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REVIEW

Inflammation and Immune Escape in Ovarian Cancer: Pathways and Therapeutic Opportunities

Chunyan Liu[1,*], Qinan Yin[2,3,*], Zhaoying Wu[1], Wenhui Li[1], Jun Huang[1], Bo Chen[1], Yanjun Yang[1], Xuewei Zheng[3], Li Zeng[3], Jingjing Wang[3]

[1]Department of Obstetrics and Gynecology, China-Japan Friendship Hospital, Beijing, People's Republic of China; [2]Department of Radiation Oncology, First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, Luoyang, People's Republic of China; [3]Precision Medicine Laboratory, School of Medical Technology and Engineering, Henan University of Science and Technology, Luoyang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chunyan Liu, Department of Obstetrics and Gynecology, China-Japan Friendship Hospital, No. 2 Yinghua Dongjie, Chaoyang District, Beijing, 100029, People's Republic of China, Email juneliu2022@126.com

Abstract: Ovarian cancer (OC) remains one of the most lethal gynecological malignancies, largely due to its late-stage diagnosis and high recurrence rates. Chronic inflammation is a critical driver of OC progression, contributing to immune evasion, tumor growth, and metastasis. Inflammatory cytokines, including IL-6, TNF-α, and IL-8, as well as key signaling pathways such as nuclear factor kappa B (NF-kB) and signal transducer and activator of transcription 3 (STAT3), are upregulated in OC, promoting a tumor-promoting environment. The tumor microenvironment (TME) is characterized by immune cells like tumor-associated macrophages (TAMs) and regulatory T cells (Tregs), which suppress anti-tumor immune responses, facilitating immune evasion. Furthermore, OC cells utilize immune checkpoint pathways, including PD-1/PD-L1, to inhibit cytotoxic T cell activity. Targeting these inflammatory and immune evasion mechanisms offers promising therapeutic strategies. COX-2 inhibitors, Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway blockers, and NF-kB inhibitors have shown potential in preclinical studies, while immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 have been explored with mixed results in OC. Additionally, emerging research on the microbiome and inflammation-related biomarkers, such as microRNAs (miRNAs) and exosomes, points to new opportunities for early detection and precision medicine. Future approaches to OC treatment must focus on personalized strategies that target the inflammatory TME, integrating anti-inflammatory therapies with immunotherapy to enhance patient outcomes. Continued research into the interplay between inflammation and immune evasion in OC is essential for developing effective, long-lasting treatments.

Keywords: ovarian cancer, inflammation-driven mechanisms, evasion of immune response, therapeutic strategies

Introduction

Ovarian cancer (OC) is one of the most lethal gynecological malignancies, with a high mortality rate due to its late-stage diagnosis and frequent recurrence. It is one of the most common cancers among women worldwide, and despite advances in surgery and chemotherapy, the overall five-year survival rate remains less than 50%.[1,2] Over the last decade, cost-effective strategies for early detection and prevention of OC have been explored. However, OC remains one of the most financially burdensome cancers to treat, with the average initial treatment cost reaching approximately USD 80,000 in the first year and escalating to USD 100,000 or more in the final year of care.[3] Most OC patients are diagnosed at an advanced stage, when the disease has already spread beyond the ovaries.[4]

This delayed diagnosis is primarily due to the asymptomatic nature of early-stage ovarian cancer and the lack of reliable screening methods.[5] Currently, CA125 and HE4 are the only approved biomarkers for use in epithelial ovarian cancer (EOC), but they are insufficient for early detection. To address these limitations, multivariate index (MVI) assays, such as the Risk of Malignancy Algorithm (ROMA), have been developed. ROMA integrates menopausal status, CA125, and HE4 levels to improve diagnostic accuracy, particularly during the pre-surgical evaluation of adnexal masses. Additionally, microRNAs (miRNAs) show promising potential in various aspects of EOC prediction. However, further

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work is needed to establish their characterization and clinical utility as biomarkers.[6] Even though treatments such as surgery and platinum-based chemotherapy can initially be effective, most patients eventually develop resistance to treatment, leading to disease recurrence and poor outcomes.[7] Among the key mechanisms driving OC progression, the PI3K pathway is frequently upregulated in EOC and plays a pivotal role in chemoresistance and the preservation of genomic stability. This pathway is critical for regulating DNA replication and cell cycle progression. However, inhibition of PI3K can disrupt these processes, leading to genomic instability and mitotic catastrophe. Specifically, reduced activity of the spindle assembly checkpoint protein Aurora kinase B may result in increased occurrence of lagging chromosomes during prometaphase, contributing to mitotic failure and cell death.[8] These clinical challenges highlight the urgent need for a deeper understanding of the underlying mechanisms driving OC progression and for the development of new therapeutic strategies.

Chronic inflammation has been increasingly recognized as a key factor in the development and progression of many cancers, including OC.[9] Inflammation is a complex biological response to harmful stimuli, such as infection or tissue damage, and is characterized by the activation of immune cells, the release of pro-inflammatory cytokines, and the recruitment of additional immune cells to the site of injury.[10] While acute inflammation is a protective response that facilitates tissue repair and resolution of infection, chronic inflammation can lead to tissue damage, genomic instability, and the promotion of cancerous growth.[11] The chronic inflammation has been linked to several risk factors, including endometriosis, pelvic inflammatory disease, and obesity in OC.[12] These conditions create a pro-inflammatory environment that promotes tumorigenesis through the sustained activation of inflammatory pathways and immune cell infiltration into the tumor microenvironment (TME).[13]

The TME in OC is a complex and dynamic system that plays a critical role in disease progression. It is composed of cancer cells, stromal cells, immune cells, and various soluble factors such as cytokines and chemokines.[14] Chronic inflammation within the TME creates conditions that promote the survival, proliferation, and dissemination of cancer cells.[11] Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) are frequently upregulated in OC and have been shown to promote tumor growth and metastasis.[15] These cytokines activate key signaling pathways such as the nuclear factor kappa B (NF-kB) and signal transducer and activator of transcription 3 (STAT3) pathways, which are known to drive cell survival, proliferation, and resistance to apoptosis.[16,17] Moreover, chronic inflammation can lead to the recruitment of TAMs and other immunosuppressive cell types, which further exacerbate tumor progression by promoting immune evasion.[18]

One of the hallmark features of cancer is its ability to evade the immune system, and chronic inflammation plays a pivotal role in facilitating this immune evasion.[13] In OC, tumor cells exploit the inflammatory microenvironment to escape immune surveillance by downregulating the expression of major histocompatibility complex (MHC) molecules, which are critical for antigen presentation to T cells.[19] This prevents the immune system from recognizing and eliminating cancer cells.[19] In addition, OC cells often overexpress immune checkpoint molecules such as programmed death-ligand 1 (PD-L1), which binds to programmed death-1 (PD-1) receptors on T cells, leading to the suppression of T cell activity and the inhibition of antitumor immune responses.[20] This immune checkpoint pathway has become a major target for cancer immunotherapy, and several clinical trials are currently investigating the efficacy of PD-1/PD-L1 inhibitors in OC.[21]

Another important mechanism by which inflammation promotes immune evasion in OC is through the recruitment of immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[22] These cells secrete anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which suppress the activation and function of cytotoxic T cells.[23] This creates an immunosuppressive environment that allows OC cells to thrive and metastasize. The presence of high levels of Tregs and MDSCs in OC has been associated with poor prognosis and resistance to immunotherapy.[24] Therefore, targeting these immunosuppressive cells and their associated signaling pathways may represent a promising therapeutic strategy for overcoming immune evasion in OC.

Given the critical role of inflammation in OC progression and immune evasion, there has been growing interest in developing anti-inflammatory therapies as potential treatments for this disease. Several preclinical and clinical studies have investigated the use of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and corticosteroids in OC.[25–27] COX-2 is an enzyme that is upregulated in many cancers, including OC, and is involved in the production of pro-inflammatory prostaglandins that promote tumor growth and metastasis.[28] COX-2 inhibitors have

shown promise in reducing tumor growth and enhancing the efficacy of chemotherapy in preclinical models of OC.[29] However, the clinical benefits of these agents in OC patients have been limited, and further research is needed to determine their potential as part of combination therapy regimens.[30]

In addition to traditional anti-inflammatory drugs, targeted therapies that inhibit key inflammatory signaling pathways such as NF-kB and STAT3 are also being explored. These pathways are frequently dysregulated in OC and play a central role in mediating the effects of chronic inflammation on tumor growth and immune evasion.[31] Inhibitors of these pathways have shown efficacy in preclinical models, but their clinical utility in OC remains to be fully established. Furthermore, the combination of anti-inflammatory therapies with immunotherapies, such as immune checkpoint inhibitors, represents a promising approach for enhancing anti-tumor immune responses and improving patient outcomes.

Recent studies have highlighted the pivotal role of the microbiome in ovarian cancer, demonstrating that oncobiosis—characterized by microbial dysbiosis and increased inflammatory potential—may contribute to ovarian cancer initiation and progression.[32] Additionally, the cervicovaginal and gut microbiota have shown potential as biomarkers and therapeutic targets, opening new avenues for early diagnosis and innovative treatment strategies.[33] However, significant gaps remain in understanding the causal relationships between microbiome dysbiosis and ovarian cancer, the precise mechanisms driving inflammation-mediated carcinogenesis, and the validation of microbiome-based diagnostics and therapies in large-scale clinical settings.

Here, this review focuses on exploring the intricate inflammatory pathways and immune evasion mechanisms involved in OC. We also highlight potential therapeutic targets and relevant biomarkers that could lead to improved treatments and outcomes for patients.

Overview of OC Subtypes

OC is not a single disease but a group of tumors that originate from different tissues within the ovary, each with its distinct biology, prognosis, and treatment approaches. The three major subtypes of OC are epithelial ovarian cancer (EOC), germ cell tumors, and stromal tumors.[34]

EOC is by far the most common subtype, accounting for more than 90% of OC cases.[4] Among the EOC subtypes, high-grade serous ovarian carcinoma (HGSOC) is the most aggressive and prevalent.[35] Genomic analysis, such as The Cancer Genome Atlas (TCGA), has revealed that HGSOC is characterized by widespread TP53 mutations and chromosomal instability, which contribute to rapid disease progression and resistance to therapy.[36] These genetic alterations, particularly mutations in BRCA1/2, are also associated with defects in DNA repair mechanisms, such as homologous recombination deficiency, making these tumors initially sensitive to platinum-based chemotherapy.[37] BRCA1/2 germline mutations, which are found in 6–15% of women diagnosed with EOC, are the strongest known genetic risk factors for the disease. Importantly, BRCA1/2 carriers exhibit better responses to platinum-based chemotherapies compared to non-carriers, resulting in improved survival outcomes despite often being diagnosed at a later stage and higher grade.[38] However, resistance to chemotherapy often develops over time, leading to treatment failure and poor survival outcomes.

Germ cell tumors account for less than 5% of OC cases and typically affect younger women. These tumors arise from the reproductive cells of the ovary and include types such as dysgerminomas and teratomas.[39] Studies demonstrated that germ cell tumors are highly responsive to platinum-based chemotherapy, with excellent survival rates even in advanced cases.[40] Although ovarian germ cell tumors are uncommon in postmenopausal women, they should be considered in patients presenting with an ovarian mass and elevated serum alpha-fetoprotein (AFP) levels. Recognizing this diagnostic challenge is critical for ensuring timely and accurate diagnosis in this unique patient population.[41] The germ cell tumours are also characterized by faster rate of growth, unilateral localisation (95% of cases), and early-stage disease (60–70%).[42] Additionally, studies also underscored the importance of early detection and appropriate chemotherapy regimens for this subtype, which can achieve cure rates exceeding 90% for localized tumors.[39]

Stromal tumors, though rare, originate from the connective tissue within the ovary.[43] These tumors include granulosa cell tumors, which are often hormonally active and can lead to symptoms like abnormal uterine bleeding due to estrogen production.[44] It has been emphasized the need for long-term monitoring of patients with stromal tumors, as these tumors tend to recur years after initial treatment.[45] Although stromal tumors generally have a better prognosis than epithelial subtypes, the risk of late recurrence warrants prolonged surveillance. In assessing stromal

tumors, miRNAs such as miR-202-3p and miR-513c-5p are significantly higher compared to germ cell tumors, with miR-202-3p being proposed as a specific marker for sex-cord stromal tumors. This miRNA is expressed in Sertoli and granulosa cells and is correlated with the expression of the transcription factor FOXL2. Furthermore, studies have identified recurrent somatic mutations in FOXL2 as a hallmark of granulosa cell tumors of the ovary, reinforcing its diagnostic and prognostic significance.[46]

Pathophysiology of OC and Inflammation-Driven Mechanisms

TME in OC

The TME plays an essential role in OC development and progression. It is a dynamic system comprising cancer cells, immune cells, stromal cells, endothelial cells, and extracellular matrix (ECM) components. This complex network not only supports tumor growth but also shapes the immune response, promoting immune evasion and metastasis.[47]

One of the most significant components of the TME in OC is the TAM. TAMs are immune cells that are recruited to the tumor site, where they often adopt a pro-tumorigenic M2-like phenotype. These cells are central to promoting tumor growth, angiogenesis, and immunosuppression.[48] A study by Hagemann et al demonstrated that high levels of TAMs in OC tissues correlate with poor patient prognosis.[49] TAMs secrete a range of cytokines, such as IL-6 and TNF-α, which enhance tumor cell proliferation and survival, while also facilitating the remodeling of the ECM to support metastasis.[50]

T cells are also critical components of the immune landscape in OC. While cytotoxic T cells can directly kill tumor cells and are generally associated with improved patient outcomes, their activity is often suppressed within the TME. This suppression is largely mediated by Tregs, which dampen the anti-tumor immune response. Curiel et al found that the recruitment of Tregs to ovarian tumors was associated with reduced survival rates.[51] The presence of Tregs creates an immunosuppressive microenvironment that inhibits the activation of cytotoxic T cells, allowing the tumor to evade immune surveillance.[52] On the other hand, a high infiltration of cytotoxic T cells is linked to better outcomes, as these cells can directly target and kill cancer cells.[53]

Natural killer (NK) cells also play a role in the early immune response to tumors. However, NK cell function is often inhibited by factors secreted by the tumor, which downregulate activating receptors on NK cells in OC.[54] This suppression of NK cell activity allows tumor cells to evade early immune detection and continue growing unchecked.

Inflammation and Pathways in OC

Chronic inflammation is a well-established driver of cancer progression, and OC is no exception. A variety of inflammatory mediators, including cytokines and chemokines, are upregulated in the OC microenvironment, promoting tumor growth, immune evasion, and metastasis.

IL-6

IL-6 is one of the most studied cytokines in OC and plays a crucial role in activating the STAT3 pathway. IL-6 is elevated in the OC microenvironment and drives the expression of genes involved in cancer cell survival, proliferation, and immune evasion.[55–57] It has been shown that high levels of IL-6 in OC patients were associated with poor survival, suggesting that IL-6 could be a valuable therapeutic target.[58] IL-6 stimulates the activation of STAT3, which in turn promotes the expression of anti-apoptotic and pro-survival genes, further supporting tumor growth and resistance to chemotherapy.[9] The STAT3 pathway is frequently activated in OC, primarily through IL-6 signaling.[59] Persistent activation of STAT3 promotes tumor growth, immune suppression, and the recruitment of immunosuppressive cells such as TAMs and Tregs.[60] It has been demonstrated that blocking STAT3 activation significantly reduced tumor growth and enhanced anti-tumor immune responses in OC models.[61] Targeting STAT3 has emerged as a promising therapeutic approach, particularly in combination with other treatments that modulate the immune response.

TNF-α

TNF-α is another key pro-inflammatory cytokine in OC. It has been demonstrated that TNF-α is essential for creating a pro-inflammatory microenvironment that supports tumor growth and metastasis.[62] Inhibiting TNF-α has been shown to reduce tumor growth in preclinical models, making it a potential target for therapeutic intervention.[63] It is well known

that TNF- α contributes to tumor progression by activating the NF-kB pathway. NF-kB is a transcription factor that regulates the expression of genes involved in inflammation, cell survival, and angiogenesis. TNF-α induces the activation of NF-kB, which promotes tumor cell survival and proliferation.[64] In OC, chronic activation of NF-kB promotes tumor cell survival and resistance to apoptosis, which contributes to the aggressiveness of the disease. Recent study showed that NF-kB activation in OC cells is associated with chemotherapy resistance, particularly to platinum-based agents like cisplatin.[65] This finding highlights the potential of targeting NF-kB as a strategy to overcome drug resistance in OC.

IL-8

IL-8 plays a key role in promoting angiogenesis and metastasis in OC. IL-8 is upregulated in response to hypoxic conditions within the TME, and its expression is associated with increased vascularization and tumor spread.[66] Studies found that elevated levels of IL-8 in OC patients were correlated with poor outcomes, highlighting the potential of targeting IL-8 in anti-cancer therapies.[63,67–69]

CXCL12

Chemokines such as CXCL12 and their receptors are also critical in regulating immune cell migration and metastasis. The CXCL12/CXCR4 axis is particularly important in OC, where it promotes the migration of cancer cells to the omentum, a common metastatic site.[70] A report highlighted the importance of targeting the CXCL12/CXCR4 signaling axis to prevent OC metastasis.[71]

COX-2 and Prostaglandins

Chronic inflammation plays a pivotal role in the development and progression of OC, and the enzyme COX-2 is central to this process. COX-2 is overexpressed in many ovarian cancers, where it catalyzes the production of prostaglandin E2 (PGE2), a key mediator of inflammation.[72] PGE2 promotes the recruitment of Tregs and TAMs to the tumor microenvironment, both of which contribute to immune evasion.[73]

In addition to its role in immune suppression, PGE2 has been implicated in promoting angiogenesis, the process by which tumors develop new blood vessels to support their growth.[74] By inhibiting the activity of NK cells and cytotoxic T cells, PGE2 creates an immunosuppressive environment that allows OC cells to evade immune detection and destruction.[75]

COX-2 inhibitors, such as NSAIDs, are being explored as potential adjuvants in OC therapy[76] These inhibitors have shown promise in preclinical studies by reducing the production of PGE2, thereby disrupting the immunosuppressive tumor environment and enhancing anti-tumor immunity.[77] Inflammatory mediators and their roles in OC progression has been summarized in Table 1.

Chronic Inflammation Driving Genomic Instability in OC

Chronic inflammation not only promotes immune evasion but also contributes to genomic instability, which drives the progression of OC. Inflammatory cytokines such as IL-6, TNF-α, and IL-1β induce the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) within the tumor microenvironment.[78,79] These reactive molecules cause oxidative stress, which leads to DNA damage and increases the likelihood of mutations.[78,79]

Over time, this chronic inflammation-driven DNA damage fosters genomic instability, which is a hallmark of aggressive tumor behavior. Tumors with high levels of genomic instability tend to exhibit more mutations, making them more resistant to standard therapies such as chemotherapy. Furthermore, inflammation-induced genomic instability contributes to tumor heterogeneity, making it more difficult to target the tumor with precision therapies.

Key inflammatory pathways, such as the NF-kB and STAT3 signaling pathways, play central roles in mediating the effects of chronic inflammation in OC. Targeting NF-kB and STAT3 with specific inhibitors has shown promise in preclinical studies as a strategy to reduce chronic inflammation, limit DNA damage, and improve therapeutic outcomes in OC.[31]

Immune Evasion in OC

OC is notorious for its ability to evade immune detection and leverage chronic inflammation to support its growth, survival, and progression. Immune evasion allows tumor cells to escape immune surveillance, while inflammation

Table 1 Inflammatory Mediators and Their Roles in OC Progression

Inflammatory Mediator	Associated Pathways	Role in OC Progression	Therapeutic Potential	References
IL-6	STAT3	Promotes tumor cell survival, proliferation, immune evasion	Targeting IL-6 can inhibit STAT3 signaling, reduce tumor growth	[55,58]
TNF-α	NF-kB	Activates NF-kB, enhances cell survival and metastasis	Inhibiting TNF-α can disrupt NF-kB pathway and reduce tumor growth	[62,64]
IL-8	Angiogenesis	Promotes angiogenesis, associated with tumor spread	Targeting IL-8 may reduce vascularization and metastasis	[66,67]
CXCL12	CXCR4/ CXCL12 axis	Regulates immune cell migration, contributes to metastasis	Inhibiting CXCL12/CXCR4 axis can prevent metastasis	[70,71]
COX-2	PGE2	Promotes immune evasion, angiogenesis, tumor growth	COX-2 inhibitors reduce PGE2 production, disrupt immunosuppressive environment, enhance immunity	[72,74]

provides a microenvironment conducive to malignancy. This combination is one of the critical reasons for the high mortality rate associated with OC. By understanding the mechanisms involved, researchers and clinicians can identify therapeutic targets and develop strategies to overcome inflammation and immune suppression.

TAMs and Their Pro-Tumor Role

TAMs play a critical role in shaping the immune landscape of OC. TAMs typically exhibit an M2-like, pro-tumorigenic phenotype. These macrophages promote tissue remodeling, angiogenesis, and immune suppression. Instead of attacking cancer cells, M2-like TAMs secrete cytokines such as IL-6 and TNF-α, which facilitate tumor growth by promoting angiogenesis and creating an immunosuppressive microenvironment.[18]

In OC, TAMs are commonly recruited in large numbers, and their presence correlates with poor prognosis.[80] Their role in suppressing anti-tumor immune responses is significant, as they hinder the activation and function of cytotoxic T cells and NK cells, which are essential for identifying and eliminating cancer cells. Moreover, TAMs release immunosuppressive molecules like TGF-β and IL-10, which dampen the immune response, allowing the tumor to evade immune detection.[81]

Efforts to target TAMs as part of cancer therapy have gained momentum in recent years. One approach is to block the recruitment of TAMs to the TME. Another strategy is to reprogram TAMs from a tumor-promoting M2 phenotype to a tumor-suppressing M1 phenotype, which supports anti-tumor immune responses and inhibits tumor growth.[82]

Tregs and Immune Suppression

Tregs are another critical player in the immune evasion strategies of OC. Tregs function to maintain immune homeostasis by preventing excessive immune responses, but in the context of cancer, they suppress anti-tumor immunity. In OC, tumors actively recruit Tregs to the TME, where they suppress the activity of effector T cells, including cytotoxic T cells, which are responsible for attacking and killing tumor cells.[83]

High levels of Tregs within the OC microenvironment are associated with poor patient outcomes, as they hinder the ability of the immune system to mount an effective anti-tumor response.[84] Tregs suppress immune function through the production of anti-inflammatory cytokines such as IL-10 and TGF-β, which inhibit the proliferation and activity of cytotoxic T cells.[85] They also express immune checkpoint molecules such as CTLA-4, which blocks the activation of effector T cells, further contributing to immune suppression.[86]

Given their crucial role in immune evasion, strategies targeting Tregs have been explored as potential cancer therapies. For instance, depleting Tregs or inhibiting their suppressive functions may restore anti-tumor immune responses and enhance the efficacy of immunotherapies like immune checkpoint inhibitors.[87]

Tumor Cell Downregulation of MHC Molecules to Evade Antigen Presentation

One of the hallmark mechanisms by which OC cells evade immune detection is by downregulating major histocompatibility complex (MHC) molecules, particularly MHC class I. MHC class I molecules are critical for presenting tumor antigens to cytotoxic T cells, allowing them to recognize and eliminate cancer cells.[88] Without adequate MHC class I expression, cancer cells become invisible to cytotoxic T cells, preventing immune-mediated destruction.[89]

Additionally, OC cells frequently overexpress immune checkpoint proteins such as PD-L1, which binds to the PD-1 receptor on T cells, further inhibiting their function and promoting immune evasion.[20] The combination of reduced antigen presentation through MHC downregulation and increased immune suppression via checkpoint pathways allows OC to thrive in the presence of an otherwise functional immune system.

Efforts to restore MHC class I expression and block immune checkpoints have shown promise in preclinical and clinical studies. Immune checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 therapies, have demonstrated efficacy in enhancing T cell function and improving immune-mediated tumor clearance.[90] Recent therapeutic strategies have explored combining PARP inhibitors with immunotherapies, such as anti-CTLA-4 and PD-1/PD-L1, particularly in BRCA1/2-mutated or homologous recombination (HR)-deficient tumors. These tumors display a higher neo-antigen load compared to HR-proficient cancers, leading to more robust anti-tumor immune responses. Additionally, BRCA deficiency has been shown to activate a STING-dependent innate immune response, inducing type I interferons and pro-inflammatory cytokines, which further enhances immune-mediated tumor suppression. Clinical models have also demonstrated that PARP inhibition can inactivate GSK3 and upregulate PD-L1 in a dose-dependent manner, suppressing T-cell activation and promoting enhanced cancer cell apoptosis. These findings highlight the potential of combining PARP inhibitors with immune checkpoint inhibitors to optimize therapeutic outcomes in ovarian cancer.[91] Immune Evasion Mechanisms in OC is summarized in Table 2.

Diagnostic and Prognostic Biomarkers

Inflammatory Markers as Diagnostic Tools

The detection of systemic inflammation is a common feature in OC patients, and several inflammatory markers have been proposed as potential diagnostic and prognostic tools. C-reactive protein (CRP), a well-established acute-phase protein,

Table 2 Immune Evasion Mechanisms in OC

Immune Evasion Mechanism	Role in Immune Evasion	Therapeutic Potential	References
TAMs and Pro-Tumor Role	M2-like TAMs promote angiogenesis, tissue remodeling, and immune suppression by secreting cytokines such as IL-6 and TNF-α	Target TAM recruitment or reprogram TAMs from M2 to M1 phenotype to enhance anti-tumor immunity	[18,80,81]
Tregs and Immune Suppression	Tregs suppress cytotoxic T cells through anti-inflammatory cytokines like IL-10 and TGF-Î², reducing anti-tumor immunity	Target Tregs by depleting them or inhibiting their suppressive functions to restore anti-tumor immune responses	[83–85]
Downregulation of MHC Molecules	OC cells downregulate MHC class I molecules, preventing antigen presentation and cytotoxic T cell recognition	Restore MHC class I expression and block immune checkpoint proteins (eg, PD-L1) to enhance T cell function	[88–90]
PARP Inhibition and Immune Therapy	PARP inhibitors combined with immune checkpoint inhibitors (eg, anti-CTLA-4, PD-1/PD-L1) enhance anti-tumor responses in BRCA1/2-mutated and HR-deficient tumors. These tumors exhibit higher neo-antigen loads, activate STING-dependent innate immunity, and upregulate PD-L1 expression, enhancing T-cell-mediated tumor suppression.	Combining PARP inhibitors with immunotherapies can improve therapeutic outcomes by enhancing immune responses, promoting cancer cell apoptosis, and overcoming immune evasion in BRCA-deficient ovarian cancer.	[91]

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has gained attention due to its role in inflammation. CRP levels increase in response to pro-inflammatory cytokines, particularly IL-6, and can reflect tumor burden and the extent of inflammation in OC patients.[92] Numerous studies have linked elevated CRP levels to poor prognosis, increased tumor stage, and the presence of metastasis in OC patients. In addition to CRP, IL-6 serves as both a diagnostic and prognostic biomarker. Elevated serum levels of IL-6 correlate with advanced-stage OC and poor survival rates.[93]

The relationship between chronic inflammation and OC has also led to the use of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic indicators. A high NLR is indicative of an inflammatory response driven by neutrophils, which are recruited to the tumor site, while a decrease in lymphocytes signals immune suppression. Several studies have demonstrated that a high NLR and PLR are associated with decreased survival in OC patients.[94]

Role of Immune Checkpoint Molecules in Prognosis

Immune checkpoint molecules, such as PD-1 and PD-L1, are central to immune evasion in OC. The interaction between PD-1, expressed on T cells, and its ligand PD-L1, expressed on tumor cells and immune cells within the TME, inhibits T cell activation and allows the tumor to evade immune detection. PD-L1 expression has been linked to poor prognosis in OC, with higher levels of PD-L1 expression correlating with shorter overall survival and progression-free survival.[20] Furthermore, tumors with high PD-L1 expression tend to have a more immunosuppressive microenvironment, characterized by increased Treg infiltration, and reduced cytotoxic T cells activity.[95,96]

The prognostic value of PD-L1 expression has led to the exploration of immune checkpoint inhibitors, such as anti-PD-1/PD-L1 antibodies, as therapeutic agents. The response to checkpoint inhibitors appears to be better in tumors with higher PD-L1 expression and higher levels of TILs in OC patients, which suggests that these markers could be useful in predicting treatment response.[95,97]

Molecular Markers for Treatment Response

Biomarkers Predicting Response to Immunotherapy

With the advent of immunotherapy, including immune checkpoint inhibitors and adoptive T cell therapy, the search for biomarkers that predict treatment response has intensified. Tumor mutational burden (TMB) has emerged as a promising biomarker for predicting response to immunotherapy in several cancers, including OC.[98] High TMB is associated with an increased number of neoantigens, which makes the tumor more recognizable by the immune system.[99] This, in turn, enhances the efficacy of immunotherapies that rely on reactivating the immune system, such as anti-PD-1/PD-L1 antibodies.

Another crucial biomarker is the presence of TILs. OCs with a higher density of TILs tend to respond better to immunotherapy because TILs represent an active anti-tumor immune response. Studies have shown that the presence of CD8+ T cells within the tumor correlates with improved survival and a better response to immunotherapy.[100] Conversely, tumors with low levels of TILs or high levels of immunosuppressive cells, such as Tregs and TAMs, are often resistant to immunotherapy.

Role of Inflammation-Related miRNAs and Exosomes in Diagnosis and Prognosis

In recent years, miRNAs and exosomes have emerged as promising biomarkers in OC. MiRNAs are small non-coding RNAs that regulate gene expression and are involved in numerous cellular processes, including inflammation, immune response, and cancer progression.[101] Exosomal miR-21-5p promotes ovarian cancer progression by enhancing cell proliferation, migration, and invasion, while inhibiting apoptosis through the regulation of CDK6, making it a potential therapeutic target.[102] ROS-induced downregulation of exosomal miR-155-5p promotes tumor growth by enhancing immunosuppressive macrophage activity and PD-L1 expression, while targeting miR-155-5p restores anti-tumor immunity, offering a novel therapeutic strategy for ovarian cancer.[103] MiR-146a has also been found to inhibit ovarian tumor growth in vivo via targeting immunosuppressive neutrophils and enhancing CD8+ T cell infiltration.[104]

Exosomes, which are small vesicles secreted by cells, play a significant role in cell-cell communication within the TME. Tumor-derived exosomes carry proteins, lipids, and nucleic acids, including miRNAs, that influence immune cell function and promote tumor progression.[105] Exosomes have been shown to modulate the immune system by suppressing

T cell activity, promoting the recruitment of TAMs, and enhancing the immunosuppressive properties of Tregs.[106] Inflammation-related exosomal miRNAs, such as those involved in the NF-kB and STAT3 pathways, have been explored as diagnostic and prognostic biomarkers in OC.[107] The ability to isolate and analyze exosomal miRNAs from blood samples offers a non-invasive method for early detection and monitoring of OC.

The potential of miRNAs and exosomes as biomarkers extends beyond diagnosis. They are also being investigated as predictors of treatment response, particularly in the context of chemotherapy and immunotherapy. For instance, patients with high levels of specific miRNAs, such as miR-21, have been found to be resistant to platinum-based chemotherapy, which is the standard treatment for OC.[108] Similarly, exosomal PD-L1 levels are being explored as a potential biomarker for predicting response to immune checkpoint inhibitors.[109]

Inflammation-associated biomarkers are essential tools for improving the diagnosis, prognosis, and treatment of OC. Markers such as CRP, IL-6, PD-L1, and inflammation-related miRNAs provide valuable insights into the disease's progression and its response to therapy. As our understanding of the role of inflammation in OC deepens, these biomarkers will likely play an increasingly important role in guiding personalized treatment approaches. The development of non-invasive methods for detecting biomarkers, such as exosomal miRNAs, will also enhance early detection and monitoring, ultimately improving outcomes for OC patients. Inflammation-associated biomarkers in OC are summarized in Table 3. The chronic inflammation, immune response, tumor growth, and metastasis in OC is illustrated in Figure 1.

Current and Emerging Therapeutic Strategies Targeting Inflammation in OC

Current therapeutic strategies in OC target inflammation, a key driver of cancer progression, immune evasion, and metastasis. Anti-inflammatory treatments, such as COX-2 inhibitors, block prostaglandin synthesis to reduce immune suppression and enhance chemotherapy. Targeting key inflammatory pathways like JAK/STAT and NF-kB also holds potential, with inhibitors disrupting tumor growth and survival. Immunotherapies, including immune checkpoint inhibitors (PD-1, CTLA-4) and CAR-T cell therapy, show promise but are often limited by the tumor's immunosuppressive environment. Emerging combination therapies integrating anti-inflammatory agents, chemotherapy, and immunotherapy aim to enhance patient outcomes. Lifestyle interventions, including diet and exercise, are also explored to reduce inflammation and improve prognosis.

Challenges and Future Directions in Targeting Inflammation in OC

OC presents significant challenges due to the dual role of inflammation in both promoting and inhibiting tumor progression. Chronic inflammation within the TME can enhance immune evasion, angiogenesis, and metastasis through the actions of cytokines like IL-6 and TNF-α, while also activating immune responses such as cytotoxic T cells that target

Table 3 Inflammation-Associated Biomarkers in OC

Biomarker	Role in OC Progression	Therapeutic Potential	References
CRP	Reflects tumor burden and inflammation, linked to poor prognosis	Can be used as a diagnostic and prognostic tool for OC, guiding treatment decisions	[92,93]
IL-6	Correlates with advanced-stage OC and poor survival rates	Targeting IL-6 may reduce immune suppression and improve survival	[93,94]
PD-L1	Associated with immune evasion and poor prognosis in OC	Blocking PD-1/PD-L1 interaction improves immune response, prolonging survival	[20,95,96]
TMB	Predicts better response to immunotherapy by increasing neoantigen recognition	Higher TMB suggests better efficacy of immune checkpoint inhibitors	[98,99]
TILs	High TIL density correlates with improved survival and immunotherapy response	TIL levels help predict immunotherapy response, indicating active anti-tumor immunity	[100]
miR-21	Promotes OC progression, resistance to chemotherapy, and inhibits apoptosis	Targeting miR-21 may overcome chemotherapy resistance and enhance apoptosis	[102,108]
Exosomal miR-155-5p	Promotes tumor growth by enhancing immunosuppressive macrophage activity and PD-L1 expression	Restoring miR-155-5p function offers a potential therapeutic strategy by reactivating anti-tumor immunity	[103,109]

https://doi.org/10.2147/JIR.S503479

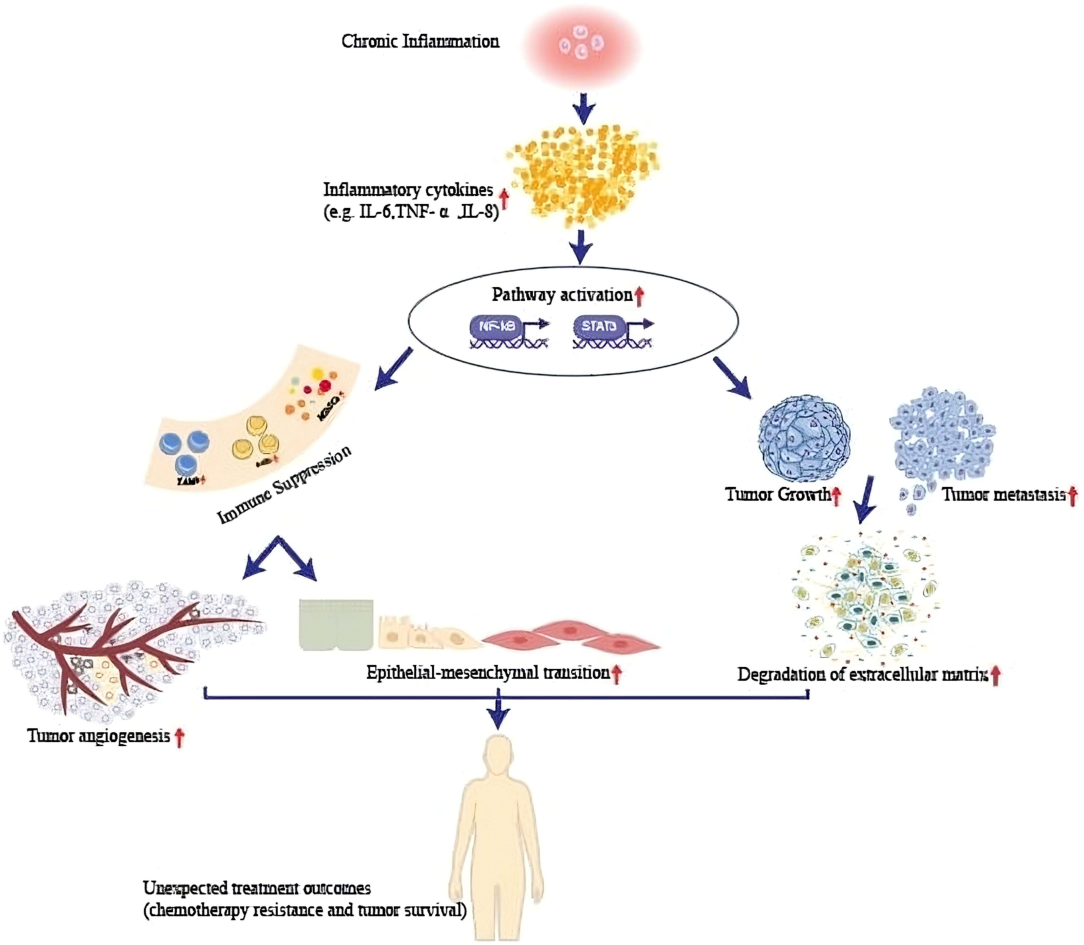

Figure 1 Chronic Inflammation, Immune Response, Tumor Growth, and Metastasis in OC. This figure illustrates the key pathways and mechanisms linking chronic inflammation to immune suppression, tumor growth, and metastasis in OC. Chronic inflammation induces the release of inflammatory cytokines such as IL-6, TNF-α, and IL-8, which activate critical signaling pathways, including NF-κB and STAT3. This activation promotes immune suppression mediated by tumor-associated macrophages (TAMs), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs), alongside tumor growth and metastasis. Tumor progression is facilitated by angiogenesis through VEGF activation, epithelial-mesenchymal transition (EMT), and extracellular matrix (ECM) degradation driven by matrix metalloproteinases (MMPs). These processes collectively contribute to chemotherapy resistance and tumor survival in OC.

cancer cells. Personalized therapies that disrupt tumor-promoting inflammation while enhancing anti-tumor immunity are critical. Current anti-inflammatory therapies face limitations, including toxicity and resistance. Targeting inflammatory pathways like NF-kB and JAK/STAT with inhibitors can suppress immune responses and lead to complications such as infections. Emerging areas of research focus on the role of the microbiome in regulating inflammation, which could lead to novel therapies such as probiotics to modulate the TME. Additionally, biomarkers like circulating miRNAs show promise for early detection of OC and tailoring treatments to individual patients. Long-term research is necessary to understand the full impact of immunotherapy on inflammatory pathways, as these therapies can modulate inflammation, potentially influencing recurrence, and resistance.

Conclusion

In OC, inflammatory pathways such as NF-kB, JAK/STAT, and COX-2 play a central role in tumor progression, immune evasion, and resistance to therapy. Targeting these pathways has significant therapeutic implications, as it allows for the reduction of inflammation-driven tumor growth while potentially enhancing the effectiveness of immunotherapy and chemotherapy. COX-2 inhibitors, JAK/STAT pathway blockers, and NF-kB inhibitors represent key areas where anti-inflammatory treatments may provide benefit, especially when combined with immune checkpoint inhibitors. However, these strategies are not without challenges, as toxicity and resistance can limit their effectiveness.

Integrating findings on inflammation-driven pathways and immune evasion mechanisms into clinical practice holds great potential for transforming OC management.[110] For instance, targeting key pathways such as NF-κB and JAK/STAT through inhibitors has demonstrated preclinical efficacy in reducing tumor-promoting inflammation and overcoming chemoresistance.[111] Additionally, combining these approaches with immune checkpoint inhibitors (eg, PD-1/PD-L1 blockade) can synergistically enhance anti-tumor immune responses.[112] Recent advancements in microbiome research further provide novel therapeutic opportunities, with strategies like microbiota modulation showing promise in reshaping the tumor microenvironment. Future research should focus on translating these findings into personalized treatment regimens and conducting large-scale clinical trials to validate these integrated approaches.[113] Such efforts could significantly improve patient survival and quality of life, paving the way for more effective and durable therapeutic strategies.

The future of OC therapy lies in continued research into the complex interplay between inflammation and tumor biology. Investigating the role of the microbiome, novel biomarkers, and emerging combination therapies is essential to improving patient outcomes. Moreover, developing personalized approaches that target inflammation while preserving immune responses will be critical in integrating these therapies into clinical practice.

The integration of inflammation-targeting therapies into standard treatment regimens offers the potential to enhance survival and quality of life for OC patients. Continued innovation and clinical trials are crucial to refining these treatments and achieving long-term success.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. They took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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