Serican Journal of Medicine
2025, VOL. 2, NO. 2, 23662
https://doi.org/10.17161/sjm.v2i2.23662

T Cell Immunity in Pathogenesis, Progression, and Malignant Transformation of Endometriosis

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ABSTRACT

Endometriosis is a common gynecological condition characterized by special features such as invasive growth, recurrence, and potential distant metastasis. Recent studies indicate an increasing incidence of malignant transformation of endometriosis. The mechanisms underlying the occurrence, progression, and malignancy of endometriosis are multifactorial, involving genetic alterations, environmental factors, hormonal imbalances, and immuno-inflammatory responses. Various T cell subsets play crucial roles in regulating immune responses and influencing disease progression and malignant risk. CD4+ T cells, including T helper (Th) cells (Th1, Th2, and Th17), regulatory T (Treg) cells, follicular helper T (Tfh) cells, and Th9 cells, alongside CD8+ T cells are essential for maintaining the immune microenvironment in endometriosis. Disruption of the balance among these T cell subtypes can promote chronic inflammation, immune evasion, and tissue remodeling that may facilitate malignant transformation. Therapeutic strategies targeting T cell function or restoring immune homeostasis hold promise for managing endometriosis through immunomodulation or checkpoint blockade therapy to prevent its malignant progression. This article reviews the role of T cells in the malignant transformation of endometriosis and proposes potential immunoregulatory treatment approaches.

ARTICLE HISTORY

Received: Feb. 25, 2025
Revised: March 15, 2025
Accepted: March 16, 2025

KEYWORDS

endometriosis; malignant transformation; endometriosis-associated ovarian cancer; CD4+ T cells; CD8+ T cells; immune microenvironment; T cell imbalance; immunotherapy

1. Background

Endometriosis is a common benign disease affecting women of childbearing age. However, its invasive growth, tendency to recur, and potential for "distant metastasis" resemble malignant tumors, suggesting that its occurrence and development may be closely linked to tumor pathogenesis [1]. Endometriosis incidence rate is on the rise annually. In the United States, the incidence rate increased from 5-10% in 2013 to 11% in 2018 [2]. The World Endometriosis Society reported that global endometriosis patients exceeded 200 million in 2017, with Asia having more patients than all other continents combined [3]. The formation of endometriosis lesions occurs when active endometrial tissue (including glands and stroma) grows outside the normal endometrium. Endometriosis exhibits characteristics similar to malignant tumors, such as invasive growth, distant metastasis, and recurrence, with significant potential for malignant transformation [1, 4]. In recent years, this transformation has increased alongside the rising incidence of endometriosis, with literature indicating a malignant transformation rate of approximately 1% to 2.5% [5, 6]. Additionally, patients with endometriosis face an elevated risk of developing epithelial ovarian cancer (EOC), which can be as high as 4 to 4.2 times of the general female population with the incidence of ovarian malignancies in endometriosis patients ranging from about 2% to 17% [7, 8]. Endometriosis is characterized by complex pathogenesis

that involves various abnormalities within the immune system [1]. T cells, as essential components of the immune response, play a pivotal role in initiation, progression, and potential malignant transformation of endometriosis [9, 10].

2. Risk Factors for Malignant Transformation of Endometriosis

At the core of endometriosis pathogenesis lies an unclear mechanism regarding its occurrence and development. Following the classic theory of "retrograde flow of menstrual blood", several alternative theories have emerged, including "coelomic metaplasia," "Mullerian duct remnants," and "*in situ* endometrial determinism." The theory of "*in situ* endometrial determinism" posits that the biological characteristics of *in situ* endometrium in patients with endometriosis differ from those found in the normal population, leading to enhanced abilities of invasion, migration, implantation, and angiogenesis. Consequently, after retrograde flow transports menstrual blood into the abdominal cavity and other regions, there is a heightened likelihood for the formation of endometriotic lesions [11,12]. Furthermore, a growing number of scholars contend that the development of endometriotic tissue is influenced by multiple factors, including environmental factors, genetic alterations, hormonal effects, and immune inflammatory responses [9,13-15]. Considering that endometriosis predominantly affects women of childbearing age, it is noteworthy that malignant tumors associated with endometriosis tend to have an earlier onset compared to typical ovarian cancers. Furthermore, the malignancy of these tumors is influenced by the duration of the disease. As the course of endometriosis extends over time, the associated risk of malignancy may consequently increase [16].

2.1. Environmental Factors

Environmental determinants, such as microorganisms, chemical exposure, tobacco use, and alcohol consumption, may significantly influence estrogen levels and facilitate the advancement of endometriosis [17,18]. Research has demonstrated that environmental determinants, including elevated concentrations of phthalates, persistent organic chlorine pollutants, and perfluorinated compounds, may precipitate the onset of endometriosis. Environmental toxicants can disrupt the female reproductive system as endocrine disrupters. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is resistant to degradation and accumulates in fat tissue and the food chain due to its lipophilic nature. TCDD can modulate transcription at various levels, including epigenetic changes and microRNA involvement, thereby disturbing physiological processes mediated by aryl hydrocarbon receptor pathways [19]. Alcohol may promote positive feedback mechanisms involving inflammatory mediators and oxidative stress, thereby facilitating the onset and progression of endometriosis [20]. Furthermore, maternal exposure to diethylstilbestrol during gestation is associated with an augmented risk of endometriosis in female progeny [21]. It is imperative to acknowledge that environmental factors are inherently variable, and their influence can be mitigated through deliberate lifestyle modifications.

2.2. Genetic Alterations

Endometriotic malignancy shares similarities with tumors and metabolic diseases in pathogenesis. It remains unclear whether mutated genes in epithelial cells interact with epigenetic defects in stromal cells during malignant transformation. However, research indicates that both endometriosis and tumors exhibit genetic instability, with ectopic endometrial epithelial cells showing multiple gene mutations [22-24]. In a previous study, the authors identified a significant genetic overlap between endometriosis and endometrial cancer [24]. Endometriosis exhibits a pronounced genetic susceptibility, with compelling evidence supporting the association between genetic polymorphisms and the condition [24, 25]. In epigenetics, gene expression can undergo heritable changes during mitosis or meiosis without altering the DNA sequence. These changes include DNA methylation, histone modifications, and non-coding RNAs. Endometrial stromal cells do not show somatic mutations but may have specific epigenetic abnormalities that affect key transcription factor expression. Overexpression of DNA methyltransferases (DNMTs) is a prerequisite for DNA hypermethylation [26-28].

2.3. Hormonal Effects and Metabolic Related Factors

Elevated estrogen levels and associated conditions that may contribute to increased hormone concentrations are closely linked to the malignant transformation of endometriosis. Under normal physiological conditions, estrogen and progesterone, along with their signaling pathways, are meticulously regulated to maintain a healthy menstrual cycle and support pregnancy. Disruption of this balance can lead to an

imbalance in regulatory mechanisms, resulting in a disordered progesterone response throughout the reproductive tract, including the endometrium, and may ultimately lead to estrogen dominance and progesterone resistance [23, 29-30]. Such imbalances can trigger pathological changes, while elevated levels of estrogen receptor-β contribute to pelvic inflammation and the malignant transformation of ectopic lesions [23, 30].

In addition, endocrine disorders are closely linked to the body's metabolic processes. Beyond hormone levels, metabolic dysregulation may also play a role in the progression and even malignant transformation of endometriosis. Several studies have established a rat model for the malignant transformation of endometriosis induced by high estrogen levels and diabetes. These studies have demonstrated that this model exhibits similar pathological progression, histological characteristics, and biological features to those observed in human endometriosis undergoing malignant transformation [31,32]. It has been hypothesized that diabetes and abnormal glucose metabolism may serve as risk factors for the malignant transformation of endometriosis through influencing estrogen levels [31]. Previous studies have indicated that a high-fat diet, particularly the intake of saturated fats and trans fatty acids, can adversely affect metabolic processes in the body and promote chronic inflammatory responses. A high-fat diet may influence estrogen levels within the body and enhance the proliferation and invasive capacity of ectopic endometrial cells through the release of inflammatory factors. Additionally, it may increase the generation of free radicals and elevate oxidative stress levels, potentially leading to DNA damage, triggering gene mutations, and increasing the likelihood of carcinogenesis [33-35].

2.4. Immune Inflammatory Responses

Chronic inflammation is a significant pathological feature of endometriosis. Endometriosis is commonly regarded as an immune-related inflammatory disease. Research indicates that there are differences in the expression of inflammatory cytokines in the serum, peritoneal fluid, and ectopic lesions of patients with endometriosis, which may play an indispensable role in the growth, invasion, differentiation, angiogenesis, and immune evasion associated with endometriosis and its related tumors [36,37]. Various subsets of T cells play a crucial role in the inflammatory and immune pathogenesis of endometriosis and may even lead to cancer development [36]. In a recent study, menstrual fluid from women with and without endometriosis was used for immunophenotyping to establish a mouse endometriosis model. The results revealed that the ratio of aged and pro-angiogenic neutrophils in the menstrual effluent of women with endometriosis were increased compared to the controls, suggesting a potentially permissive pro-inflammatory microenvironment [38].

3. Pathological Features of Malignant Transformation of Endometriosis

Recent studies have further highlighted the role of the innate immune system in shaping the inflammatory microenvironment of endometriosis. In both endometriosis and cancer, macrophages guard the lesions from immune surveillance while promoting pathological cell growth, invasion, and metastasis [39]. Macrophages have been found to be significantly increased in the peritoneal fluid of endometriosis patients, which contribute to tissue remodeling, angiogenesis, and immune suppression, and facilitate the persistence and progression of ectopic lesions [39,40]. A study has shown that under the action of tumor necrosis factor-alpha (TNF-α), embryonic stem cells (ESC) - derived IL-6 and MCP-1 could stimulate peritoneal macrophages toward M2-polarization, which could modulate endometriosis [41]. In addition, dendritic cells in endometriotic lesions exhibit altered antigen-presenting capabilities, potentially leading to immune tolerance and disease chronicity. In addition, immune dysregulation, particularly the imbalance of Regulatory T cells (Tregs) and T-helper 17 (Th17) cells, plays a significant role in the pathogenesis of endometriosis [37, 14]. The pro-inflammatory microenvironment is characterized by elevated levels of cytokines such as TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β), which contribute to the pain, fibrosis, and lesion growth. These cytokines also activate nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3) pathways, further intensifying the inflammatory responses while enhancing the survival and invasiveness of endometriotic cells [42, 43].

The diagnostic criteria for malignant transformation of endometriosis were first proposed by Sampson and later refined by Scott, including: (1) the presence of both tumor tissue and ectopic endometrium; (2) the pathological types of malignancy resembling

those of ectopic endometrium; (3) tumors originating from ectopic endometrial lesions, excluding other primary tumors; (4) histological evidence under microscopy showing the transition from ectopic endometrium to malignancy (ectopic epithelium with atypical hyperplasia and cancer). Due to the long history of endometriosis, existing lesions may be obscured by rapidly growing cancer cells, making small lesions easily overlooked during sampling. Additionally, fully meeting these diagnostic criteria can be challenging, leading to potential missed diagnoses [4, 44].

Atypical endometriosis is regarded as a "precancerous lesion" of endometriosis prior to malignant transformation, or as a "borderline" and "transitional state," akin to the progression of endometriotic lesions into cancer. This condition is characterized by the morphological heterogeneity of endometrioid glands [45,46]. In numerous instances of malignant transformation associated with endometriosis, histological evidence of endometrial metaplasia is frequently observed, which may also represent a significant precancerous lesion. Among these, epithelial metaplasia occurring in the upper skin and ciliated fallopian tubes are the most prevalent forms. However, due to the subtle morphology exhibited by endometrial metaplasia, it is often misinterpreted as a benign alteration [46].

The ovary is the most frequently affected site in cases of endometriosis-associated malignancy, which may arise from ectopic endometrial glands and stroma. The two predominant types of endometriosis-associated ovarian cancer (EAOC) are ovarian clear cell carcinoma (OCCC) and ovarian endometrioid carcinoma (OEC), both characterized by glandular formation. Additionally, ectopic endometrial stroma can give rise to endometrial stromal sarcoma [47,48]. In the study conducted by Matalliotakis et al., it was found that endometrioid carcinoma accounted for 60% of cases, followed by clear cell carcinoma at 20%, with serous and invasive adenocarcinoma also comprising 20% [43]. In addition, a small portion of malignant transformation occurs outside the ovaries, known as extraovarian endometriosis-associated cancer (EOEAC). This includes all potential sites of endometriosis such as the intestine, pelvic peritoneum, vaginal rectovaginal septum, vagina, cesarean scar, external and perineal incisions, bladder, ureter, etc [49].

4. T Cells and Malignant Transformation of Endometriosis

4.1. CD4+ T cells

CD4+ T cells are crucial in the immune microenvironment of endometriosis and cancer as summarized in Table 1 and Figure 1. Different subtypes can either promote or inhibit disease progression, underscoring their complex roles in these conditions.

4.1.1. Th1 Cells

Th1 cells are crucial for anti-tumor immunity by secreting cytokines like interferon-gamma (IFN-γ), which activate macrophages and cytotoxic T lymphocytes (CTLs) to improve tumor cell recognition and destruction. They can directly induce tumor cell apoptosis through the Fas/FasL pathway and enhance the immune response by releasing IFN-γ, which also reduces regulatory T cells (Tregs), thereby boosting CTL-mediated cytotoxicity [50, 51]. The levels of IFN-γ in the peritoneal fluid of endometriosis patients are reduced, indicating impaired Th1 cell function. This may lead to decreased immune surveillance, allowing ectopic endometrial cells to survive, grow, and undergo malignant transformation [52]. However, Th1 cell function is often suppressed in cancer patients, weakening their immune response. Research shows that Th1 cytokines such as IFN-γ and IL-2 are significantly reduced in laryngeal and bladder cancer patients, while Th2 cytokines (IL-10, IL-6) are overexpressed, resulting in a Th1-to-Th2 shift that impairs cellular immunity [53]. Recent studies suggest that the IFN-γ-signal transducer and activator of transcription 1 (STAT1) pathway upregulates regulator of G-protein signaling-1 (RGS1) expression in Th1 cells, inhibiting their migration into tumors. Targeting RGS1 may enhance T-cell infiltration, suppress tumor growth, and improve immunotherapy efficacy [54].

4.1.2. Th2 Cells

In endometriosis patients, the Th1/Th2 ratio significantly shifts towards Th2 dominance. This results in an enhanced humoral immune response and a relatively weakened cellular immune response [55]. Abnormal activation of Th2 cells can promote the occurrence, development, and malignancy of endometriosis through immune suppression, chronic inflammation, and angiogenesis. Th2 cells secrete IL-4, IL-5, IL-10, and IL-13, which aid tissue repair but

also suppress anti-tumor immunity. These cytokines can induce tumor-associated macrophages (TAM) to polarize towards the M2 phenotype. M2-type TAMs have immunosuppressive functions that inhibit effector T cell activity by releasing inhibitory cytokines like IL-10 and TGF-β, thereby weakening the body's anti-tumor response [52, 56]. Additionally, Th2 cells suppress CD8+ cytotoxic T cells and natural killer (NK) cell activity, and cytokines such as IL-4 and IL-13 further promote chronic inflammation that creates a local tumor microenvironment favorable for cancer progression [57]. Moreover, IL-4 and IL-13 from Th2 cells activate the STAT6 signaling pathway to enhance vascular endothelial growth factor (VEGF) expression, increasing tumor angiogenesis and supplying nutrients and oxygen for tumor growth and metastasis [58].

4.1.3. Th17 Cells

Th17 cells secrete various pro-inflammatory cytokines and immune regulatory factors involved in inflammation, autoimmune diseases, and cancer progression. Th17 cells secrete IL-17, which plays a crucial role in recruiting neutrophils and promoting inflammation [59,60]. IL-17 has been implicated in tumor progression through the mechanism of chronic inflammation. It facilitates angiogenesis and formation of new blood vessels, thereby supporting tumor survival [60-62]. The tumor-associated macrophages in the tumor microenvironment produce high levels of chemokines, attracting tumor antigen-specific T cells to the periphery and activating them. These T cells subsequently activate inflammatory pathways in macrophages, recruit neutrophils, and trigger angiogenesis, ultimately promoting liver cancer progression [62]. They are also involved in epithelial-mesenchymal transition (EMT), a critical process in cancer invasion and metastasis [63]. Elevated levels of Th17 cells have been observed in both endometriotic lesions and endometriosis-associated cancers, establishing a link between chronic inflammation and malignancy [64]. Additionally, Th17 cells also secrete IL-17F, IL-21, IL-22, and TNF-α . IL-17F enhances inflammatory responses but has lower activity than IL-17A. IL-21 promotes Th17 cell proliferation and boosts B cell differentiation and antibody production. IL-22 supports epithelial cell proliferation and survival, potentially contributing to autoimmune diseases by stimulating inflammation [65].

4.1.4. Regulatory T cells (Treg)

Regulatory T cells (Tregs) play a complex role in the occurrence, development, and potential carcinogenesis of endometriosis. On one hand, Tregs are crucial for maintaining immune tolerance and controlling inflammation. Their deficiency leads to increased pro-inflammatory factors like TNF-α, IL-6, IL-17, and IFN-γ, resulting in heightened local inflammatory responses. Lack of Tregs can cause uncontrolled inflammation and abnormal angiogenesis, facilitating the implantation and growth of endometriosis [66,67]. On the other hand, Tregs promote blood vessel formation in ectopic endometrial tissue by secreting angiogenic factors such as vascular endothelial growth factor (VEGF), which supports lesion nourishment and growth [68]. Disruption of Treg function may impair anti-tumor immune responses, allowing abnormal cells to evade immune surveillance. Cytokines like TGF-β can induce epithelial-mesenchymal transition (EMT), increase cell invasiveness, and elevate cancer risk [68]. Recent studies on patients with endometriosis have focused on naive/resting $FOXP3^{low}CD45RA^{+}$ Treg cells that differentiate into activated/effector $FOXP3^{high}CD45RA^{-}$ Treg cells upon stimulation via the T cell receptor, demonstrating strong immunosuppressive activity [69].

4.1.5. Tfh cells

Follicular helper T cells (Tfh cells) are a specialized subset of CD4+ T cells that primarily facilitate humoral immune responses by assisting in B cell differentiation and antibody production. Within the tumor microenvironment, Tfh cells exhibit complex roles as they may indirectly promote tumor immune evasion by supporting specific B cell subsets that produce inhibitory antibodies or regulatory cytokines [70]. Although direct investigations into the role of Tfh cells in endometriosis are still emerging, current findings suggest a potential link between Tfh cell-mediated humoral immunity and the pathogenesis of this condition. Emerging studies indicate that in endometriosis the local immune environment is altered, with Tfh cells potentially playing a contributory role. In cases of chronic endometrial inflammation, an increase in either the number or activity of Tfh cells could drive aberrant B cell responses and autoantibody production. This dysregulation may further exacerbate the inflammatory microenvironment,

potentially contributing to lesion persistence and adverse reproductive outcomes [71]. Additionally, Tfh cells possess the capacity to regulate macrophages, which play a crucial role in mediating cell-to-cell interactions, particularly M2 macrophages [72]. Therefore, Tfh cells may play a role in endometriosis and its malignancy through the following mechanisms: abnormal B cell activation and autoantibody production to exacerbate chronic inflammation, promoting M2 macrophage polarization, enhancing the immunosuppressive microenvironment; and facilitating angiogenesis to improve tumor adaptability [70-72].

4.1.6. Th9 Cells

Currently, the specific mechanisms by which Th9 cells influence cancer are still under active investigation. The role of Th9 cells in oncogenesis often exhibits a "double-edged sword" effect as they may enhance anti-tumor immunity, but in certain contexts, they may facilitate tumor growth [73]. Their precise function is intricately linked to factors such as tumor type, microenvironment, and the local cytokine network [74-75]. Th9 cells primarily secrete interleukin-9 (IL-9), which exerts pro-inflammatory effects in chronic inflammatory diseases. However, the precise role of IL-9 in endometriosis remains unclear and may be associated with the promotion of cytokines such as IL-8, thereby enhancing inflammatory responses [76]. Overall, the involvement of Th9 cells in endometriosis and tumorigenesis appears to be context-dependent, potentially amplifying inflammation through IL-9 while also interacting with the local immune microenvironment in ways that could either suppress or promote disease progression.

4.2. CD8+ T Cells

CD8+ T cells are the primary cytotoxic T cells in the body, playing a critical role in immune surveillance by identifying and eliminating abnormal or mutated cells. Under normal conditions, CD8+ T cells target potential tumor cells through the release of effector molecules such as perforin and granzyme, thereby preventing malignant transformation [77,78]. In patients with endometriosis, CD8+ T cells may be suppressed, affecting their quantity, activity, and function. This hinders the clearance of ectopic endometrial cells and may contribute to endometriosis progression.CD8+ cytotoxic T lymphocytes (CTLs) are key immune cells for targeting cancer. During cancer progression, CTLs often experience dysfunction and exhaustion due to immune tolerance and suppression in the tumor microenvironment

Table 1. CD4+ T cell subtypes and their roles in the immunity of endometriosis and tumor.

CD4+ T Cell Subtype	Key Cytokines	The role in endometriosis	The role in tumor
Th1 Cells [50-54]	IFN-γ, IL-12	Activate macrophages to eliminate ectopic endometrial tissue, but excessive activation may cause chronic inflammation	Enhance CD8+ T cell cytotoxicity; chronic inflammation may lead to tissue damage
Th2 Cells [55-58]	IL-4, IL-5, IL-13	Promote B cell antibody production, suppress Th1 responses, leading to immune evasion	Promote TAMs, which suppress antitumor responses*
Th17 Cells [59-65]	IL-17, IL-22, IL-21	Induce chronic inflammation, enhance angiogenesis in ectopic endometrial tissue, promote disease progression	Recruit neutrophils and promote tissue inflammation; chronic inflammation and angiogenesis (new blood vessel formation) may support tumor growth
Treg Cells [66-69]	IL-10, TGF-β	Suppress excessive inflammation, maintain immune tolerance, but excessive function may allow immune evasion of ectopic tissue	Suppress CD8+ T cells, NK cells, and Th1 responses, leading to tumor immune evasion
Tfh Cells [70-72]	IL-21, IL-6	Promote B cell activation, possibly enhance antibody-mediated inflammation	Help B cells produce high-affinity antibodies, which may aid antitumor responses; may promote B cell-driven immunosuppressive environments
Th9 Cells [73-76]	IL-9	May enhance inflammatory responses	Enhance antitumor immunity by recruiting mast cells and promoting CD8+ T cell function; overactive Th9 responses may lead to excessive inflammation

*TAMs: tumor-associated macrophages.

(TME), promoting adaptive immune resistance. Cancer-associated fibroblasts (CAFs), M2 macrophages, and regulatory T cells (Tregs) can create immunologic barriers against CD8+ T cell-mediated antitumor responses [79]. Accompanying changes in CD4+ T cells, there may be a significant reduction in effector CD8+ T cell populations and natural killer (NK) cells, while monocytes/macrophages increase, particularly in peripheral blood and peritoneal fluid. The activity of CD8+ T cells may be suppressed or exhibit signs of exhaustion, characterized by decreased secretion of cytotoxic factors alongside increased expression of inhibitory immune checkpoints such as programmed cell death protein 1(PD-1) [78,80-82].

5. The T Cell Imbalance in EAOC

Various Th cells interact with Treg cells in terms of quantity and function. When the balance between Th cells and Treg cells is disrupted, the immune microenvironment may lean towards an immunosuppressive state. This state not only weakens the clearance of potential malignant cells in endometriosis lesions but may also provide favorable conditions for tumor growth and metastasis, especially effector T helper cells (such as Th1 and Th17 cells) and regulatory T cells (Treg cells) play a key role in regulating immune responses [52-55,61]. In patients with endometriosis, there is a significant shift in the balance of Th cell subsets. The Th1/Th2 ratio changes to a predominance of Th2 cells in endometriosis patients. Their secreted cytokines, such as IL-4, IL-10, and IL-13, are highly expressed in the serum of these patients, while Th1-related cytokines like interferon-γ (IFN-γ) are relatively low. This advantage of Th2 cells leads to a dominant humoral immune response, which may reduce the immune monitoring and clearance ability of ectopic endometrial tissue, promoting its survival, growth, and potential malignancy at ectopic sites [55]. The interaction between Tregs and Th17 cells leads to an immunological imbalance that sustains chronic inflammation and hinders the immune-mediated clearance of ectopic endometrial tissue. This imbalance may also promote lesion persistence and malignant progression by creating a permissive inflammatory and immunosuppressive microenvironment [83]. It has been reported that the Th17 and Treg cells were both found in peripheral blood and ascites among individuals with tumors, but the balance between Th17 and Treg cells was disrupted [83-85]. Furthermore, a study quantified the ratio of Treg/Th17 cells to investigate their prognostic impact in high-grade serous tubal ovarian cancer and found that the lower ratios positively influenced overall survival in patients [86].

The imbalance among T helper cells, Treg and CD8+ T cells in endometriosis leads to a chronic inflammatory and immunosuppressive microenvironment. In this context, the predominance of Th2 cells reduces immune surveillance, while inflammation driven by Th17 facilitates the persistence of lesions. Furthermore, Treg cells inhibit anti-tumor immunity, and dysfunction of CD8+ T cells undermines cytotoxic responses. Moreover, autoantibodies in the T-cell immune network contribute to immune dysregulation. The immune suppression observed within the endometriosis-associated ovarian cancer microenvironment promotes tumor immune evasion, growth, and metastasis. Collectively, these factors enhance the survival of ectopic tissue, facilitate malignant transformation, and drive disease progression [52-55,61,83-86].

6. Potential Therapeutic Strategies

The balance among Th cells, CD4+ T cells, and CD8+ T cells, is crucial for immune defense, tumor immunity, chronic infections, and autoimmune diseases. Future research and immunotherapeutic strategies may modify these immune regulatory mechanisms to enhance anti-tumor and anti-infective immunity. Given the role of T cells in endometriosis and its associated ovarian cancer, targeting T cell pathways may guide future immunotherapy for prevention and treatment. T cell-targeted therapies include: IL-17 inhibitors (e.g., Secukinumab) to suppress Th17-mediated inflammation; TGF-β pathway inhibitors to block Tregs-mediated immune suppression and epithelial-mesenchymal transition (EMT); PD-1/PD-L1 checkpoint inhibitors (e.g., Nivolumab) that restore CD8+ T cell activity; VEGF inhibitors (e.g., Bevacizumab) that inhibit angiogenesis; and Th1 stimulation therapies (e.g., IFN-γ enhancers) to boost Th1 activity for improved immune surveillance [87-89]. In 2018, U.S. Food and Drug Administration (FDA) granted approval for the use of Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), in conjunction with chemotherapy for patients diagnosed with stage III or IV ovarian cancer following initial surgical intervention. This was subsequently followed by its administration as monotherapy [87-89]. Atezolizumab is a monoclo-

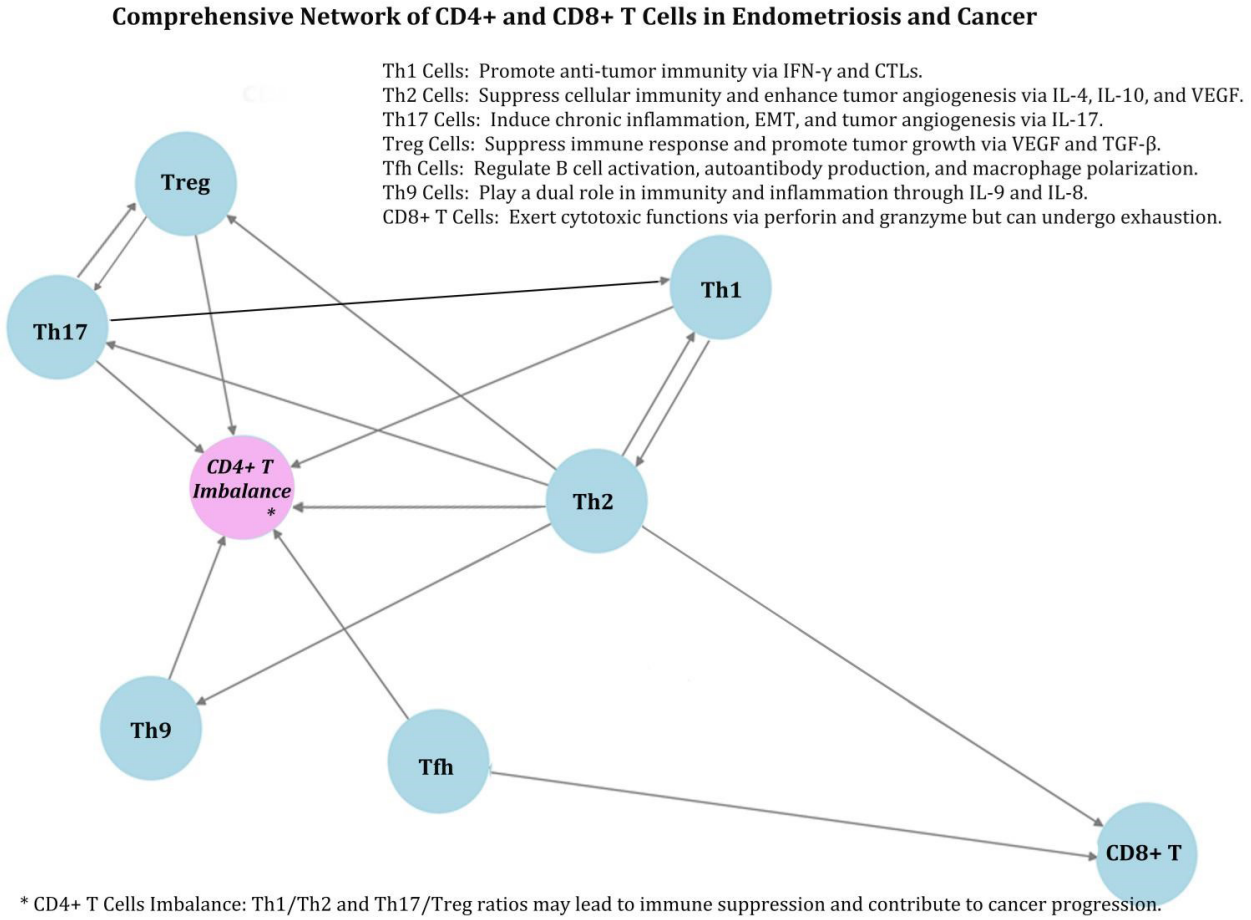

Figure 1. T cell network associated with endometriosis and its malignant transformation.

nal antibody targeting PD-L1, which enhances the anti-tumor activity of T cells by inhibiting the interaction between PD-L1 and its receptors, PD-1 and CD80. Atezolizumab has received approval from the FDA for the treatment of urothelial carcinoma, non-small cell lung cancer, among other indications; however, its application in ovarian cancer remains under investigation [90].

As mentioned earlier, functional defects in CD8+ T cells are linked to the onset and progression of endometriosis and endometriosis associated ovarian cancer. Appropriate immunotherapy can reactivate or initiate CD8+ T cells, transforming them into effector CTLs that infiltrate tumors and effectively kill cancer cells. Checkpoint receptors such as programmed death-1 (PD-1) and CTL associated antigen 4 (CTLA-4) can be targeted to reduce CD8+ T cell depletion and renew their activation, aiding in the elimination of antigen-secreting cancer cells [79]. Ipilimumab is a humanized IgG1 monoclonal antibody targeting CTLA-4, approved by the FDA for treating metastatic melanoma. Research shows that combining ipilimumab with other immune checkpoint inhibitors (like PD-1 inhibitors) can significantly enhance efficacy in certain cancer patients. In endometriosis and related cancers, CTLA-4 may play a role in disease development, but its specific mechanisms require further investigation [91].

In addition, research has found a positive feedback loop between tumor-infiltrating effector T cells and TAMs. IFN-γ produced by T cells polarizes TAMs to an M1-like phenotype, which in turn remodels the tumor microenvironment to enhance T cell infiltration, immune function, and tumor rejection. Enhancing the role of TAMs in the tumor microenvironment may also represent a potential direction for cancer therapy [92]. Recent studies indicate that the unique environment of mediastinal lymph nodes influences CD8+ T cell priming, which is crucial for lung cancer immune responses. The level of Th1 polarization in Treg cells among cancer patients is associated with unfavorable outcomes in check-

point inhibition immunotherapy. Furthermore, Type 1 conventional dendritic cells (DC1s) in the mesenteric lymph nodes are ineffective at eliciting robust cytotoxic T cell responses. High levels of IFN-γ can drive the differentiation of Treg cells into Th1-like effector Treg cells, thereby enhancing anti-tumor effects [93]. Furthermore, calcitonin gene-related peptide (CGRP) significantly influences pain mechanisms in endometriosis by altering macrophage phenotypes to a pro-endometriosis state. CGRP-stimulated macrophages showed impaired efferocytosis and promoted endometrial cell growth in a RAMP1-dependent manner [94]. FDA has approved several medications that block the calcitonin gene-related peptide (CGRP), including Amikacin, Galcanalizumab, and Remdesipram. The potential application of these drugs in the management of endometriosis is currently under investigation [94,95].

7. Conclusion

T cells play an important role in the pathogenesis, progression, and potential malignant transformation of endometriosis. The imbalance of helper T cell subsets, dysfunction of CD8+ T cells, and changes in the immune microenvironment may all influence disease progression. Further research on the role of T cells in endometriosis can provide new insights for the diagnosis and treatment of this condition.

Acknowledgements: Dr. Kana Wang was supported by the Natural Science Foundation of Sichuan Province (No. 2022NSFSC0790).

Conflicts of interest: The authors have no conflicts of interest to declare.

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