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The Immune System in the Pathogenesis of Ovarian Cancer

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Abstract

Clinical outcomes in ovarian cancer are heterogeneous even when considering common features such as stage, response to therapy, and grade. This disparity in outcomes warrants further exploration into tumor and host characteristics. One compelling host characteristic is the immune response to ovarian cancer. While several studies have confirmed a prominent role for the immune system in modifying the clinical course of the disease, recent genetic and protein analyses also suggest a role in disease incidence. Recent studies also show that anti-tumor immunity is often negated by immune suppressive cells present in the tumor microenvironment. These suppressive immune cells also directly enhance the pathogenesis through the release of various cytokines and chemokines, which together form an integrated pathologic network. Thus, future research into immunotherapy targeting ovarian cancer will likely become increasingly focused on combination approaches that simultaneously augment immunity while preventing local immune suppression or by disrupting critical cytokine networks.

Keywords

Cytokines; T cells; macrophages; single nucleotide polymorphisms; dendritic cells

II. INTRODUCTION

Ovarian cancer has the highest mortality rate of the cancers unique to women. According to Siegel and colleagues, in 2012 there were an estimated 22,280 new cases of ovarian cancer and estimated 15,500 deaths.¹ Moreover, the majority (65%–75%) of women with ovarian cancer are diagnosed with advanced stage disease (III and IV), and only about 15%–20% of these women are free of disease recurrence at ten years.^{2–4} Major subtypes of ovarian cancer include serous, endometrioid, clear cell and mucinous histologies, with heterogeneous characteristics.⁵ There are nevertheless unique features about ovarian cancer that may shed

light on its basic biology, hopefully leading to improvements in therapeutics and outcome. One of those unique features is the complex interaction of the immune system in both ovarian cancer initiation and progression which has been well documented over the last two decades and is the central topic of this review. We will cover a broad range of topics related to inflammation and ovarian cancer, beginning with epidemiologic and genetic evidence in ovarian cancer risk. We will then discuss how immune mediators might serve as biomarkers for detection and diagnosis of ovarian cancer. Finally, we will focus on tumor microenvironment and consider how different subsets of immune cells and cytokines can either promote tumor growth and progression or target tumor cells for destruction and improve patient survival.

III. THE IMMUNE SYSTEM IN DISEASE ONSET AND INITIATION

A. Models of inflammation in ovarian cancer initiation

The immune system is thought to be an important mediator of ovarian carcinogenesis.⁶ There are two models for the role of the immune system in ovarian cancer, incessant ovulation and chronic inflammation. The incessant ovulation hypothesis proposes that ovulation damage, due to rupturing of the ovulating follicle, traumatizes the ovarian surface causing an immediate inflammatory response and wound repair. The process of continuous damage and epithelial proliferation to repair the wound places strain on the epithelium and increases the risk of malignant transformation. Several epidemiologic studies beginning around five decades ago have implicated increased number of ovulations as a risk factor for ovarian cancer.⁷ Protection from ovarian cancer has been observed in association with increased parity,^{8,9} oral contraceptive use,^{10,11} breast feeding,^{12,13} older age at first menses (for premenopausal women),¹⁴ which all impact number of lifetime ovulations. One of these early studies, which has been further substantiated by more recent investigations, found protective effects of “anovulatory time” by combining information on both increased oral contraceptive use and parity as well as age at first and last menses,¹⁵ supporting the theory of incessant ovulation as an underlying mechanism of carcinogenesis. Although the proliferative effect of hormones on ovarian epithelium is one postulated biological mechanism explaining these associations, emerging studies support a role of macrophages in inducing DNA damage. For example, a recent study found not only that superovulated mice had elevated macrophage counts in their oviducts, but that oxidative stress induced by hydrogen peroxide or macrophage secreted mediators initiated DNA damage in immortalized baboon tubal epithelial cell lines.¹⁶ *In vivo*, it has been clearly established that macrophages are abundant within epithelial inclusion cysts.¹⁷

As with the incessant ovulation hypothesis, the chronic inflammation model of carcinogenesis proposes that chronic exposures to external or endogenous triggers of immunity and persistent immune cells that cause injury to surrounding epithelium, damage DNA through release of reactive oxygen species, or produce cytokines that promote proliferation. One proposed environmental exposure shown to induce inflammation in animal models and human lungs is talcum powder.¹⁸ Composed primarily of magnesium silicate, this moisture absorbing substance has been linked to ovarian cancer risk in a number of studies,^{6,19–21} although selection bias and confounding were strong concerns for the studies that found these associations.^{22,23} The strong correlation between endometriosis and ovarian cancer also supports the chronic inflammation hypothesis. Endometriosis involves endometrial cells growing outside of the uterus and has been investigated extensively as a risk factor for ovarian cancer. Several epidemiologic studies have found an association between history of endometriosis and invasive epithelial ovarian cancer and most recently a pooled analysis of 13 case-control studies demonstrated that history of endometriosis increased risk of clear cell, low grade serous, and endometrioid invasive ovarian cancers, but not mucinous or high grade serous ovarian cancers.²⁴ Evidence strongly

suggests that endometriosis is a pelvic inflammatory condition.²⁵ Although the causes are unknown, the results of some studies suggest that endometriosis may be caused by toxic inflammation-inducing substances, especially poly-halogenated aromatic hydrocarbons and xeno-estrogens.²⁶

Exposure to pathogens might also cause chronic inflammation that would aid in tumor promotion and progression. Retrograde menstruation provides a potential mechanism by which pathogens could reach fallopian tube epithelial cells to establish infection.²⁷ While there is little evidence that specific pathogens contribute to most ovarian cancer cases, some studies have found a relationship between pelvic inflammatory disease and ovarian cancer risk.^{6, 28, 29} Lastly, consistent with the idea that chronic inflammation - whether mediated by ovulation induced damage, foreign agents, or both - is an underlying cause of ovarian cancer, non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with a decreased risk of ovarian cancer, but results have been inconsistent.^{6, 21, 30}

B. Inherited variation and risk: Germline polymorphisms in immune-related genes and ovarian cancer risk

Inherited single nucleotide changes in genes can affect expression and function of their protein products.³¹ Apart from typical epidemiologic approaches, the ability to examine the impact of genetic variation in disease processes over the past decade represents a significant advance in understanding the role of the immune system in disease risk. While genome wide association studies to date have found significant associations with ovarian cancer and single nucleotide polymorphisms (SNPs) in genes that are not directly immune-related,^{32–34} several groups have carried out candidate gene studies that examined polymorphisms in immune-related genes in risk of ovarian cancer. NF- κ B is a pro-inflammatory transcription factor complex that can be activated by multiple pathways. In addition to hematopoietic cells, epithelial cells also use NF- κ B to produce signals that alert the immune system to stress and infection. The *NFKB1* gene encodes the p50 subunit of the NF- κ B protein and the deletion allele of the *NFKB1* variant (–94 ins/del ATG) was previously reported to have reduced promoter activity by luciferase assay in HeLa or HT-29 cell lines.³⁵ This variant was also recently evaluated in a Chinese case-control study, where those homozygous for the insertion had increased risk of advanced ovarian cancer (OR=2.7, 95% CI: 1.4–5.1) compared with those homozygous for the deletion.³⁶

One mechanism through which NF- κ B is activated is by NOD2 in response to muramyl dipeptide from intracellular bacterial lipopolysaccharide. The *NOD2* 3020insC polymorphism results in a frameshift and premature stop codon, truncating the NOD2 protein.³⁷ A Polish case-control study found an increased risk for all ovarian cancer (OR=1.6, 95% CI: 1.1–2.3) with the *NOD2* 3020insC allele.³⁸ SNPs in two NF- κ B inhibitor genes, *NFKBIA* and *NFKBIB*, were assessed in an ovarian case-control study from two sites (Mayo Clinic and Duke University). A marginally statistically significant association was found between the *NFKBIA* synonymous coding SNP rs1957106 and reduced risk of all epithelial ovarian cancer (EOC) (OR_{ABvsAA}=0.8, 95% CI: 0.6–0.9, OR_{BBvsAA}=0.9, 95% CI: 0.6–1.3; p=0.03), and in the Mayo Clinic study only an increased risk for all EOC with 5' upstream SNP rs3138050 in the recessive model (OR=2.2, 95% CI: 1.1–4.6; p=0.03).³⁹ No known functional studies to date have assessed the direct effect these SNPs have on protein levels or function. No associations were found with EOC and the *NFKBIB* SNPs genotyped in this study.³⁹

Caspase-8 (CASP8) is activated following ligation of several important immune receptors to their ligands, including T cell receptors, tumor necrosis factor receptor, and Fas. This activation ultimately leads to apoptosis. Ma and colleagues examined 8 tag SNPs in the *CASP8* gene for association with risk of epithelial ovarian cancer of combined histologies in

a Chinese population case-control study.⁴⁰ They found that several SNPs in this gene were associated with reduced risk of developing EOC, including promoter indel SNP rs3834129 ($OR_{\text{allelic}}=0.6$, 95% CI: 0.5–0.8; $p=0.002$), intronic rs3769827 ($OR_{\text{allelic}}=0.6$, 95% CI: 0.5–0.8; $p=0.0008$), and intronic rs6704688 ($OR_{\text{allelic}}=0.7$, 95% CI: 0.5–0.9; $p=0.004$).⁴⁰ Participants carrying at least one copy of the minor allele for rs3834129 and rs3769827 were also more likely to have an older age of disease onset.⁴⁰ The rs3834129 result is not surprising, as the deletion removes the stimulatory protein 1 transcription factor binding site, resulting in reduced caspase-8 activity and reduced activation induced cell death in T-cells after exposure to cancer cells.⁴¹ In a cohort of *BRCA1/2* mutation carriers of European descent from the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), the *CASP8* D302H variant was significantly associated with decreased risk of ovarian cancer in *BRCA1* mutation carriers ($HR_{\text{allelic}}=0.7$, 95% CI: 0.5–0.9).⁴² This group also assessed a functional polymorphism in the gene for a *CASP8* cooperating protein, *CASP10*, and found no association with ovarian cancer risk in either *BRCA1* or *BRCA2* carriers.⁴² When this SNP, also known as rs1045485, was assessed in a population that was not restricted on *BRCA1* carriers, it was not found to be associated with invasive EOC ($OR_{\text{minor allele homozygous}}=0.81$, 95% CI: 0.59–1.12) in participants of European descent in a large consortium of 14 case-control studies, the Ovarian Cancer Association Consortium.⁴³

Mannose-binding lectin is a component of the complement system, recognizing microbial and tumor associated mannose and initiating activation of the complement cascade, another important pathway in both the innate and adaptive immune responses.^{44, 45} A functional polymorphism in exon 1 of *mannose-binding lectin* was recently assessed in relation to vaginal concentrations of the protein in study participants. This polymorphism, also known as rs1800450 was also analyzed for frequency among healthy controls, patients with benign conditions, and patients with gynecologic malignancies, including ovarian cancer.⁴⁶ They found that the variant allele was elevated in ovarian cancer patients (17.1%) compared to healthy women (8.7%, $p=0.02$) and women with benign conditions (8.4%, $p=0.03$) and that this allele was associated with lower concentrations of vaginal mannose-binding lectin, suggesting a role of this pathway in disease pathogenesis.⁴⁶

Cyclooxygenase 2, or prostaglandin endoperoxide synthase 2 (*PTGS2*), is an enzyme involved in synthesis of prostaglandin, an important mediator of inflammation. A pooled analysis of two population-based case-control studies (Hawaii Ovarian Cancer Case-Control Study and the New England Case-Control Study) of combined non-serous ovarian cancer found the C allele of *PTGS2* SNP rs5275, found in one study to be associated with a modest reduction of *PTGS2* mRNA levels in lymphoblastoid cell lines,⁴⁷ was also associated with reduced risk of combined non-serous subtypes of ovarian cancer ($OR_{\text{recessive}}=0.7$, 95% CI: 0.4–0.98).⁴⁸ When all invasive ovarian cancers were assessed together information on rs5275 genotype and NSAID use were combined, non-aspirin NSAID users with the CC genotype had the lowest risk of developing ovarian cancer compared to NSAID nonusers with TT genotype.⁴⁸ Pinheiro et al also assessed associations with NSAID use in a case-control study including participants from the New England Case-Control study and the Nurses' Health Studies. They however, did not find an association with ovarian cancer risk, nor did they find significant interactions between NSAID use and the rs5275 or the rs20417 *PTGS2* polymorphism in relation to ovarian cancer risk.⁴⁹ In a recent report by White et al, a panel of inflammation related genes, eight *PTGS2* tagSNPs were included and no association with EOC in a case-control study combining two US study sites (Mayo Clinic and North Carolina Ovarian Cancer Study).⁵⁰ However, the same study revealed an association between *ALOX5* SNP, rs1864414, and EOC, an association which remained even after combining these studies with additional Ovarian Cancer Association Consortium studies ($OR=0.9$, 95% CI: 0.8–0.95; $p=0.002$).⁵⁰ Arachidonate 5-lipoxygenase (*ALOX5*) converts arachidonic acid into leukotrienes.

Several associations between cytokines and cytokine receptors also suggest a relationship between inflammation and immunity and ovarian cancer initiation. The *IL1A* gene encodes the IL-1 α cytokine that binds to IL-1R1 and is an important inflammatory mediator. The case-control study reported above by White et al, also assessed several cytokine gene polymorphisms. The strongest association was seen between the minor allele of the *IL1A* SNP rs17561, which results in a missense mutation, and an elevated risk of clear cell (OR=0.8, 95% CI: 0.6–0.9), mucinous (OR=0.8, 95% CI: 0.7–0.96), and endometrioid (OR=0.8, 95% CI: 0.7–0.96), but not serous ovarian cancers.⁵⁰ The minor (T) allele of rs17561 leads to an amino acid change to serine at position 114 in pro-IL-1 α , which has been shown to be more sensitive to calpain cleavage than the major (G) allele encoded alanine at this position.⁵¹ The cleaved form has recently been demonstrated to have higher binding affinity to IL-1R1 and leading to increased cytokine expression at lower concentrations than the uncleaved form.⁵² When examining polymorphisms in miRNA binding sites of immune-related genes in a US population case-control study, Liang and colleagues found that a SNP (rs3917328) in a putative miR-335 binding site in the *IL1R1* gene was related to increased risk of developing EOC (OR_{dominant}=1.6, 95% CI: 1.0, 2.6).⁵³

IL-18 promotes IFN- γ production in NK and TH1 cells. Assessment of 11 *IL18* tagSNPs in the North Carolina Ovarian Cancer Study found one SNP, rs1834481 was related to risk of advanced ovarian cancer (OR_{per-allele}=1.2, 95% CI: 1.1–1.4). However, when they assessed this SNP in a larger ovarian cancer consortium, the Ovarian Cancer Association Consortium, the significance was attenuated (OR_{per-allele}=0.99, 95% CI: 0.9–1.05).⁵⁴ Interestingly, in a genome-wide association study that assessed 704,409 SNPs for association with IL-18 levels in a cohort of 1523 women (with and without type 2 diabetes) from the Women's Health Study and 435 women (with no history of chronic disease) from the Women's Genome Health Study, rs1834481 was significantly associated with plasma IL-18 levels.⁵⁵ It should be noted that a number of SNPs in other immune-related genes assessed for association with ovarian cancer risk were not found to be significantly associated.⁵⁰ While this is not an all-inclusive list of studies that have assessed immune related SNPs in relation to ovarian cancer risk, it does start to provide insight into contribution of immune genes in this disease.

C. Protein-based inflammatory markers: Association with risk of developing ovarian cancer

In addition to the genetic approaches there has been interest in developing protein-based biomarker studies that can aid in diagnosis. The suggestion that initiation of ovarian cancer is mediated by inflammation is somewhat supported by studies evaluating systemic markers of inflammation such as C-reactive protein (CRP). CRP levels in the blood rise rapidly in response to IL-6 released during local inflammatory processes, and thus it is not a disease-specific marker.⁵⁶ Its physiological role is to bind to phosphocholine on the surface of dead or dying cells in order to activate the complement system. CRP protein levels in the blood are associated with a wide range of diseases, such as diabetes and atherosclerosis.⁵⁷ Toriola and colleagues conducted a prospective population based case-control study of serum CRP nested within the Finnish Maternity Cohort to determine if there is an association between elevated pre-diagnostic CRP levels in the blood and ovarian cancer.⁵⁸ In the Finnish Maternity Cohort, 170 women developed ovarian cancer. and CRP levels were found to be associated with ovarian cancer in samples collected and average of 6.4 years prior to diagnosis (OR=2.0, 95% CI: 1.1–3.4 but not those collected an average of 8.9 years prior to diagnosis (OR=1.6, 95% CI: 0.9–2.8). They also reported an increase over time with CRP serum levels and ovarian cancer risk (OR=1.9, 95% CI: 1.1–3.2).⁵⁸ In another analysis, which included participants from three pooled prospective nested cohort studies, Lundin and colleagues reported a similar finding in which high levels of CRP (>10mg/ml) were associated with a 4.4 fold increased risk of developing ovarian cancer.⁵⁹

The increased availability of assays to determine cytokine levels has recently led to studies evaluating other circulating markers of inflammation. Using a nested approach with three prospective cohort studies, Clendenen and colleagues found that IL-6, as well as IL-2, IL-4, IL-12, and IL-13 levels were significantly associated with increased risk of developing epithelial ovarian cancer of combined histologies.⁶⁰ The majority of cases were serous and the results looked similar when they restricted on serous subtype.

Overall, the studies demonstrating that elevated CRP and IL-6 levels are associated with an elevated risk of ovarian cancer support a role for inflammation, likely subclinical, in initiating the disease. The recent findings of genetic associations with risk further support this contention. Furthermore, recent data showing elevated IL-2, IL-4 and IL-13 years prior to diagnosis, although not definitive, suggest that the chronic inflammation may have an adaptive T and B cell component that remains to be discovered.

In summary, there is some support of the notion that chronic inflammation in the reproductive tract is involved in ovarian cancer development. Unfortunately, to the best of our knowledge no studies have been reported which directly compare in either a prospective cohort or case-control setting that smoldering subclinical inflammation drives the development of neoplasia of the ovary. The two models of ovarian cancer initiation involving the immune system that have been proposed, the incessant ovulation and chronic inflammation models, also likely are not exclusive and could act together to increase incidental ovarian cancer. With high-throughput genetic approaches having been developed in recent years, such as genome-wide SNP analysis and multiplexed cytokine analysis, it has become possible to interrogate mechanisms at the population level. Although difficult and with weaknesses, these population-based approaches have provided substantial additional evidence suggesting that the immune system is a mediator of epithelial transformation. The potential mediators span both innate and adaptive immunity. The studies being largely association-based, remain difficult to interpret at present, particularly the genetic studies; however, the identified targets provide a future pipeline of possible biochemical approaches evaluating the impact of their gene products.

IV. IMMUNE SIGNATURES IN THE DIAGNOSIS OF OVARIAN CANCER

There have been several reports over the decades that ovarian cancer patients have elevated levels of serum cytokines leading to speculation that the immune response against ovarian cancer may have diagnostic, in addition to prognostic, value.⁶¹ Despite that, there is a realization that that individual cytokines are of limited use as diagnostics because of specificity and sensitivity concerns. However, with the recent introduction of methods to measure a variety of cytokines, particularly in a multiplexed manner, studies are now being done to assess panels of markers as diagnostics with several significant advances.

CA-125 is the most widely used biomarker for ovarian cancer. Despite the widespread use of CA-125, this biomarker has poor positive and negative predictive value.⁶² Besides ovarian cancer, CA-125 is also elevated in a variety of other malignant and non-malignant conditions,^{63, 64} limiting its ability to distinguish benign and malignant adnexal masses. Given the growing body of evidence of a role for the immune system in the clinical course of ovarian cancer, there have been a number of studies evaluating circulating cytokine profiles as signatures of ovarian cancer. In a retrospective case control study, Egdel and colleagues found that combining plasma IL-6, IL-8, and two markers of inflammation, CRP and serum amyloid A with CA-125 levels increased diagnostic efficiency compared to CA-125 alone.⁶⁵ Despite the impressive area under the curve values of 0.988 and 0.985 for the test and validation cohorts, respectively, this phase II biomarker study did not examine the utility of this panel in distinguishing ovarian malignancies from benign masses.

Lambeck and colleagues compared several cytokines (IL-7, IL-6, IL-8, IL-10, MCP-1, and IP-10) with CA-125 for the ability to correctly predict malignancy versus benign masses⁶⁶. While none of the cytokines alone were useful in predicting malignancy, low levels of IL-7 in combination with high CA-125 resulted in a high specificity of 100% but only 56% sensitivity.

In another study, Gorelik and colleagues used multiplexed cytokine analysis to establish a signature that would distinguish early stage ovarian cancer from healthy controls and patients with benign masses.⁶⁷ Although not validated in an independent cohort, their preliminary study found that the combination of CA-125, IL-6, epidermal growth factor, vascular endothelial growth factor, and IL-8 was superior in distinguishing early stage ovarian cancer from controls with 100% sensitivity and 86% specificity. In contrast, the use of CA-125 alone in this cohort resulted in sensitivities between 70% and 80%. Further analysis showed that a five marker set (CA-125, G-CSF, IL-6, vascular endothelial growth factor and epidermal growth factor) correctly distinguished benign masses from cancer with 84% sensitivity and 76% specificity. Collectively these results, while preliminary, demonstrate that immune factors when considered in the context of complex biomarker sets may be useful for early detection and pre-surgical diagnosis.

V. IMMUNITY IN DISEASE PROGRESSION

A. Microenvironment: Role of tumor infiltrating immune cells in disease progression

A completely different kind of inflammation follows tumor development.⁶⁸ Chronic inflammation can foster and support various cellular events resulting in induction and/or selection of aggressive cancer cells. Observations that date back several decades have established that there are natural immune responses to ovarian tumors and these immune responses can have a profound impact on the clinical course of the disease. Although infiltration of immune effectors into ovarian cancers was observed as early as 1982 by Haskill and colleagues,⁶⁹ it would not be until nearly two decades later that the prognostic significance of these cells was appreciated. In their seminal publication in 2003, Zhang, Conejo-Garcia and colleagues showed that T cell infiltration into ovarian tumors was associated with improved survival.⁷⁰ Among 74 patients with complete clinical responses after debulking and platinum-based therapy, the five-year survival rate was an extraordinary 73.9% among those patients with CD3⁺ T cells within their tumor compared to 11.9% among patients without infiltrating T cells.⁷⁰ This study also revealed that in tumors with high numbers of tumor-infiltrating T cells, the expression of monokines induced by IFN- γ , macrophage-derived chemokines, and secondary lymphoid-tissue chemokines were significantly increased as compared with tumors lacking T cells, suggesting that these chemokines may be involved in modulating the local anti-tumor response and therefore represent novel targets for improving anti-tumor immunity.⁷⁰

CD8 cytotoxic T lymphocytes (CTL) are generally thought to be the primary mediators of anti-tumor immune responses. These cells recognize antigens displayed in the context of major histocompatibility complex (HLA) class I molecules expressed on ovarian cancer cells. Upon recognition of their cognate antigen, CD8 T cells release, among several mediators, perforin and granzyme which induce apoptosis in target cells.⁷¹ To examine a role for CTL in ovarian cancer, Sato and colleagues studied 117 ovarian cancer cases and observed improved survival in patients who had higher numbers of intraepithelial CD8⁺ T cells compared to patients without intraepithelial CD8 T cells (median survival 55 vs. 26 months).⁷² These findings were largely confirmed by Leffers and colleagues in an independent cohort.⁷³ Although the recent identification of regulatory subsets of CD8 T cells has clouded interpretations of tumor-infiltrating CD8 cells, the idea that the vast majority of CD8 T cells are cytotoxic is reasonable given recent findings of a strong positive

correlation between levels of CD8 T cells and granzyme B within tumors.^{74, 75} Gene expression profiling of serous ovarian tumors with high and low CD8 T cell infiltration found two genes differentially expressed in cancers with high versus low CD8 T cell infiltration: interferon regulatory factor 1 and C-X-C chemokine receptor 6.^{76, 77} Upregulation of interferon regulatory factor 1 results in both major histocompatibility complex class I and II expression thereby fostering a tumor immune microenvironment favoring immune recognition. Paradoxically, while C-X-C chemokine receptor 6 expression enhances T cell proliferation to foster immune eradication of tumor, upregulation of C-X-C chemokine receptor 6 has been associated with tumor promotion and metastasis of several cancers.⁷⁸ These findings highlight the double edged nature of the immune system in cancer. A recent meta-analysis combined results of 10 prior studies that had examined intraepithelial tumor infiltrating lymphocyte numbers in relation to ovarian cancer survival. Utilizing studies that assessed either CD3 (a pan-T cell marker) or CD8 (a cytotoxic T cell marker) positive cells, they found that the presence of tumor infiltrating lymphocytes, as indicated by either marker, favored overall survival for patient populations that included mixed histologies and grades of ovarian cancer, although most were serous and high grade.⁷⁹

The role of CD4 helper T cell infiltration is less clear due to shared marker expression with regulatory T cells (Tregs). Both Sato and Milne observed similar outcomes among patients with or without CD4+ T cell staining within tumors,^{72, 74} while Le Page observed that increased CD4+ cells in 199 high grade serous cancers were associated with improved survival.⁸⁰ Kryczek and colleagues found that high levels of IL-17 were associated with greatly improved outcome suggesting that Th17 cells, a subset of CD4 helper T cells that produce IL-17, may have a direct role eradicating tumor.⁸¹ Given the abundant expression of IL-17 among innate immune effectors, it is difficult to draw a conclusion as to whether intratumoral Th17 cells might impact the clinical course of the disease,⁸² however, the fact that levels of Th17 cells have a strong inverse correlation with Tregs, suggests that they might be associated with tumor eradication.⁸¹

Other specific subsets of antitumor immune effectors have also been studied but with less than clear results. One example is the subset of natural killer (NK) cells, a group of cytotoxic lymphocytes that have two different mature phenotypes: CD16+ CD56^{dim} NK cells found in the periphery, which have high cytolytic function, and CD16- CD56^{bright} NK cells found in the secondary lymphoid tissue with inefficient cytotoxicity.⁸³ NK cells have two types of surface receptors: activating (i.e., NKG2) receptors and inhibitory (i.e., KIR) receptors, and can lyse cells without having to recognize specific antigens.⁸⁴ The balance between inhibitory and activating signals through the different NK receptors is important in the NK cell activation process. NK cells can also be activated in an antigen-dependent manner to mediate antigen-dependent cellular cytotoxicity, which involves binding of cell bound antibodies to Fc receptors on the NK cells. The activating NKG2 receptors bind to stress ligands such as MICA, MICB, and ULBP1–3, while KIR receptors bind to major histocompatibility complex class I and class I associated ligands.^{84, 85} Like other cancers, nearly all ovarian cancers express MICA, MICB and ULBP2.⁸⁶ Furthermore, higher NK cell activity in the peripheral blood of ovarian cancer patients at the time of surgery is predictive of improved progression-free survival.⁸⁷ However, increased numbers of NK cells in peritoneal and pleural effusions of metastatic ovarian carcinoma have been associated with poorer prognosis.⁸⁸

The generation of antibody responses to ovarian cancer is a common observation suggesting a role for B cells in disease prognosis.^{89–91} Although antibody-secreting B cells do not need to be at the tumor site to exert antitumor activity, studies evaluating whether B cell infiltration is associated with improved survival show mixed results.^{74, 88} Another recent evaluation of infiltrating cells constructed from tumors of women with high grade serous

ovarian cancer from 3 patient cohorts, found that infiltration of tumors by both CD8+ and CD20+ (B cell marker) lymphocytes (the two subsets were correlated and often found near each other within the tumor) was associated with increased survival.⁹² The CD20+ B cells did not express CD27, a memory B cell marker, but IgG sequencing suggested they had been exposed to antigen. The authors hypothesized that these cells are likely involved in modulating CTL recruitment or activity.⁹²

Although studies are somewhat limited in regard to immune cell profiles by histologic subtype, recently, Milne and colleagues assessed leukocyte infiltration and immune marker expression in a large group of ovarian cancer specimens, including 199 high grade serous, 31 mucinous, 125 endometrioid and 132 clear cell EOC cases. They found that high-grade serous had the highest number of tissue cores that stained with the pan leukocyte marker, CD45, and also more frequently contained other immune cell marker positive infiltrates, such as FoxP3, CD25 and CD20, compared to the other subtypes. Tumors with endometrioid histology had the second highest and clear cell and mucinous subtypes had lower percentages with infiltrates overall.⁷⁴ This study underscores the possibility that the subtypes of ovarian cancer are uniquely recognized by the immune system and, thus, may require different immunotherapeutic approaches.

Evidence suggests that ovarian cancer cells, like other malignancies, manipulate cytotoxic and other effector cells in the microenvironment to suppress cytotoxic responses.⁹³ While CTL are known to be involved in immune surveillance and tumor clearance in ovarian cancer,^{94, 95} it is well accepted that Tregs and tumor-associated macrophages (M2) inhibitor these cells in the tumor microenvironment.^{96–98} The term Treg, as previously alluded to, most commonly refers to CD4+CD25+ T cells that were either selected early in development in the thymus with the function of protecting against autoimmune reactions (natural Tregs) or developed in the periphery to regulate immune response to other antigens (adaptive Tregs).⁹⁹ Several studies have assessed the presence of Tregs in ovarian tumors and found them to be positively associated with poor prognosis/outcome^{72, 100, 101} or unfavorable clinical characteristics, such as high grade, advanced stage and suboptimal tumor debulking.¹⁰² Tregs have multiple tumor promoting effects. In addition to their direct immune suppressive effects, Treg-derived factors such as TGF- β act directly on tumor cells to induce increased aggressiveness.¹⁰³

Under normal healthy conditions, macrophages are localized to tissue where they carry out various functions including surveying for infectious agents and phagocytizing dead cells. When faced with an infectious challenge, they typically activate and acquire an immune activating phenotype often referred to as an M1 phenotype. Macrophages that infiltrate tumors adopt an alternative phenotype referred to as an M2 phenotype characterized by enhanced tissue regenerative responses and local immune suppression. Tumor associated macrophages (M2) express different markers than classically activated macrophages (M1). Hagemann and colleagues demonstrated that ovarian cancer cells were capable of inducing macrophages to become M2.¹⁰⁴ A few studies assessed the presence of infiltrating macrophages using CD68, but did not find an association between these cells and ovarian cancer survival.^{74, 105} However, one study that assessed M2 marker, CD206, found that patients with tumors that had a higher proportion of CD206+/CD68+ cells also had an increased risk of disease progression.⁸⁰

In addition to macrophages, ovarian tumors have a pronounced infiltration by dendritic cells (DCs). DCs are classified into two subtypes according to their lineage: plasmacytoid DCs and myeloid DCs.¹⁰⁶ Under quiescent conditions, DCs are present in the body in an immature form and are responsible for detecting danger and sampling of antigens. Upon detection of danger through their pathogen-associated molecular pattern receptors or danger-

associated molecular pattern receptors, DCs mature and migrate to the lymph nodes to activate T helper cells and CTL.¹⁰⁶ Although tumors are able to produce danger signals, they are ineffective in inducing DC maturation and trafficking to lymph nodes which is thought to be due to tumor-induced alterations in DC differentiation thus reducing the number of functional cells available for effective T cell activation.¹⁰⁷ For example, ovarian cancers secrete large amounts of IL-10 which promotes differentiation of DC to CD14+CD1a- macrophage-like cells with reduced T cell activation properties.¹⁰⁷

Human ovarian cancers contain plasmacytoid and myeloid DCs as well as their precursors. CXCR4+ plasmacytoid precursor cells are attracted into the tumor microenvironment by tumor derived stroma-derived factor 1. Plasmacytoid precursor cells recruited into the ovarian cancer microenvironment induce T cells to release large amounts of IL-10 preventing local T cell activation.¹⁰⁸ Myeloid-derived DCs (MDCs) are the dominant DCs in the blood under normal health conditions. Some early studies appear to suggest that there is little accumulation of MDCs in ovarian cancer,¹⁰⁸ but more recent studies demonstrate their infiltration. Their role in local immune suppression remains unclear, and may differ in the solid tumor mass compared to actions in ascites fluid.¹⁰⁹ Immature MDCs promote angiogenesis and vasculogenesis during tumor growth.^{110–112} One study suggests that MDCs mediate local immune suppression in ovarian cancer by suppressing the effector function of T cells through the engagement of MDC expressed B7-H1.¹¹³ DCs expressing B7-H1 have been shown to inhibit T cell proliferation directly and also indirectly by promoting the induction of CD25^{high}FoxP3+ Tregs, thus suggesting that B7-H1 is a key player in the tumor microenvironment immune suppression.¹¹⁴ B7-H1 is expressed on the surface of several gynecological cancers including ovarian and is associated with poor overall survival in ovarian cancer.^{115–117} PD-1 was also shown to be expressed on various adaptive immune effectors in the ovarian tumor microenvironment, notably CD4 and CD8 T cells, where it negatively regulates cell activation.^{118–121} The molecular interactions, particularly those associated with PD-1 remain elusive.¹¹³ MDCs mediate local immune suppression not only by expressing PD-1 and B7-H1 but also by generating immune suppressive mediators including arginase, indoleamine 2,3-dioxygenase, nitric oxide and reactive oxygen species.^{122–124} Overall, the DC component of ovarian cancers remains an intriguing and underexplored area of ovarian cancer research.

One mechanism by which several different types of immune cells are suppressed in the tumor microenvironment is through the production of indoleamine 2,3-dioxygenase (IDO).^{125, 126} IDO mediates immune tolerance in T cells and natural killer cells by consuming tryptophan and forming kynurenine resulting in inhibition of proliferation and functional impairment.^{127–131} It also promotes a regulatory T-cell phenotype.^{132–134} IDO is expressed by many tumor types, including ovarian cancer.^{135–137} Takao and colleagues reported protein expression of IDO in serous (57.5%), clear cell (49.2%), and endometrioid (73.3%) ovarian adenocarcinomas.¹³⁷ They additionally found an association between IDO staining in ovarian cancer tumors and lower overall survival for serous ovarian cancer patients with advanced stage disease who had optimal surgery and were given first-line paclitaxel-carboplatin chemotherapy.¹³⁷ Inaba and colleagues reported a similar association between high compared to low expression of IDO in ovarian cancer tumors of mixed histology, stage and grade and lower overall and progression-free survival. In addition, they found reduced numbers of CD8+ TILs in the tumors expressing high IDO.¹³⁵ Finally, they reported that SCID mice given IDO-transfected SKOV3 human ovarian cancer xenografts had higher peritoneal dissemination of the tumor compared to mice given the cell line xenograft with a control vector.¹³⁵ IDO plays an important role in immune suppression and tumor immune evasion and may have potential as a therapeutic target

Several studies have investigated the efficacy of blocking IDO in tumor models.^{135, 138–142} Several matters complicate this, however. First, two IDO genes (*IDO1* and *IDO2*) contribute to tryptophan metabolism, and the contribution of each is not entirely clear (reviewed in Soliman et al.).¹⁴³ Common polymorphisms in *IDO2* have been identified that render it inactive in as many as 50% of Caucasians, making it less likely to contribute to any immunosuppressive effects.^{144, 145} Second, two isomers of the most commonly studied inhibitor, 1-methyl-tryptophan, exist.^{146, 147} Many early studies used a racemic mixture of the two, however a study by Metz and colleagues found that the L isomer of 1-methyl-tryptophan preferentially inhibits IDO1 while the D isomer preferentially inhibits IDO2.¹⁴⁴ *In vitro* studies demonstrated that the L isoform was superior in restoring T cell and antigen presenting functions *in vitro*. However, the D isomer, in conjunction with conventional chemotherapy drugs, was more potent than the L isomer in *in vivo* studies, which led to using this form in early clinical trials.¹⁴⁴ Currently, which isoform to use is still contentious. Third, in addition to IDO1 and IDO2, increased expression of TDO (tryptophan 2,3-dioxygenase), normally expressed at high levels in the liver, has recently been reported in several different tumor types, including ovarian cancer.¹⁴⁸ Kynurenin, one of the metabolites of tryptophan metabolism, was found to bind to the aryl hydrocarbon receptor, causing this transcription factor to translocate to the nucleus and activate several genes, including those supporting the promotion of regulatory T cells.^{148, 149} The structure of TDO differs greatly from IDO1 and IDO2, and neither isomer of 1MT is able to inhibit it. Pilotte and colleagues found that a derivative (LM10) of a known TDO inhibitor (680C91) was bioavailable in mice after oral administration and able to prevent the growth TDO positive tumors.¹⁵⁰ Several phase 1 and 2 clinical trials involving IDO inhibitors are currently underway, including NCT01685255, comparing the IDO inhibitor INCB024360 to tamoxifen in biochemical recurrent ovarian cancer (<http://www.clinicaltrials.gov/ct2/search/advanced>, accessed 2/25/2013). As of yet, no results have been published on the trials.

B. Inherited variation and ovarian cancer survival

Further understanding the role of the immune system in established disease may also be attainable through evaluating associations between genetic variation and recurrence or progression in ovarian cancer. Previously, germline variation in 26 inflammation-related genes was assessed in association with survival in a population of 325 patients with invasive EOC.¹⁵¹ Of those 26 genes, SNPs in *CCR3*, *CCL2*, *IL1B*, *IL18*, and *ALOX5* were related to survival in patients with EOC. As described in the section on inherited variation and ovarian cancer risk, *IL18* and *ALOX5* encode genes with important immune functions and were found in association with ovarian cancer risk as well. *CCR3* encodes the pleiotropic chemokine receptor CCR3 which binds and responds to a variety of chemokines, including CCL11, CCL26, CCL7, CCL13, and CCL5. The receptor is involved in chemotaxis in a wide variety of leukocytes including eosinophils, basophils, and CD4 T cells. CCR2, also known as MCP1 or monocyte chemotactic protein 1, is important for chemotaxis of monocytes and basophils to sites of inflammation. Given the role of macrophages in tumorigenesis, it seems quite plausible that a SNP in this gene could alter macrophage recruitment and therefore survival. *IL1B* encodes IL1beta, a pro-inflammatory cytokine that also has pleiotropic effects on both the immune system and directly on ovarian cancer cells.¹⁵² Still another prospective study of 147 advanced ovarian cancer patients found an association between two *IL10* promoter polymorphisms and disease-free and overall survival, possibly due to its relationship with optimal tumor debulking.¹⁵³ Lastly, in addition to cytokines, genes encoding other modulators of the immune system have been implicated in disease recurrence and progression. TLR4, normally expressed at high levels on immune cells, detects lipopolysaccharide from Gram-negative bacteria and is important in the activation of the innate immune system through NF-κB. In a clinical outcomes study of ovarian cancer patients, a putative microRNA binding site polymorphism in Toll-like

receptor 4 (*TLR4*) (rs7869402) was associated with inferior survival and response to treatment.⁵³ Another putative microRNA binding site SNP in *NFKB1B* (rs3136642) examined in this study was also marginally associated with superior survival.⁵³

In conclusion, it is clear from the multitude of reports that the immune system is a central component of the ovarian cancer microenvironment and contributes to the variable outcomes seen in patients. Figure 1 shows that there are many immune effectors that favor tumor progression either by releasing factors that directly promote growth or through direct blockade of immune effectors that elicit immune destruction. Based on this paradigm, there has been significant interest in combination approaches that induce T cell immunity in conjunction with other agents that reduce suppressive cells. Much work has focused on blocking Tregs along with CTL inducing vaccines. Agents like cyclophosphamide which augment immune-based therapies in both human and mouse studies are thought to have pro-immune functions due to dose-dependent Treg depletion.¹⁵⁴ Other strategies that are being explored to inhibit the function of Tregs include anti-CTLA-4 monoclonal antibodies and CD25-targeted agents such as Denileukin Diftitox.¹⁵⁵

VI. MOLECULAR INTERACTIONS IN THE OVARIAN CANCER IMMUNE MICROENVIRONMENT: THE TNF α , CXCL12, IL-6 AXIS

In contrast to agents that directly increase or decrease specific immune cell subsets, another concept that has recently been introduced is the disruption of integrated cytokine networks. One integrated cytokine network for which there is considerable published support, termed the ‘TNF network’ – consisting of TNF, CXCL12, and IL-6 – was recently identified by Kulbe and colleagues in human ovarian cancer specimens.¹⁵⁶ High level expression of IL-6 has been found in multiple cancers, including ovarian,¹⁵⁷ breast,^{158, 159} prostate,¹⁶⁰ colon,^{161, 162} lung,¹⁶³ and multiple myeloma.^{164–166} In addition to direct synthesis by cancer cells, infiltrating T cells and macrophages are also major sources of IL-6. IL-6 directly promotes cancer growth and progression through several mechanisms, including proliferation, angiogenesis, and decreased sensitivity to apoptotic signals.^{167, 168} High levels of IL-6 in the serum of ovarian cancer patients have been associated with shorter survival.^{169, 170} Additionally, high levels of IL-6 are often detected in the malignant ascites of ovarian cancer patients.¹⁷¹ IL-6 mediates its pathologic effects on cancers via several mechanisms. First, IL-6 signaling results in the activation of several pathways, including the JAK/STAT, PI3K/Akt, and Ras/MEK/IRK pathways.^{169, 170, 172, 173} Second, phosphorylated Stat3, resulting from the JAK/STAT pathway activation, can bind to and inhibit p53 responses to pro-apoptotic signals.¹⁶⁷

Because of the multiple pro-tumor effects of IL-6, it has emerged as a logical candidate for targeted therapy [reviewed in ^{167, 174}]. Several antagonists have been developed to inhibit IL-6 signaling. BE-8, a murine anti-IL-6 monoclonal antibody was initially used in clinical trials; however, the short half-life and inability to block higher levels of IL-6 often seen in patients make it a less than ideal choice for advanced studies.¹⁷⁵ Siltuximab (CNTO328), a human-mouse chimeric IL-6 antibody, has been used in multiple clinical trials for a variety of cancers, including ovarian, renal, and prostate.^{156, 176–179} CNTO328 is generally well tolerated, however, responses are mixed. In a phase II trial of 18 ovarian cancer patients, one individual had a partial response and 7 had stable disease for a period of time.¹⁶⁸ The effects of IL-6 blockade appear to be cancer specific. For example, a phase I study using CNT0328 in castration-resistant prostate cancer patients resulted in decreased expression of genes downstream of the IL-6 signaling pathway but no improvement in outcome.¹⁷⁸ Additional strategies, such as targeting the IL-6R (Tocilizumab) or inhibition of Jak/Stat signaling through a Jak inhibitor, have been tried in various cancers and diseases; at this point it is not clear if these will offer a benefit over targeting IL-6 directly.^{180–184}

CXCR4 has been previously reported to be constitutively expressed in ovarian cancer; the corresponding ligand, CXCL12 is secreted by supporting stromal and endothelial cells in addition to ovarian cancer cells [reviewed in ¹⁸⁵]. High levels of CXCL12 are also found in malignant ascites.^{186–188} Chemokine signaling through CXCR4 has multiple effects, including stimulation of proliferation, vascular endothelial growth factor-mediated angiogenesis, and altered recruitment of immune cells toward tumors.^{189–192} Righi and colleagues studied the effects of CXCL12 blockade in an immunocompetent mouse model.¹⁹² Syngeneic tumor cells expressing CXCL12 and CXCR4 were injected intraperitoneally into mice and chemokine signaling was interrupted by either knocking down expression of CXCL12 or via administration of AMD3100, a CXCR4 antagonist. Not only did blockade of the CXCL12/CXCR4 signaling increase survival and tumor cell apoptosis, it also resulted in a specific shift of the types of T cells recruited to the tumors. Tregs express higher levels of CXCR4 than CD8 T cells do, making them more sensitive to changes in availability of the ligand. Thus, blockade of the CXCL12/CXCR4 signaling cascade resulted in decreased recruitment of Tregs to the tumor and a subsequent significant increase in the CD8/Treg cell ratio and an increase in the antitumor immune response.¹⁹²

TNF α expression in various cancers including ovarian cancer has long been studied. Its expression is highly correlated with increased expression CXCL12 and IL-6,¹⁹³ and this results in the ability of TNF α to mediate a variety of effects. The resultant effect of TNF α on a tumor can depend on both the timing and dosage; a single, high-dose exposure may promote tumor regression while chronic, low-dose expression of TNF α may be part of a tumor promoting network in ovarian cancer.^{194, 195} *In vitro*, exposure of ovarian surface epithelial cells grown as organoids to TNF α resulted in a precancerous phenotype marked by increased proliferation, decreased cellular organization, disruption of epithelial cell polarity, multilayer stratification, and loss of a functional basement membrane.¹⁹⁶ At the same time, the cells increased expression of CA125, MUC1, Claudin 4, and CXCR4.¹⁹⁶ *In vitro* studies of ovarian cancer cell lines using RNAi to decrease expression of TNF α did not result in any changes in proliferation or apoptosis; however, when the same cells were injected *in vivo*, a decrease in tumor burden, restricted distribution, and increased apoptosis was evident compared to control cells.¹⁹³ Kulbe and colleagues suggest that these differential effects of TNF α blockade *in vivo* are due to disruption of a multi-cytokine network constituted by TNF α , CXCL12 and IL-6 that results in reduced angiogenesis, infiltration of myeloid cells and NOTCH signaling (Figure 2).¹⁵⁶

VII. IMMUNE INTERACTIONS IN THE DEVELOPMENT OF CHEMORESISTANCE

Expression of IL-6 has also been linked to increased expression of the multidrug resistance gene 1, leading to resistance to paclitaxel.^{169, 197} Paclitaxel is useful in treating ovarian cancer as it binds to microtubules, preventing their depolymerization, resulting in an interruption of mitosis and pro-apoptotic signaling. Paclitaxel exposure can also increase the expression of IL-6, resulting in a positive feedback loop promoting increased drug resistance and additional IL-6 expression.¹⁷³ Development of chemoresistance is a major hurdle in the treatment of ovarian cancer.¹⁹⁸ Several factors related to inflammation have been shown to modulate the response of ovarian cancer cells to the common therapeutic agents, paclitaxel and cisplatin. However, it is notable that paclitaxel has also been shown to be able to bind and activate TLR4.¹⁹⁹ As mentioned above, TLR4, is normally expressed at high levels on immune cells, detects bacterial lipopolysaccharide and is important in the activation of the innate immune system. TLR4 is expressed on many ovarian cancer cell lines and in ovarian tumors; expression of the TLR adaptor protein MyD88 is cell line specific, however.¹⁹⁹ Several studies have shown that MyD88 positive ovarian cancer cells are resistant to

paclitaxel while the MyD88 negative counterparts remain sensitive.^{199–203} The mechanisms for resistance include increased expression of anti-apoptotic proteins BCL2 and XIAP, activation of Akt survival signaling, and increased production of pro-inflammatory cytokines such as IL-6, IL-8, and RANTES through activation of NFκB.^{199, 202, 203} The sum of these pro-inflammatory pro-survival signals is the ability of paclitaxel to prevent the induction of apoptosis. Thus, paclitaxel can paradoxically cause increased apoptosis or survival, depending on the MyD88 and TLR4 status of the cells. In addition to binding lipopolysaccharide and paclitaxel, in recent years it has become clear that TLR4 is also able to bind host derived products. Heparan sulfate is one such product of relevance to ovarian cancer, as its degradation fragments are known to be potent ligands for TLR4.²⁰⁴ Furthermore, overexpression of the enzyme that generates these fragments, heparanase, correlates with poor survival in ovarian cancer.²⁰⁵

VIII. CONCLUSIONS

From initiating events to long-term survival, the immune system plays a multifaceted role in ovarian cancer pathogenesis. Although most studies to this point have been limited in numbers to determine subtype-specific immune profiles, there is some evidence to suggest different immune gene products (e.g. cytokines and chemokines) and cells may play an integrated role in development and progression of ovarian cancer. Thus, it appears that ovarian cancer, because of its complex interactions with the immune system must be thought of in a systems biology model in order to achieve a better understanding of how to employ novel immune therapies to determine risk, diagnose, treat and understand the prognosis of those afflicted by this detrimental disease.

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Abbreviations

ALOX5	arachidonate 5-lipoxygenase
CASP8	caspase-8
CRP	C-reactive protein
CTL	cytotoxic T lymphocyte
DC	dendritic cell
EOC	epithelial ovarian cancer
IDO	indoleamine 2,3-dioxygenase
MDC	myeloid-derived dendritic cell
NK	natural killer (cell)
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
PTGS2	prostaglandin endoperoxide synthase 2
SNP	single nucleotide polymorphism

TLR4	toll-like receptor 4
Treg	regulatory T cell

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Figure 1.
The immune system favors tumor progression in ovarian cancer

Figure 2.
The TNF network contributes to ovarian cancer pathogenesis