Unveiling the mysteries of C1QBP in gynecological tumors (Review)

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Abstract. The morbidity and mortality of gynecological tumors have been increasing globally in recent years. The identification of new biomarkers and drug targets has become an opportunity and challenge in the treatment of these tumor types. In recent years, the role of mitochondrial oxidative phosphorylation in the development of gynecological tumors has attracted attention, and existing studies have shown that complement component 1 Q subcomponent-binding protein (C1QBP) is involved in critical biological processes such as proliferation, migration and invasion of these tumors. However, the specific mechanism and function of C1QBP in gynecological tumors remain unknown and further studies are still needed to reveal its role and clinical application prospects. Therefore, the present review describes the changes and mechanism, such as in the apoptosis and invasion of tumor cells, of C1QBP in cervical, ovarian and endometrial cancer. The present review examines the current research progress on C1QBP in gynecological tumors to provide new ideas and methods for diagnosing and treating this disease.

Contents

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1. Introduction

The incidence of gynecological tumors in China is increasing annually, accounting for 15-20% of female malignant tumors; its overall incidence is on the rise (1) and has become the third most lethal disease among female tumors (2). For patients with early-stage gynecological tumors, standard treatment can notably improve prognosis. Nevertheless, for recurrent, metastatic and drug-resistant patients, there is often a lack of effective therapeutic measures in the early stage of disease. Besides, research into the mechanisms contributing to the poor prognosis of tumor therapy remains insufficient. Therefore, discovering new biomarkers and therapeutic targets is the top priority for curing gynecological tumors.

Complement component 1 Q subcomponent-binding protein (C1QBP), a multifunctional protein, is upregulated in a variety of tumor types (3-5). C1QBP plays a vital role in both normal physiological processes and the development of various tumors such as cervical, ovarian and endometrial cancer, particularly by regulating critical biological processes such as proliferation, migration and invasion (3-7). However, multiple questions still remain concerning the specific mechanism or the role of C1QBP in gynecological tumors and its potential as a therapeutic target. In view of these findings, the present review summarizes the research progress on C1QBP in gynecological tumors in recent years, explores its mechanism of action in tumorigenesis and development and assesses its potential as a biomarker and therapeutic target, with the aim of providing a theoretical basis for subsequent research. A search for articles was conducted using databases such as Web of Science (https://www.web of science.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and CNKI (https://www.cnki.net/). The key words included 'gynecological tumors', 'ovarian cancer', 'endometrial cancer', 'cervical cancer', 'mitochondria', 'C1QBP protein', 'tumor pathogenesis', 'clinical' and 'non-clinical'. Literature published in Chinese and English were focused on the reduce information overload and improve research efficiency. Additionally, literature within a 16-year range (2010-2016) was focused on, but earlier literature was included if the content was particularly relevant to the topic. To the best of our knowledge, the present review is the first to

provide a detailed description of the role of C1QBP in gynecological tumors and its related mechanisms and to summarize the retrospective research results in recent years.

2. Structure and function of C1QBP

C1QBP was initially isolated from human Burkitt lymphoma cell membranes (8). C1QBP, also known as p32 or gC1qR, is a multifunctional and evolutionarily conserved protein predominantly localized in the mitochondrial matrix. The C1QBP gene is located on chromosome 17 and p53 can bind to the promoter region of the C1QBP gene to influence its transcription (9,10). The C1QBP precursor protein consists of 282 amino acids and eventually forms a mature protein of 209 amino acids (8) (Fig. 1). C1QBP is a donut-shaped, acidic protein located in the mitochondrial matrix. Crystal structure analysis reveals that it folds into a characteristic trimeric architecture, with each monomer consisting of seven antiparallel β-strands (β1-β7), in which a highly distorted antiparallel β-fold is formed where the β_1 strand is positioned almost perpendicular to β_7 (11). This β-fold consists of an N-terminal α-helix and two C-terminal α-helices, whose distinctive features add to the stability of the structure (11). The high negative charge density and asymmetric charge distribution result in functional roles on both sides of the protein that are asymmetric, which is essential for protein-protein interactions and ligand binding (11,12).

C1QBP is widely expressed in several subcellular compartments, including the nucleus, Golgi, endoplasmic reticulum and mitochondria. C1QBP fulfills specific biological functions according to the distribution states in different microenvironments (13). For example, C1QBP in the nucleus participates in the regulation of RNA metabolism and a study has reported that C1QBP distributed in the Golgi network participates in cellular mitosis (14). C1QBP also has an important role in the morphology and structure of the endoplasmic reticulum under normal cellular conditions. For instance, a lack of C1QBP leads to fragmentation of the endoplasmic reticulum structure, dissociation of ribosomes and ultimately the inability to synthesize proteins, lipids and other substances in normal cells (15). In addition, when localized in mitochondria, C1QBP is involved in mitochondrial quality control and metabolism (16), maintenance of oxidative phosphorylation (OXPHOS) (12) and the synthesis of mitochondrial proteins (8).

C1QBP also participates in the regulation of immune cells. Gotoh *et al* (17) reported that C1QBP supports the maturation of dendritic cells, which induces primary immune responses. C1QBP is closely related to the regulation of humoral immunity. After complement activation, the generated fragments, such as C3d, covalently bind to the surface of the activating antigen involving a pathogen and immune complex (18). B cells recognize C3d through their complement receptor 2 and obtain a strong co-stimulatory signal, enhancing the immunogenicity of the antigen. C1QBP indirectly controls this key process by regulating the complement activation front (12). By binding to C1q in its soluble form, C1QBP inhibits classical pathway activation and subsequent C3d production. Conversely, when expressed on the cell surface under pathological conditions, C1QBP can directly activate the classical complement pathway, leading to enhanced C3d deposition and modulation of B cell co-stimulatory signals (12). Furthermore, C1QBP mediates the clearance of complement component 1q (C1q)-coated immune complexes and apoptotic cells by phagocytes. The absence of C1q or the presence of anti-C1q antibodies can lead to the deposition of immune complexes in tissues such as the kidneys, triggering autoimmune diseases such as lupus nephritis, which is a pathological form of humoral immunity (19). Additionally, C1QBP can promote the coagulation process by inhibiting fibrin polymerization (20). C1QBP is involved in the regulation of nuclear function; it not only regulates apoptosis but also regulates the splicing process through the interaction of the function and/or localization of different splicing factors (21,22). C1QBP also promotes the occurrence of microbial infection. *Staphylococcus aureus* protein A contributes to pathogenesis by interacting with the host complement receptor C1QBP (23). Hepatitis C virus, human immunodeficiency virus, herpes simplex virion type 1 and Epstein-Barr virus can bind to C1QBP on the surface of T lymphocytes and inhibit the proliferation of T cells, thus exerting immunosuppressive effects (12,24,25). *Plasmodium falciparum* infected red blood cells can not only use C1QBP as a receptor to bind to human endothelial cells but also bind to C1QBP on platelets to form clumps, thereby mediating vascular endothelial cell proliferation. These two factors are the key mechanisms of malaria pathogenesis (26). In summary, C1QBP is related to humoral immunity, coagulation and fibrin polymerization as well as microbial infection, which is summarized in Fig. 2.

As aforementioned, the unique structural features of C1QBP allow it to interact with several different ligands and regulate their functions. At present, the main ligands identified are C1q, calreticulin, hyaluronic acid (HA), the splicing factor ASF/SF2 and CD44 (27). C1QBP was initially identified as a receptor for C1q in the study by Ghebrehiwet *et al* (12), and initiates organismal immunity by activating the classical complement pathway. The binding of C1QBP to calreticulin is related to the adhesion and spreading of endothelial cells (28). Furthermore, the binding of C1QBP to HA promotes the adhesion and de-adhesion of cells (29). The binding of C1QBP to ASF/SF2 blocks ASF/SF2 phosphorylation and inhibits its binding to pre-messenger RNA, thereby inhibiting its role as an initiator of pre-spliceosome formation (30). Besides, the interaction of C1QBP with CD44v6 in lipid rafts, a cholesterol-rich and sphingomyelin-rich microstructural domain of plasma membranes, promotes the phosphorylation of insulin-like growth factor 1 receptor, thereby activating downstream PI3K and MAPK signaling pathways that mediate the metastatic potential of pancreatic cancer cells (31). In summary, C1QBP is involved in regulating gene expression, splicing, mitochondrial metabolism and cell signaling and plays a vital role in tumor development.

The mitochondrial localization of C1QBP is associated with multiple biological processes, including mitochondrial morphology regulation, metabolic regulation, cell fate determination and disease (32). Knockdown of C1QBP leads to abnormal mitochondrial morphology and ultrastructural damage, indicating its key role in maintaining the dynamic balance of the mitochondrial network (15). C1QBP is a key regulator of Y-box binding protein 1 (YBX1), enhancing the expression of respiratory complexes, ATP production and reactive oxygen species (ROS) generation through promoting the

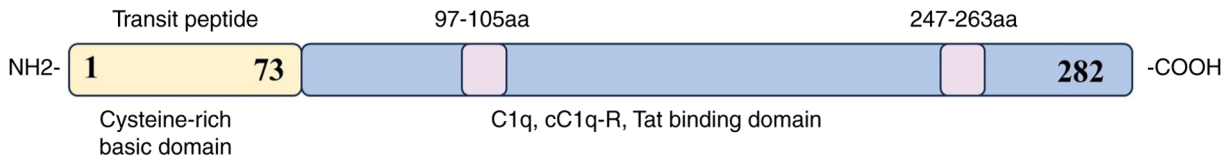

Figure 1. Schematic of C1QBP and notable amino acid sites.

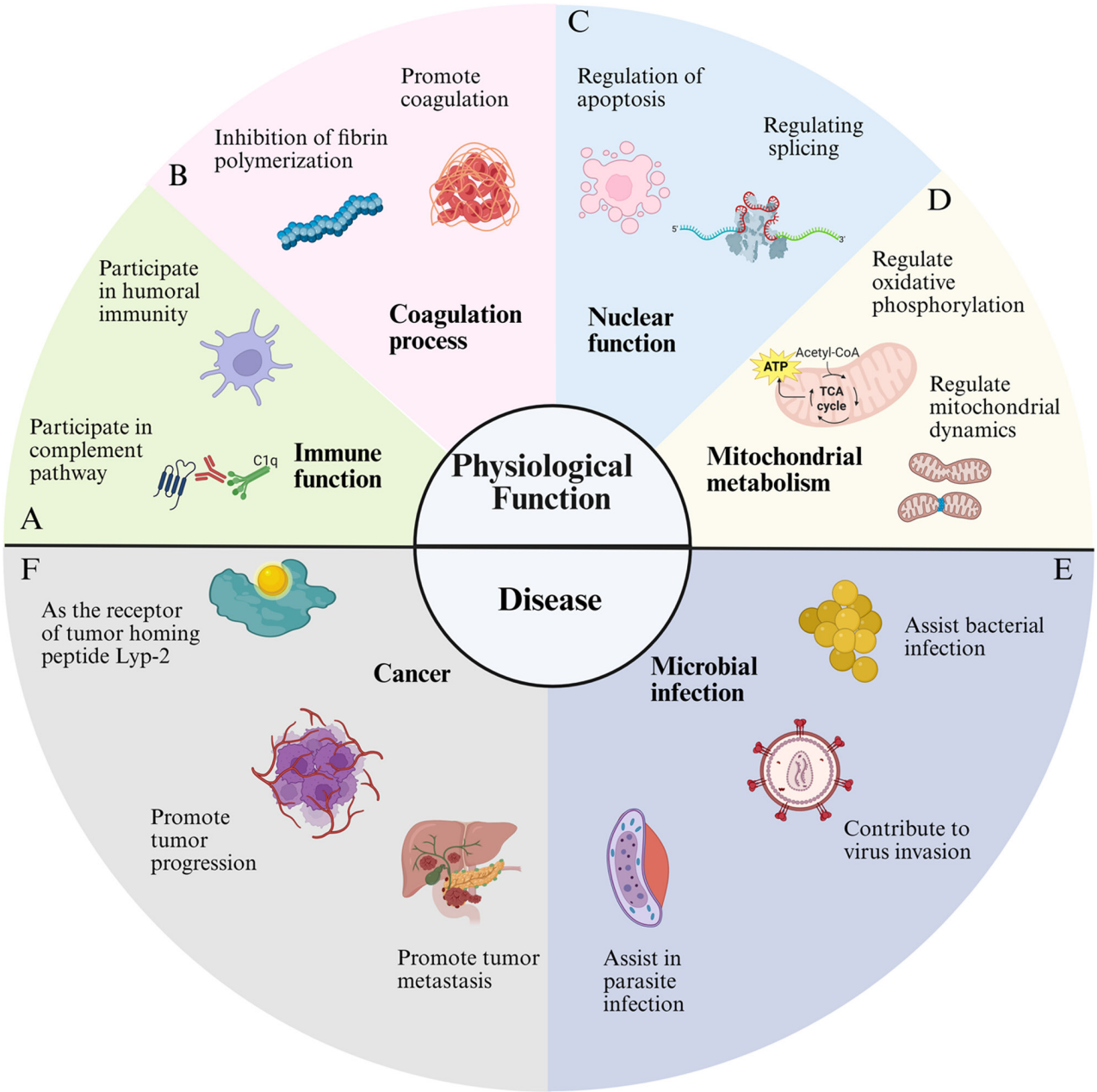

Figure 2. C1QBP can interact with a number of ligands with different properties and positions. (A) C1QBP is involved in the regulation of immune function. C1q is the initial molecule of the classical complement pathway, which can recognize immune complexes and initiate the classical pathway of the complement system (12). (B) C1QBP can promote the coagulation process by inhibiting fibrin polymerization (20). (C) C1QBP is involved in the regulation of nuclear function; it can not only be used as a regulator of apoptosis, but also regulates the splicing process through the interaction with various splicing factors and modulating their function (8). (D) C1QBP is involved in the regulation of mitochondrial metabolism. C1QBP plays a vital role in the biosynthesis of proteins encoded by the mitochondrial genome, especially in maintaining oxidative stress (20). C1QBP has also been found to affect mitochondrial metabolism and kinetic processes in recent years (16). (E) C1QBP promotes the occurrence of microbial infection. The process of *Staphylococcus aureus* protein A recognizing platelet C1QBP is key to the pathogenesis of *S. aureus* (23). HCV, HIV and other virions can bind to C1QBP on the surface of T lymphocytes and inhibit the proliferation of T cells, thus exerting immunosuppressive effects (24). *Plasmodium falciparum* infected red blood cells can not only use C1QBP as a receptor to bind to human endothelial cells but also bind to C1QBP on platelets to form clumps, thereby mediating vascular endothelial cell proliferation. These two factors are the key mechanisms of malaria pathogenesis (1). (F) C1QBP is involved in the occurrence, progression, metastasis and prognosis of cancer and can also be used as a molecular target for cancer treatment (32,103). TCA cycle, tricarboxylic acid cycle; C1QBP, complement component 1 Q subcomponent-binding protein; HVC, hepatitis C virus; HIV, human immunodeficiency virus.

Table I. Summary of the clinicopathological factors associated with C1QBP expression.

First author, year	Tumor type	Sample size	Testing method	Relevant indicators related to C1QBP	(Refs.)
Zhang *et al*, 2017	Cervical cancer	30 cervical intra-epithelial neoplasia and 118 CC specimens compared with 10 normal cervical specimens	Immunohistochemistry	FIGO stage, poor histological grade, large tumor volume, lymphatic vessel interstitial infiltration, deep interstitial infiltration, lymph node metastasis and disease-free survival	(3)
Yu *et al*, 2013	Ovarian cancer	161 patients with epithelial ovarian cancer	Immunohistochemistry and western blotting	FIGO stage, peritoneal dissemination, lymph node metastasis, degree of tissue differentiation and residual tumor size	(4)
Zhao *et al*, 2015	Endometrial cancer	188 endometrial cancer specimens, 43 benign endometrial lesion specimens and 41 normal endometrium specimens	Immunohistochemistry and western blotting	FIGO stage, high histological grade, deep myometrial infiltration, lymphatic vessel interstitial infiltration, lymph node metastasis and recurrence, disease-free survival and overall survival	(5)

CC, cervical cancer; FIGO, International Federation of Gynecology and Obstetrics.

translation of mitochondrial gene-encoded proteins (33). The mitochondrial dysfunction of C1QBP is also closely related to cancer, including gynecological cancer (Table I).

3. Role of C1QBP in cancer

C1OBP is highly expressed in epithelial tumors of the breast, lung, liver, prostate and colon, as well as in squamous and basal cell carcinoma (34-39). The expression level of C1QBP is also increased in inflammatory lesions and cells with a high cell division rate (32). The data accumulated so far indicate that C1QBP is upregulated in most cancer cells and it not only participates in shaping the inflammatory tumor microenvironment, but also regulates mitochondrial metabolism and dynamics, angiogenesis, metastasis and cell proliferation (40). Moreover, C1QBP enhances anti-apoptotic ability and induces resistance to cisplatin (41). The key regulatory roles of C1QBP in different physiological and pathological processes are summarized in Fig. 2.

Tumor migration and invasion. Cell migration is the hallmark of cancer, regulating the anchorage-independent growth and invasiveness of tumor cells (42). C1QBP plays a crucial role in the growth, survival, metastasis and invasion of tumor cells. The expression level of C1QBP is associated with the stage, grade, size and clinical prognosis of the tumor (3-5). In breast cancer, the upregulation of C1QBP is significantly associated with distant metastasis, higher TNM stage, larger tumor volume, axillary lymph node metastasis and poor prognosis (43,44). Furthermore, when C1QBP is absent, the proliferation, migration and invasion of liver cancer cells is reduced, while cell apoptosis increases (45). C1QBP induces tumor cell migration and tumor growth by interacting with integrin and activating matrix metalloproteinase-2 through a nuclear factor-κB-dependent mechanism (32,46). C1QBP interacts with YBX1, inhibiting the activation of YBX1 by altering its phosphorylation and nuclear transport (47). This inhibition of YBX1 leads to the suppression of its activity in renal cell carcinoma cells, potentially preventing the migration and invasion of renal cell carcinoma (48). The inhibition of YBX1 might involve altering the matrix metalloprotease 9 signaling pathway (48). Besides, C1QBP promotes melanoma progression and metastasis by targeting epithelial mesenchymal transition markers, the Akt/protein kinase B pathway and the tumor microenvironment (49,50). Additionally, the enhanced migration, invasion and proliferation of oral squamous cell carcinoma cells in vitro is dependent on C1QBP (51). In conclusion, C1QBP regulates tumor growth and invasion through multiple pathways (40). In cancer cells, C1QBP further enhances OXPHOS activity by stabilizing proteins such as PA28y, thereby supporting the energy and biosynthesis required for tumor growth, and high expression of C1QBP promotes malignant progression by regulating cell proliferation, migration, apoptosis and differentiation, whereas its inhibition can induce apoptosis and enhance glycolysis (52).

Mitochondrial metabolism and dynamics. Studies have shown that the absence of the C1QBP gene activates the

overlapping activity with m-AAA protease, thereby cleaving optic atrophy 1, leading to mitochondrial division and swelling, accompanied by altered expression of Mitofusin1 and Mitofusin2 (53,54). C1QBP is also crucial for maintaining metabolic homeostasis and stress responses; it supports cell survival during nutrient deprivation by facilitating autophagic flux and preserving mitochondrial OXPHOS function, processes vital for adaptation to starvation (55). The tumor occurrence mediated by C1QBP is closely related to the maintenance of mitochondrial metabolism. Reducing the expression of C1OBP in human cancer cells significantly alters their metabolic patterns, reprogramming metabolism from OXPHOS to glycolysis (56,57). The absence of C1QBP leads to a reduced ability of tumors to form within the body, which may be due to a decrease in the synthesis of OXPHOS proteins encoded by mitochondrial DNA. Glutamine is an important substrate for mitochondrial metabolism. The higher the degree of tumor progression, the greater the amount of glutamine oxidation in the body, reflecting an increased demand for mitochondrial anaplerosis to fuel the tricarboxylic acid (TCA) cycle. This heightened state of glutamine metabolism stands in stark contrast to the metabolic state observed upon C1QBP loss, where impaired OXPHOS and a shift toward glycolysis suggest an inability to effectively utilize such mitochondrial substrates (58). Myc upregulates the transcription of C1QBP, thereby regulating glutamine metabolism (45). In malignant brain cancer, a high level of Myc is accompanied by an increase in C1QBP expression (59,60). Research indicates the proto-oncogene c-Myc directly regulates C1QBP expression at the transcriptional level. First identified in cholangiocarcinoma, this mechanism involves c-Myc binding to the C1QBP promoter to activate its transcription, subsequently driving tumor proliferation (45). The mitochondrial dysfunction of C1QBP is closely related to cancer progression. For example, in triple-negative breast cancer (TNBC), targeting C1QBP can induce mitochondrial damage and tumor regression; its expression level is related to the prognosis of patients, making it a potential target for cancer treatment (41). Studies have shown that C1QBP is highly expressed in gynecological tumor tissues and may be used as a biomarker to predict the progression and prognosis of gynecologic tumors (3-5). However, few studies have investigated the specific mechanism of C1QBP in gynecological tumors, and the role of C1QBP in these tumor types requires further experimental and clinical validation.

Furthermore, C1QBP has been demonstrated to be associated with mitochondrial-dependent tumor cell apoptosis. Knockdown of C1QBP enhances mitochondrial fragmentation, accompanied by the loss of detectable levels of mitochondrial fusion intermediates Mitofusin1/2 (53). Proteasome activator and C1QBP are co-localized in mitochondria and promote mitochondrial fusion by upregulating optic atrophy 1, Mitofusin1/2, respiratory complex expression, OXPHOS, ATP production and ROS generation. Mitochondria are highly dynamic organelles that constantly undergo division and fusion (61,62).

Immunoregulation. C1QBP is related to the immune process during the occurrence and development of tumors, such as the regulation of T cells and macrophages, as well as the proliferation and invasion of tumors (52,58,59). Studies have shown that C1QBP also participates in regulating the differentiation of effector $CD8^+$ T cells, thereby influencing their antiviral and antitumor immune responses (56,63,64). In immune cells, the absence of C1QBP intrinsically inhibits effector $CD8^+$ T cell differentiation by impairing mitochondrial respiratory capacity and increasing sensitivity to defective OXPHOS, leading to metabolic reprogramming, epigenetic disorders and a subsequent disruption of the antitumor immune response (56). Knocking out the C1QBP protein can regulate T cells by impairing mitochondrial fitness, leading to the accumulation of ROS and the loss of mitochondrial membrane potential, thereby compromising mitochondrial health and function (56). The absence of C1QBP weakens the infiltration of T cells into tumors and exacerbates the exhaustion of tumor-infiltrating T lymphocytes (65,66).

Furthermore, C1QBP is also related to the regulation of macrophages (6). The vitronectin secreted by tumor cells interacts with C1QBP located on the surface of tumor-associated macrophages, inhibiting the phagocytic activity of tumor cells and causing the macrophages to transform into the M2 subtype in the tumor microenvironment (67). Mechanistically, the vitronectin-C1QBP axis promotes Shp1 uptake induced by FcyRIIIA/CD16, thereby reducing the phosphorylation of Syk (67). This reduction in Syk phosphorylation impairs downstream phagocytic signaling, ultimately inhibiting the phagocytic activity of macrophages against tumor cells. Tumor cell-derived vitronectin (Vin) suppresses phagocytosis through its interaction with C1QBP on the macrophage surface (63). Moreover, the combination of Vin knockdown and the anti-CD47 antibody effectively enhances the phagocytic activity and infiltration of macrophages, thereby reducing tumor growth *in vivo*. Further studies have shown that C1QBP may promote the polarization of macrophages from macrophages to M2 and M3 types (67,68). Mitochondrial function not only affects the occurrence, progression and distant metastasis of tumors, but also regulates the maturation, differentiation and long-term maintenance of immune cells.

Angiogenesis. The secreted form of C1QBP can upregulate the expression of the inducible bradykinin receptor I through autocrine action, thereby exacerbating vascular leakage and opening channels within the cells, allowing tumor cells to escape and metastasize to distant sites for metastatic invasion (6,69). Proliferating tumor cells rely on angiogenesis to maintain survival, development and escape to secondary sites for metastatic invasion. Multiple studies have confirmed that the hypoxic tumor microenvironment plays a role in promoting angiogenesis (27,70-72). The expression level of C1QBP is higher in the hypoxic regions of tumors, indicating that the tumor microenvironment is associated with the expression level and function of C1QBP in cancer (34). Additionally, hypoxia induces an increase in the C1QBP expression level in TNBC cells through the hypoxia-inducible factor α transcription factor (69,73). The neutralizing effect of anti-C1QBP antibodies on C1QBP located on the cell surface also inhibits angiogenesis, as this anti-C1QBP antibody prevents the activation of receptor tyrosine kinase stimulated by growth factors, the formation of pseudopodia, cell migration and the formation of capillary tubes (74).

4. C1QBP and gynecological tumors

C1QBP and cervical cancer. The incidence of cervical cancer has declined slightly over the past decade, but it remains the second most common cause of cancer-related death among women in developing countries (75). The primary causative agent of cervical cancer is oncogenic human papillomavirus (HPV), of which HPV 16 and HPV 18 are predominant (76). Identifying genes involved in cervical carcinogenesis and progression may help elucidate the underlying molecular mechanisms and provide valuable therapeutic targets.

Current research progress on cervical cancer and C1QBP has conflicting results. Some studies have shown that C1QBP is associated with the promotion of cervical cancer development, while others have indicated that C1QBP is related to the inhibition of cervical cancer. Zhang *et al* (3) first reported that C1QBP is upregulated in cervical tumor tissues and that the degree of elevated expression is associated with advanced international Federation of Gynecology and Obstetrics (FIGO) stage (P=0.001), poor histological grade (P=0.013), large tumor volume (P=0.025), lymphatic vessel interstitial infiltration (P=0.024), deep interstitial infiltration (P=0.001) and lymph node metastasis (P=0.023). This study also demonstrated that elevated C1QBP expression is an independent predictor of disease-free survival (P=0.007) in patients with cervical cancer via multivariate Cox regression analysis. Due to insufficient sample size, more experimental results should be obtained with larger sample sizes in future to obtain more representative conclusions.

Conversely, another study has shown that, compared with normal cervical tissue, the expression of C1QBP protein in human cervical squamous cell carcinoma tissue is significantly decreased (3). C1QBP is associated with the apoptosis, survival, migration and proliferation of cervical squamous cell carcinoma cells (3). Relevant pathways have also been explored in existing studies. After transfection of C33a cells with the C1QBP overexpression vector, the apoptosis rate and the expression of p38 mitogen-activated protein kinase (p38 MAPK) significantly increased. Moreover, when C1QBP was overexpressed, the changes in the survival rate, migration ability and proliferation ability of C33a cells could be eliminated with the p38 MAPK inhibitor SB202190 (77). Chen *et al* (78) reported that when C1QBP is overexpressed, Ca^{2+} overload in mitochondria, increased ROS and decreased mitochondrial membrane potential lead to reduced cell viability, which leads to the induction of apoptosis, confirming the involvement of C1QBP in the p53-dependent apoptotic pathway. Moreover, the involvement of C1QBP in inducing apoptosis in cervical cancer cells via another pathway, p38 MAPK/JNK, was also identified in a study by Gao *et al* (79). Itahana and Zhang (80) and Liu *et al* (81) also reported that apoptosis was increased when C1QBP was overexpressed in cervical tumor tissues. These data indicate that C1QBP inhibits the survival, migration and proliferation of cervical squamous cell carcinoma cells through the p38 MAPK signaling pathway (79).

A persistent infection of high-risk HPV type has been correlated with the development of cervical cancer (78). The HPV 16 genome is composed of six regulatory proteins, composed of E1, E2, E4, E5, E6 and E7, which regulate the life cycle, gene expression and the function of cervical cancer. HPV 16 E2 induces the apoptosis of tumor cells and inhibits tumor growth in cervical cancer by increasing the expression of C1QBP. Compared with non-cancerous cervical samples, the expression levels of the HPV-16 E2 and C1QBP genes were significantly decreased in human cervical squamous cell carcinoma samples (78). In C33a and SiHa cells transfected with a vector encoding HPV-16 E2, the expression of the C1QBP gene significantly increased, which was accompanied by mitochondrial dysfunction and the upregulation of apoptosis; transfecting with C1QBP small interfering RNA (siRNA) could limit these phenomena. These data support a mechanism in which C1QBP plays an important role in the HPV-16 E2-induced apoptosis of human cervical squamous cell carcinoma cells through a mitochondrial-dependent pathway (78). The C33a and SiHa cells transfected with the HPV16 E2 vector also showed a significant increase in the activation of p38 MAPK/JNK. Moreover, the changes in the survival rate, migration ability and proliferation ability of C33a cells after HPV 16 E2 transfection were eliminated after treatment with the p38 MAPK inhibitor SB203580 and the JNK inhibitor SP600125. These data support the mechanism that HPV16 E2 induces cell apoptosis by silencing the C1QBP gene or inhibiting the p38 MAPK/JNK signaling pathway in cervical squamous cell carcinoma (78). Another study revealed that HPV E2 could induce apoptosis in cervical cancer cells through the upregulation of C1QBP (81).

The E6 and E7 proteins encoded by high-risk HPV types are also associated with the function of C1QBP in cervical cancer, and their functions are different from those of the aforementioned E2 type. Under the influence of the E6 and E7 proteins encoded by high-risk HPV, C1QBP promotes the immune escape of cervical cancer cells (79). Gao *et al* (79) examined C1QBP protein levels in C-33A cells transfected with or without the HPV-16 E6 and E7 oncogenes and reported that C1QBP protein expression was significantly lower in HPV-16 E6- and E7-treated C-33A cells than in untreated C-33A cells. The excessive expression of C1QBP in cells induces apoptosis, mediated by the activation of caspase-3 and the onset of mitochondrial dysfunction. Cells transfected with the GFP-C1QBP vector showed increased expression of C1QBP protein and a gradual increase in ROS production. Additionally, the increase in ROS production and Ca^{2+} influx in mitochondria led to the loss of mitochondrial transmembrane potential. Notably, when C1QBP was overexpressed in C-33A cells and the cells were treated with metformin, cell apoptosis was significantly inhibited, which may be due to the protection of mitochondrial function by metformin (79). These data suggest that C1QBP may play an important role in the immune escape of cervical cancer triggered by HPV-16 E6 and E7, depending on its expression level and cellular subcellular localization. Specifically, E6 and E7 downregulate C1QBP expression, thereby relieving its pro-apoptotic effect, which is mediated by caspase-3 activation, ROS production and mitochondrial dysfunction. This suppression of C1QBP-dependent apoptosis allows HPV-infected cells to evade immune clearance and persist, contributing to cervical carcinogenesis. Rangsee *et al* (13) reported that HPV-E7 can also inhibit C1QBP by increasing C1QBP promoter methylation in HPV-positive cervical cancer cell lines and decreasing its protein abundance, which ultimately promotes

cervical carcinogenesis. HPV-16 is closely associated with the occurrence of 50% of cervical cancer cases (79).

In summary, C1QBP is associated with the apoptosis, survival, migration and proliferation of cervical squamous cell carcinoma cells. There is a close link between HPV-related proteins and C1QBP. C1QBP has context-dependent conflicting roles in HPV-associated cervical cancer, functioning as an anti-tumorigenic factor in the presence of HPV E2 and as a pro-tumorigenic factor in the presence of high-risk HPV E6 and E7 oncogenes. These findings provide new ideas for the identification of new therapeutic targets for the treatment of human cervical cancer. However, the specific mechanism involved is still unclear and needs to be further verified by a number of basic experiments. Besides, although previous cervical cancer-related studies have analyzed cervical cancer samples, the statistical power of stratified analyses, such as different histological types or clinical stages, may be insufficient, which leads to the results being susceptible to confounding factors and difficulties verifying their universality. The clinical significance of C1QBP in cervical cancer is mostly based on data from single centers, lacking independent multi-center cohort verification. Moreover, the application of functional experiments in cervical cancer cell lines is limited, which restricts the ability of causal inference. At present, experiments have been largely limited to a few cell lines, such as C-33A and SiHa, making it difficult to generalize the conclusions to cervical cancer of all HPV subtypes and genetic backgrounds. Besides, the inconsistent results of C1QBP in cervical cancer research may be caused by small sample size, different population characteristics, inconsistent tissue preservation methods, differences in detection methods, data collection biases, short follow-up time or insufficient control of confounding factors. At present, there are relatively few studies examining the mechanistic pathways and clinical research between C1QBP and cervical cancer; therefore, further research and discussion are needed.

C1QBP and ovarian cancer. Among the gynecological malignancies, ovarian cancer is the most common cause of death (82). Despite patients receiving advanced tumor cytoreduction and chemotherapy, 5-year survival rates still remain low. The use of multiple biomarkers is an accurate method for preoperatively predicting the risk of ovarian cancer in patients with metastases. Therefore, testing for new biomarkers may improve the sensitivity and specificity of predicting disease.

Yu *et al* (4) reported that C1QBP upregulation in epithelial ovarian cancer was associated with FIGO stage (P=0.0074), peritoneal dissemination (P<0.0001), lymph node metastasis (P<0.0001), degree of tissue differentiation (P<0.0001) and residual tumor size (P=0.0013). They collected paraffin-embedded specimens from 161 patients with epithelial ovarian cancer (EOC) and found that C1QBP was lowly expressed in benign ovarian tissues via western blot analysis. Low levels of C1QBP expression were also detected in the tissues of patients without peritoneal and lymph node metastasis; however, high levels were detected in the tissues of patients with peritoneal and lymph node metastasis. The same results were confirmed by immunohistochemical staining. Moreover, within the same patients, the intensity and frequency of C1QBP staining increased from the primary lesion to peritoneal dissemination and lymph node metastasis. Therefore, it was noted that elevated C1QBP expression may be a new indicator of lymph node and peritoneal metastasis in patients with EOC. Besides, regarding the differences in expression and function of C1QBP in different pathological subtypes such as serous ovarian cancer and endometrioid ovarian cancer, current research is limited and there are no published data for reference. This is also a promising research direction.

In a study by Yu *et al* (83), C1QBP was found to be only weakly to non-expressed in all normal ovarian tissues, highly expressed in plasmacytoid ovarian cancer tissues, more highly expressed in poorly differentiated plasmacytoid ovarian cancer tissues than in moderately differentiated ovarian cancers (P=0.0182) and significantly elevated in patients with lymph node metastasis (P=0.0021). Univariate analysis revealed that C1QBP upregulation was a significant predictor of poor progression-free survival and overall survival (83). Due to limitations such as insufficient sample size and the regional nature of sample collection, the reliability of these findings needs to be further validated in larger, multi-center cohorts.

Duan *et al* (84) have designed a novel C1QBP probe based on 99mTc-radiolabeled siRNA, which can non-invasively detect C1QBP expression *in vivo*, thus enabling the early diagnosis of ovarian cancer. Hunt *et al* (85) also reported that C1QBP can be inhibited by the intraperitoneal injection of linTT1 peptide-guided proapoptotic nanoparticles to treat peritoneal metastatic cancer caused by ovarian cancer dissemination.

Moreover, C1QBP also has a role in the drug resistance of ovarian cancer cells. Yu *et al* (4) reported that the expression of C1QBP was increased in cisplatin-resistant ovarian cancer and that the staining intensity and frequency in chemotherapy-resistant ovarian tumor tissues were significantly greater than that in chemotherapy-sensitive ovarian tumor tissues.

In conclusion, C1QBP is closely related to lymph and lesion metastasis in ovarian cancer, which is a research direction that can be further explored in the future. Further studies are needed to confirm whether the C1QBP protein has the potential to serve as a predictive marker for the clinical progression of ovarian cancer alone or in combination with other markers. In addition, the detailed mechanism by which increased C1QBP expression leads to ovarian cancer metastasis still remains unclear and should be further explored in future basic studies and clinical trials.

C1QBP and endometrial cancer. The incidence of endometrial cancer has been increasing worldwide in recent year (86). In total, 80% of endometrial cancer cases are estrogen-related and the pathological type is predominantly endometrioid, with early-stage patients tending to have an improved prognosis and patients with advanced, recurrent or high-grade lesions having a poor prognosis (87,88). However, few therapeutic agents are available to achieve durable remission in patients with recurrent or advanced disease. Therefore, developing novel molecular biomarkers that may be involved in the molecular mechanisms of endometrial carcinogenesis and progression is imperative.

Rubinstein *et al* (89) examined C1QBP expression in endometrial cancer via immunohistochemical staining and reported that no significant differential expression of C1QBP

was detected compared with non-malignant tissues of the same histology. However, another study noted that, compared with normal endometrium, C1QBP was more highly expressed in endometrial cancer and endometrial benign lesions and that the expression of C1QBP in endometrial carcinoma was significantly greater than that in endometrial benign lesions. In the study, high C1QBP expression was significantly associated with advanced International Federation of Gynecology and Obstetrics stage (P=0.019), high histological grade (P<0.001), deep myometrial infiltration (P=0.013), lymphatic vessel interstitial infiltration (P=0.010), lymph node metastasis (P=0.015) and recurrence (P=0.009). The results of the multivariate Cox regression analysis revealed that the C1QBP expression status was an independent prognostic factor for disease-free survival (P=0.022) and overall survival (P=0.025) in patients with endometrial cancer (5). Due to the limitations of the sample size and its single-region nature, further research is needed to reach a more definite conclusion. The research on C1QBP in endometrial cancer may have a relatively small sample size and insufficient statistical power, which limits the generalizability of the results. Moreover, if the data comes from a single medical institution, it may not be representative of the heterogeneity of a multi-center population. The results may not be representative of other populations with different environmental exposures. Therefore, large-scale, multi-center studies with diverse geographic cohorts are warranted to validate the independent prognostic value of C1QBP in endometrial cancer. Furthermore, since the patient groups were formed based on historical data rather than random allocation, the baseline characteristics, such as age, molecular subtype and treatment regimen, may be unbalanced, which could potentially confound the effect estimation. Comorbidities, treatment intensity or hormone receptor status may lead to the association between C1QBP and the outcome being partially attributed to unmeasured factors.

There are similar pathological and physiological connections among obesity, diabetes and endometrial cancer. The occurrence of endometrial cancer is related to factors such as hormonal level changes, metabolic abnormalities and chronic inflammation. Obese women have higher levels of estrogen in their bodies, which may stimulate the abnormal proliferation of endometrial cancer cells (85). Endometrial cancer also has an association with hypertension, mainly related to the shared metabolic abnormalities such as obesity and insulin resistance (90-92). The long-term chronic inflammation and hormone imbalance in the body of patients with hypertension may indirectly increase the risk of endometrial cancer, but the specific mechanism still needs further research (93). Moreover, women who experience menopause later in life have a relatively higher risk of endometrial cancer (94). The mechanism of endometrial cancer and C1QBP protein is still poorly understood at present. It is well established that estrogen and metabolic disorders are risk factors for endometrial cancer, and that C1QBP plays a central role in mitochondrial metabolism and tumorigenesis (95,96). Moreover, indirect evidence suggests that estrogen can regulate C1q, the primary ligand of C1QBP (97-99). Estrogen signaling and metabolic disorders such as obesity and diabetes may be associated with the potential role of C1QBP in the occurrence of endometrial cancer; however, there are no direct experimental data to support this conclusion at present and it should be regarded as a knowledge gap. Diabetes is an important risk factor for endometrial cancer in women and it has a negative impact on the survival rate and prognosis of patients. Molecular mechanisms such as the insulin-like growth factor family, oxidative stress and inflammatory cytokines have been considered to explain this relationship (100). C1QBP is involved in the regulation of OXPHOS and glucose oxidation (16). The absence of C1QBP is associated with resistance to age-related and diet-induced obesity (101). C1QBP promotes lipid biosynthesis by regulating fatty acid-induced endoplasmic reticulum stress (16,101). C1QBP interacts with the endoplasmic reticulum-anchored enzyme mannosyl-oligosaccharide glucosidase I (MOGS) (100,102). We hypothesize that the C1QBP-MOGS interaction represents a novel mitochondria-endoplasmic reticulum coordination mechanism, enabling cells to synchronize energy production (via mitochondrial OXPHOS) with protein synthesis and folding (via endoplasmic reticulum glycosylation). This coordination is particularly critical in rapidly proliferating endometrial cancer cells, which require both robust energy supply from mitochondria and extensive protein production from the endoplasmic reticulum. The findings highlight important directions for future research aimed at elucidating the precise molecular mechanisms by which C1QBP exerts its diverse biological functions. Few studies have explored the relationship between endometrial cancer and C1QBP and numerous basic studies are needed to further demonstrate the association between C1QBP and endometrial cancer and its specific molecular mechanisms.

5. Clinical applications of C1QBP in cancer

C1QBP, as a key protein highly expressed in various types of cancer, has demonstrated potential in clinical applications as a diagnostic biomarker, prognostic predictor and therapeutic target. C1QBP is involved in the occurrence, progression, metastasis and prognosis of cancer and can also be used as a molecular target for cancer treatment (32,103). C1QBP is upregulated in various tumor tissues and its high expression level is significantly associated with poor prognosis in patients. For instance, in oral squamous cell carcinoma, the expression levels of C1QBP and PA28γ are positively correlated and their high co-expression indicates a poor prognosis (104). Additionally, the mRNA expression level of C1QBP is significantly higher in TNBC tissues than normal tissues and its high expression is associated with a shortened disease-free survival period (105). Moreover, a C1QBP expression change may serve as an indicator of disease progression. For instance, in pancreatic cancer, the level of the exosomal CD44v6/C1QB complex can predict the risk of liver metastasis (40). Furthermore, C1QBP can also serve as an indicator for peritoneal and lymph node metastasis in EOC. In a previous study, among the 89 patients whose primary tumor immunohistochemical staining showed high expression levels of C1QBP, 95.5% had peritoneal metastasis and 48.3% had lymph node metastasis (12). Univariate and multivariate logistic regression analyses revealed that upregulation of C1QBP was associated with peritoneal dissemination and lymph node metastasis in EOC.

C1QBP plays a crucial role in DNA damage repair. For instance, in breast cancer, C1QBP regulates homologous

combination repair by stabilizing the MRE11 protein (41). C1QBP inhibition can enhance the efficacy of chemotherapy, a mechanism that provides a new approach for overcoming drug resistance. For example, combining a C1QBP inhibitor with DNA damage drugs may improve the therapeutic effect (106). Additionally, the role of C1QBP in metabolic regulation, such as mitochondrial OXPHOS, suggests that its targeted therapy may be applicable to tumors that are metabolically dependent. C1QBP, frequently upregulated in cancer, is secreted into the tumor microenvironment where it drives metastatic progression via the complement and kinin systems. Furthermore, C1QBP participates in a novel immune checkpoint axis; cancer cell-surface C1QBP directly interacts with cytotoxic T cells to suppress their activity, analogous to the established programmed cell death ligand 1 and programmed cell death protein 1 pathway (6).

Due to limitations such as insufficient sample size and the regional nature of sample collection, subsequent researchers can improve the experimental conclusion by increasing the sample size. According to existing research, the high immunohistochemical expression of C1QBP can serve as an indicator of poor prognosis for ovarian, cervical and endometrial cancer (3-5). Measuring the level of C1QBP in serum or abdominal fluid may be used for early diagnosis or recurrence monitoring. PDBAG1, a peptide derived from the precursor protein of glycerol-3-phosphate dehydrogenase 1, can directly bind to C1QBP and induce its ubiquitin-dependent degradation (43). In the TNBC model, PDBAG1 significantly inhibits tumor growth and induces regression (100). The LyP-1 peptide can specifically bind to C1QBP on the surface of tumor cells and be used for drug delivery (107). Additionally, the green tea polyphenol epigallocatechin gallate can bind to C1QBP and inhibit tumor growth (58). In addition, as a research target, anti-C1QBP monoclonal antibodies are currently being developed to block its tumor-promoting functions. C1QBP inhibitors combined with chemotherapy, such as paclitaxel and cisplatin, may reverse drug resistance. Studies have demonstrated the feasibility of the chimeric antigen receptor (CAR)-T cell immunotherapy approach in glioblastoma (108-110). C1QBP is highly expressed on the surface of tumor cells and can be used as a target antigen for immunotherapy, such as CAR-T and peptide vaccines. At present, there are no direct CAR-T products targeting C1QBP that have been approved. However, given its central role in T-cell metabolism, enhancing the function of C1QBP or maintaining mitochondrial health may become a strategy to overcome drug resistance. Besides, at present, no C1QBP-based diagnostic or therapeutic applications have entered clinical trials.

C1QBP is expressed in multiple intracellular locations such as mitochondria, cytoplasm and cell membranes, and its structural characteristics provide binding sites for small molecule or peptide drugs. Regarding tumor specificity, C1QBP is highly expressed in various tumor types, such as TNBC, oral squamous cell carcinoma and acute myeloid leukemia, but is expressed at a lower level in normal tissues (34,65,104). For instance, the mRNA level of C1QBP in TNBC is significantly higher than that in adjacent normal tissues, and its high expression is associated with poor patient prognosis (34). This differential expression may support the selectivity toxicity of targeted therapy. Regarding the safety and toxicity of C1QBP drugs, current studies show that targeting C1QBP has acceptable safety in animal models (43,100). For example, PDBAG1 inhibits the growth of TNBC tumors without reporting significant toxicity (43). However, C1QBP participates in basic metabolic functions such as mitochondrial homeostasis in normal cells and the potential toxicity needs further evaluation. The overall safety of C1QBP-targeted drugs, involving preclinical toxicity, clinical safety and the therapeutic window, still need to be verified through preclinical and clinical trials.

6. Summary and outlook

The present review summarized the research progress of C1QBP in cervical, ovarian and endometrial cancer (Fig. 3). Early gynecological tumors often have no notable symptoms or signs, but serum tumor markers, such as the now familiar biomarkers CA125 and HE4, are elevated to varying degrees (111,112). Tumor-related markers have important guiding significance for the early screening of gynecological tumors, adjuvant diagnosis, localization and diagnosis, therapeutic efficacy evaluation, prognosis assessment and targeted therapies. Numerous studies have demonstrated the potential of targeting C1QBP to treat various tumor types (6,43,65,82,113). C1QBP affects the proliferation and metastasis of gynecological tumors and has a certain impact on drug resistance. However, the future of C1QBP in clinical use as a diagnostic and prognostic marker for gynecological tumors still needs further basic experiments and clinical trials for verification.

Research on the role of C1QBP in gynecological tumors is still in its initial stage and there are several unresolved controversies and major research gaps. Firstly, there are disputes regarding the expression and function of C1QBP in gynecological tumors. For instance, in cervical cancer, the expression level of the homologous subunit of C1QBP is related to tumor progression, but the specific mechanism is still unclear and the evidence is limited. Additionally, the expression pattern and clinical significance of C1QBP in other gynecological tumors, such as ovarian and cervical cancer, have not been systematically studied. Different studies have differing opinions on whether C1QBP can serve as an independent prognostic marker. For example, in TNBC, high expression of C1QBP is associated with poor prognosis, but similar validation is lacking in gynecological tumors. Secondly, the molecular mechanism of C1QBP in gynecological tumors has not been elucidated. Studies have shown that C1QBP promotes tumor progression by regulating mitochondrial function, but the applicability of this mechanism in gynecological tumors is unknown. Therapeutic strategies targeting C1QBP face challenges. Although a peptide inhibitor, PDBAG1, has been found to inhibit tumors by inducing C1QBP degradation in breast cancer, the feasibility of this strategy in gynecological tumors is unknown and there is currently a lack of validation of the targeted effect in gynecological tumor-specific models. Moreover, the limitations of current research methods and data restrict progress. Current evidence mostly originates from retrospective cohorts or public databases, with small sample sizes and a lack of multicenter validation.

C1QBP may promote viral replication by inhibiting immune responses. For example, both hepatitis C virus (HCV)

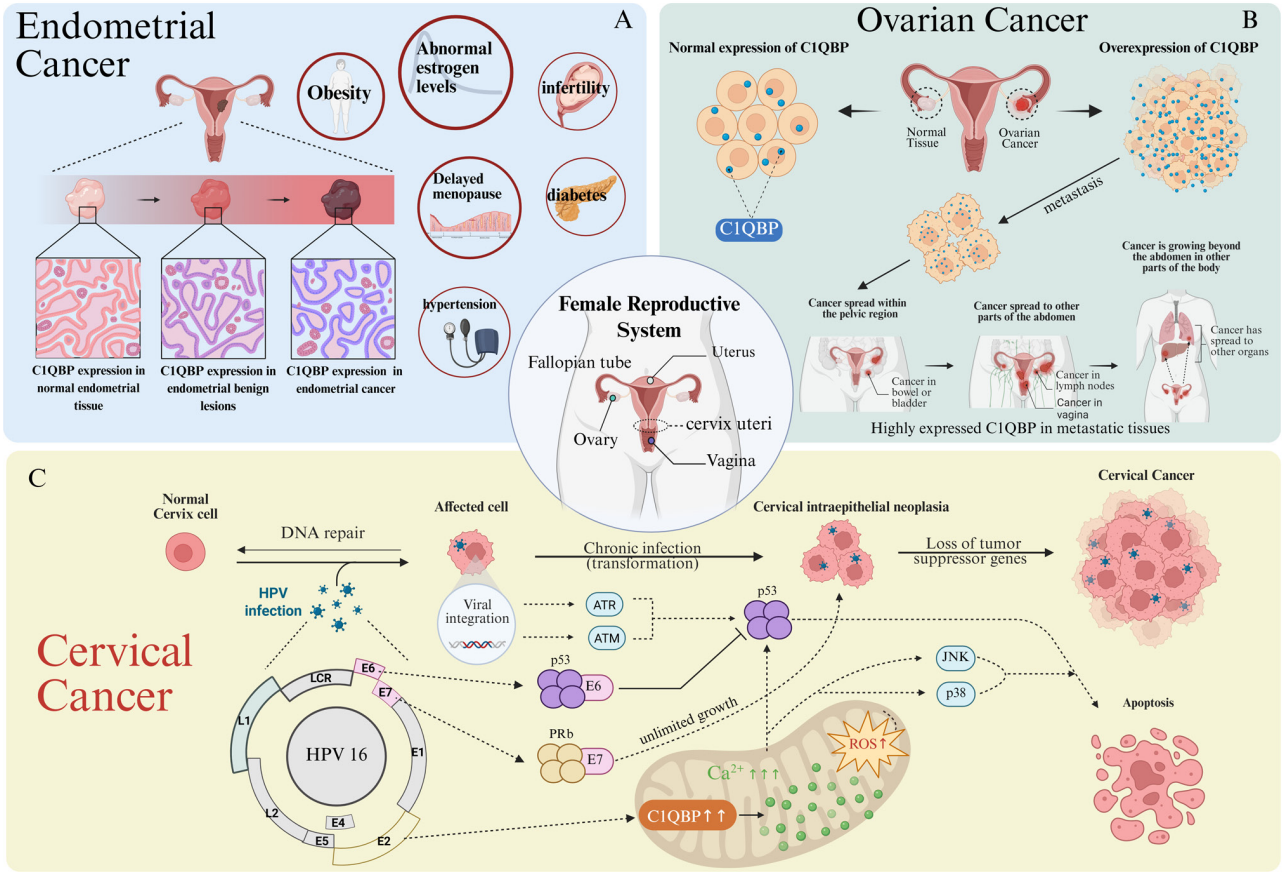

Figure 3. Role of C1QBP in gynecological tumors. (A) C1QBP and endometrial cancer. C1QBP may be used as a biomarker to predict the progression and prognosis of endometrial cancer (103). (B) C1QBP and ovarian cancer. C1QBP is highly expressed in ovarian cancer tissues and metastases and its expression level gradually increases with the grade and stage of the tumor, which is negatively correlated with the prognosis of the patient (4,64). (C) C1QBP and cervical cancer. C1QBP is involved in the immune escape of tumor cells in HPV16-induced cervical cancer. E2 induces apoptosis of cervical cancer cells by upregulating the expression of C1QBP (4,81). Another study has found two apoptosis pathways in cervical cancer cells that involve C1QBP, providing a new basis for finding new therapeutic targets for cervical cancer in the future (78). HPV, human papillomavirus; C1QBP, complement component 1 Q subcomponent-binding protein.

and human immunodeficiency virus can inhibit or destroy T cells via C1QBP, thus suppressing the body's immune response (84). The known causative virus of cervical cancer is HPV, and it is not clear whether there is a pathogenic effect between HPV and C1QBP similar to that between HIV and HCV with C1QBP. HPV-associated proteins influence cervical cancer development by affecting C1QBP. However, the exact mechanism needs to be further explored. C1QBP maintains OXPHOS and its absence increases glycolysis while impairing cell proliferation *in vitro* and tumor growth *in vivo* (114). In addition, mitochondria seem to play an intermediary role between C1QBP and gynecological tumors and it has been shown that C1QBP affects gynecological tumor development by regulating mitochondrial biogenesis and metabolic processes (16). Thus, the use of mitochondrion-targeted anticancer drugs mediated by C1QBP may constitute a novel strategy for treating gynecological tumors in the future. C1QBP may also be a potential molecular marker for diagnosing gynecological tumors and a new indicator for predicting the prognosis of this disease. Although C1QBP is highly expressed in most tumor tissues, whether it can be used as a predictive marker for the clinical progression of gynecologic tumors, either alone or in combination with other markers, needs to be confirmed by further studies.

C1QBP is a multifunctional protein that plays a crucial role in mitochondrial function, cellular metabolism and tumor progression. In the field of gynecological tumors, the research on C1QBP is still in its early stages. Future studies on C1QBP should focus on its molecular mechanisms and diagnostic and therapeutic potential while combining multidisciplinary techniques and cross-disciplinary collaborations to promote the translational application of C1QBP in gynecological oncology. These studies will not only help elucidate the pathogenesis of gynecological tumors in detail but may also provide an essential basis for the development of new diagnostic methods and therapeutic strategies. The main research focus in the future should be concentrated on the following aspects: i) Mechanism exploration: Deeply analyze the regulatory mechanisms of C1QBP in mitochondrial dynamics such as fusion and fission balance, OXPHOS activity and metabolic pathways in gynecological tumor cells, especially its role in chemotherapy resistance and the tumor microenvironment; ii) clinical relevance analysis: Through databases such as The Cancer Genome Atlas and clinical cohorts, the correlation between the expression level of C1QBP and the prognosis of patients with gynecological tumors (such as in terms of disease-free survival) should be clarified and its potential as a biomarker should be evaluated; and iii) targeted strategy

development: Explore molecular tools for direct targeting of C1QBP, such as peptide inhibitors or small molecule compounds, and draw on the strategy of PDBAG1 in TNBC research, which inhibits tumors by inducing the degradation of C1QBP, to optimize their applicability in gynecological tumor models. The transformation from basic research to clinical application needs to be carried out step-by-step: i) Based on the structural characteristics of C1QBP, such as the N-terminal functional domain, specific inhibitors can be discovered through high-throughput screening or computational simulation, and their killing effects on gynecological tumor cell lines and organoid models can be evaluated; ii) combining C1QBP-targeted drugs with existing therapies such as chemotherapy, poly ADP-ribose polymerase inhibitors or immunotherapy, to overcome drug resistance and improve efficacy, for example, by inhibiting mitochondrial function to enhance oxidative stress-induced cancer cell death; and iii) early clinical trials should be prioritized in gynecological tumors with active mitochondrial metabolism, such as ovarian cancer, while establishing biomarker detection methods to screen potential patient groups that may benefit.

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Authors' contributions

HZ contributed to conceptualization, writing the original draft, reviewing and editing the manuscript and visualization by designing and creating the mechanistic figures. JF contributed to reviewing and editing the manuscript and supervision. XZ, BL, TG and FF contributed to reviewing the manuscript and supervision. JL contributed to reviewing the manuscript, resources, supervision, funding acquisition and project administration. PZ contributed to editing the manuscript, resources, supervision and funding acquisition. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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