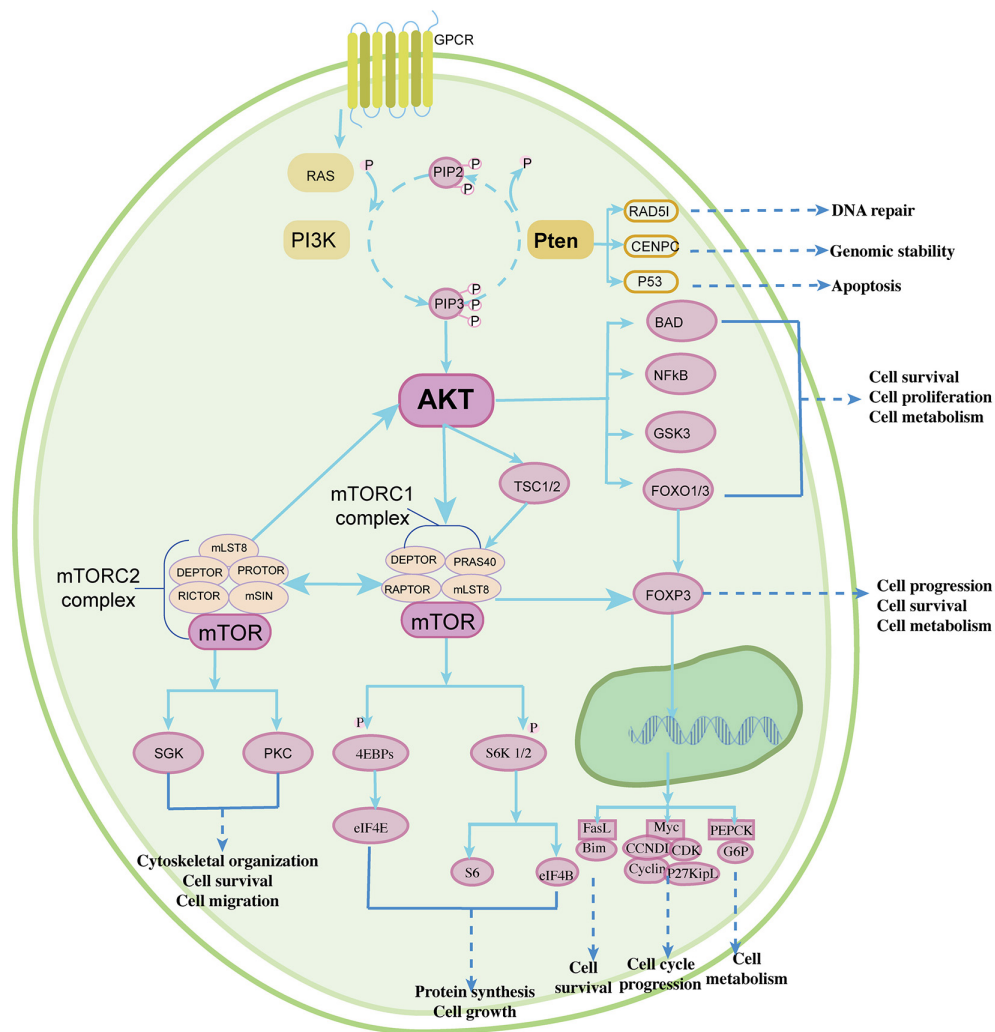


FIGURE 1. *PTEN* and AKT/mTOR pathway model in a cancer cell. PI3K activation may occur via RAS mutation by loss of *PTEN*. Activation of the *PTEN*/AKT/mTOR pathway can increase mTOR secretion, modulating cell survival, migration, growth, progression, and metabolism. (GPCR: G protein-coupled receptor; RAS: rat sarcoma; BAD: Bcl-2-associated death promoter; NF κ B: 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 11)

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-

tivated under hypoxia by its canonical upstream regulators mTORC2 and PI3K [41], indicating that the over-activation of the PI3K/AKT/mTOR pathway in local lesions could be closely related to the occurrence of cervical cancer [42]. The expression of *PTEN* was shown to relate to clinical stage and cancer size, and was negatively correlated with lymph node metastasis, while the expression of AKT/mTOR was positively correlated with lymph node metastasis [43].

In vulvar cancer, as a 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 cellosaurus-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 forkhead 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.

AUTHOR CONTRIBUTIONS

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.

ACKNOWLEDGMENT

We would like to express my gratitude to all those who helped me during the writing of this manuscript. Thanks to all the peer reviewers for their opinions and suggestions.

FUNDING

This work was supported by the National Natural Science Foundation of China (No.81572573), the National Natural Science Foundation of China (No.61875249), Key Research Development Projects of Sichuan Province (No.2020YFS0129) and New Bud Research Funding of West China Second Hospital, Sichuan University (No.Kx246).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Jiang X, Tang H, Chen T. Epidemiology of gynecologic cancers in China. *Journal of Gynecologic Oncology*. 2018; 29: e7.
- [2] He R, Zhu B, Liu J, Zhang N, Zhang W, Mao Y. Women's cancers in China: a spatio-temporal epidemiology analysis. *BMC Women's Health*. 2021; 21: 116.
- [3] Zheng R, Sun K, Zhang S, Zeng H, Zou X, Chen R, *et al*. Report of cancer epidemiology in China, 2015. *Chinese Journal of Oncology*. 2019; 41: 19–28. (In Chinese)
- [4] Armeth B. Tumor microenvironment. *Medicina (Kaunas)*. 2020; 56: 15.
- [5] Pietras K, Östman A. Hallmarks of cancer: interactions with the tumor stroma. *Experimental Cell Research*. 2010; 316: 1324–1331.
- [6] Song N, Zhang T, Xu X, Lu Z, Yu X, Fang Y, *et al*. miR-21 protects against ischemia/reperfusion-induced acute kidney injury by preventing epithelial cell apoptosis and inhibiting dendritic cell maturation. *Frontiers in Physiology*. 2018; 9: 790.
- [7] Vidotto T, Melo CM, Castelli E, Koti M, Dos Reis RB, Squire JA. Emerging role of *PTEN* loss in evasion of the immune response to tumours. *British Journal of Cancer*. 2020; 122: 1732–1743.
- [8] Li J, Yen C, Liaw D, Podsypanina K, Bose S, Wang SI, *et al*. *PTEN*, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science*. 1997; 275: 1943–1947.
- [9] Wang Y, Liu Y, Du X, Ma H, Yao J. Berberine reverses doxorubicin resistance by inhibiting autophagy through the PTEN/Akt/mTOR signaling pathway in breast cancer. *OncoTargets and Therapy*. 2020; 13: 1909–1919.
- [10] Ortega-Molina A, Serrano M. *PTEN* in cancer, metabolism, and aging. *Trends in Endocrinology & Metabolism*. 2013; 24: 184–189.
- [11] Akca H, Demiray A, Tokgun O, Yokota J. Invasiveness and anchorage independent growth ability augmented by *PTEN* inactivation through the PI3K/AKT/NFκB pathway in lung cancer cells. *Lung Cancer*. 2011; 73: 302–309.
- [12] Jiang N, Dai Q, Su X, Fu J, Feng X, Peng J. Role of PI3K/AKT pathway in cancer: the framework of malignant behavior. *Molecular Biology Reports*. 2020; 47: 4587–4629.
- [13] Liu R, Chen Y, Liu G, Li C, Song Y, Cao Z, *et al*. PI3K/AKT pathway as a key link modulates the multidrug resistance of cancers. *Cell Death & Disease*. 2020; 11: 797.
- [14] Zou Z, Tao T, Li H, Zhu X. mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. *Cell & Bioscience*. 2020; 10: 1–11.
- [15] Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. *Nature Reviews Molecular Cell Biology*. 2020; 21: 183–203.
- [16] Chen Y, Zhou X. Research progress of mTOR inhibitors. *European Journal of Medicinal Chemistry*. 2020; 208: 112820.
- [17] Xu F, Na L, Li Y, Chen L. Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. *Cell & Bioscience*. 2020; 10: 1–12.
- [18] Takahara T, Amemiya Y, Sugiyama R, Maki M, Shibata H. Amino acid-dependent control of mTORC1 signaling: a variety of regulatory modes. *Journal of Biomedical Science*. 2020; 27: 87.
- [19] Fu W, Hall MN. Regulation of mTORC2 signaling. *Genes*. 2020; 11: 1045.
- [20] Zhang Z, Chen Q, Zhang J, Wang Y, Hu X, Yin S, *et al*. Associations of genetic polymorphisms in pTEN/AKT/mTOR signaling pathway genes with cancer risk: a meta-analysis in Asian population. *Scientific Reports*. 2017; 7: 17844.
- [21] Lim HJ, Crowe P, Yang J. Current clinical regulation of PI3K/PTEN/Akt/mTOR signalling in treatment of human cancer. *Journal of Cancer Research and Clinical Oncology*. 2015; 141: 671–689.
- [22] Memarzadeh S, Zong Y, Janzen DM, Goldstein AS, Cheng D, Kurita T, *et al*. Cell-autonomous activation of the PI3-kinase pathway initiates endometrial cancer from adult uterine epithelium. *Proceedings of the National Academy of Sciences*. 2010; 107: 17298–17303.
- [23] Janku F. Phosphoinositide 3-kinase (PI3K) pathway inhibitors in solid tumors: from laboratory to patients. *Cancer Treatment Reviews*. 2017; 59: 93–101.
- [24] Barra F, Evangelisti G, Ferro Desideri L, Di Domenico S, Ferraioli D, Vellone VG, *et al*. Investigational PI3K/AKT/mTOR inhibitors in development for endometrial cancer. *Expert Opinion on Investigational Drugs*. 2019; 28: 131–142.
- [25] Hu M, Zhu S, Xiong S, Xue X, Zhou X. MicroRNAs and the PTEN/PI3K/Akt pathway in gastric cancer. *Oncology Reports*. 2019; 41: 1439–1454.
- [26] Benavides-Serrato A, Lee J, Holmes B, Landon KA, Bashir T, Jung ME, *et al*. Correction: specific blockade of Rictor-mTOR association inhibits mTORC2 activity and is cytotoxic in glioblastoma. *PLoS One*. 2019; 14: e0212160.
- [27] Wang M, Sun R, Zhou X, Zhang M, Lu J, Yang Y, *et al*. Epithelial cell adhesion molecule overexpression regulates epithelial-mesenchymal transition, stemness and metastasis of nasopharyngeal carcinoma cells via the PTEN/AKT/mTOR pathway. *Cell Death & Disease*. 2018; 9: 2.
- [28] Xing D, Fadare O. Molecular events in the pathogenesis of vulvar squamous cell carcinoma. *Seminars in Diagnostic Pathology*. 2021; 38: 50–61.
- [29] de Melo AC, Paulino E, Garces ÁHI. A review of mTOR pathway inhibitors in gynecologic cancer. *Oxidative Medicine and Cellular Longevity*. 2017; 2017: 1–8.
- [30] Zheng Y, Yang X, Wang C, Zhang S, Wang Z, Li M, *et al*. HDAC6, modulated by miR-206, promotes endometrial cancer progression

- through the PTEN/AKT/mTOR pathway. *Scientific Reports*. 2020; 10: 3576.
- [31] S. Dhanalakshmi, N. Harikrishnan, N. Janani, P. Shakthi priya, M. Srinivasan, A. Karthikeyan, *et al.* The overview: recent studies on endometrial cancer. *Research Journal of Pharmacy and Technology*. 2021; 14: 3998–4002.
- [32] Liu H, Zhang L, Zhang X, Cui Z. PI3K/AKT/mTOR pathway promotes progesterin resistance in endometrial cancer cells by inhibition of autophagy. *OncoTargets and Therapy*. 2017; 10: 2865.
- [33] Gao Y, Lin P, Lydon JP, Li Q. Conditional abrogation of transforming growth factor- β receptor 1 in PTEN-inactivated endometrium promotes endometrial cancer progression in mice. *The Journal of Pathology*. 2017; 243: 89–99.
- [34] Cheng H, Liu P, Zhang F, Xu E, Symonds L, Ohlson CE, *et al.* A genetic mouse model of invasive endometrial cancer driven by concurrent loss of Pten and Lkb1 is highly responsive to mTOR inhibition. *Cancer Research*. 2014; 74: 15–23.
- [35] Bajwa P, Nielsen S, Lombard JM, Rassam L, Nahar P, Rueda BR, *et al.* Overactive mTOR signaling leads to endometrial hyperplasia in aged women and mice. *Oncotarget*. 2017; 8: 7265–7275.
- [36] Bian X, Gao J, Luo F, Rui C, Zheng T, Wang D, *et al.* PTEN deficiency sensitizes endometrioid endometrial cancer to compound PARP-PI3K inhibition but not PARP inhibition as monotherapy. *Oncogene*. 2018; 37: 341–351.
- [37] Qin J, Fu M, Wang J, Huang F, Liu H, Huangfu M, *et al.* PTEN/AKT/mTOR signaling mediates anticancer effects of epigallocatechin-3-gallate in ovarian cancer. *Oncology Reports*. 2020; 43: 1885–1896.
- [38] Ghoneum A, Said N. PI3K-AKT-mTOR and NF κ B pathways in ovarian cancer: implications for targeted therapeutics. *Cancers*. 2019; 11: 949.
- [39] Jin C, Liu Z, Li Y, Bu H, Wang Y, Xu Y, *et al.* PCNA-associated factor P15PAF, targeted by FOXM1, predicts poor prognosis in high-grade serous ovarian cancer patients. *International Journal of Cancer*. 2018; 143: 2973–2984.
- [40] Nero C, Ciccarone F, Pietragalla A, Scambia G. PTEN and gynecological cancers. *Cancers*. 2019; 11: 1458.
- [41] Bossler F, Hoppe-Seyler K, Hoppe-Seyler F. PI3K/AKT/mTOR signaling regulates the virus/host cell crosstalk in HPV-positive cervical cancer cells. *International Journal of Molecular Sciences*. 2019; 20: 2188.
- [42] Chen F-X. Changes of PI3K/AKT/mTOR signaling pathway in the progression of cervical cancer and its target genes. *Journal of Hainan Medical University*. 2018; 24: 59–62.
- [43] Bahrami A, Hasanzadeh M, Hassanian SM, ShahidSales S, Ghayour-Mobarhan M, Ferns GA, *et al.* The potential value of the PI3K/Akt/mTOR signaling pathway for assessing prognosis in cervical cancer and as a target for therapy. *Journal of Cellular Biochemistry*. 2017; 118: 4163–4169.
- [44] Zięba S, Kowalik A, Zalewski K, Rusetska N, Goryca K, Piascik A, *et al.* Somatic mutation profiling of vulvar cancer: exploring therapeutic targets. *Gynecologic Oncology*. 2018; 150: 552–561.
- [45] Allavena P, Sica A, Solinas G, Porta C, Mantovani A. The inflammatory micro-environment in tumor progression: the role of tumor-associated macrophages. *Critical Reviews in Oncology/Hematology*. 2008; 66: 1–9.
- [46] Lei X, Lei Y, Li J, Du W, Li R, Yang J, *et al.* Immune cells within the tumor microenvironment: biological functions and roles in cancer immunotherapy. *Cancer Letters*. 2020; 470: 126–133.
- [47] Paluskiewicz CM, Cao X, Abdi R, Zheng P, Liu Y, Bromberg JS. T regulatory cells and priming the suppressive tumor microenvironment. *Frontiers in Immunology*. 2019; 10: 2453.
- [48] Wei T, Zhong W, Li Q. Role of heterogeneous regulatory T cells in the tumor microenvironment. *Pharmacological Research*. 2020; 153: 104659.
- [49] Tanaka A, Sakaguchi S. Targeting Treg cells in cancer immunotherapy. *European Journal of Immunology*. 2019; 49: 1140–1146.
- [50] Ou Y, Cannon MJ, Nakagawa M. Regulatory T cells in gynecologic cancer. *MOJ Immunology*. 2018; 6: 34.
- [51] Gandhi GR, Neta MTSL, Sathiyabama RG, Quintans JDSS, de Oliveira e Silva AM, Araújo AADS, *et al.* Flavonoids as Th1/Th2 cytokines immunomodulators: a systematic review of studies on animal models. *Phytomedicine*. 2018; 44: 74–84.
- [52] Munn DH, Sharma MD, Johnson TS. Treg destabilization and reprogramming: implications for cancer immunotherapy. *Cancer Research*. 2018; 78: 5191–5199.
- [53] You D, Wang Y, Zhang Y, Li Q, Yu X, Yuan M, *et al.* Association of Foxp3 promoter polymorphisms with susceptibility to endometrial cancer in the Chinese Han women. *Medicine*. 2018; 97: e0582.
- [54] Bruno V, Corrado G, Baci D, Chiofalo B, Carosi MA, Ronchetti L, *et al.* Endometrial cancer immune escape mechanisms: let us learn from the fetal–maternal interface. *Frontiers in Oncology*. 2020; 10: 156.
- [55] Torrey H, Butterworth J, Mera T, Okubo Y, Wang L, Baum D, *et al.* Targeting TNFR2 with antagonistic antibodies inhibits proliferation of ovarian cancer cells and tumor-associated Tregs. *Science Signaling*. 2017; 10: eaaf8608.
- [56] Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, *et al.* Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nature Medicine*. 2004; 10: 942–949.
- [57] Lin Z, Huang L, Li SL, Gu J, Cui X, Zhou Y. PTEN loss correlates with T cell exclusion across human cancers. *BMC Cancer*. 2021; 21: 429.
- [58] Zhang W, Hou F, Zhang Y, Tian Y, Jiao J, Ma D, *et al.* Changes of Th17/Tc17 and Th17/Treg cells in endometrial carcinoma. *Gynecologic Oncology*. 2014; 132: 599–605.
- [59] Driessen GJ, IJspeert H, Wentink M, Yntema HG, van Hagen PM, van Strien A, *et al.* Increased PI3K/Akt activity and deregulated humoral immune response in human PTEN deficiency. *Journal of Allergy and Clinical Immunology*. 2016; 138: 1744–1747. e1745.
- [60] Munn DH, Sharma MD, Johnson TS, Rodríguez P. IDO, PTEN-expressing Tregs and control of antigen-presentation in the murine tumor microenvironment. *Cancer Immunology, Immunotherapy*. 2017; 66: 1049–1058.

How to cite this article: Xi Zeng, Ming-Rong Xi, Hong-Wei Ma. PTEN gene and AKT/mTOR pathway in gynecological cancers and cancer immune escape. *European Journal of Gynaecological Oncology*. 2022; 43(4): 19-24. doi: 10.22514/ejgo.2022.024.