Ovarian cancer and inflammation. Part 2. Anti-inflammatory cytokines

Terlikowska KM.[1A-F], Dobrzycka B.[2B-F], Terlikowski SJ.[2*B-F]

1. Department of Food Biotechnology, Medical University of Bialystok, Poland
2. Department of Obstetrics, Gynecology and Maternity Care, Medical University of Bialystok, Poland

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ABSTRACT

Inflammation plays a key role in epithelial ovarian cancer tumorigenesis and progression. The growth and progression of epithelial ovarian cancer may be due to local cytokine-induced immunosuppression, which may lead to an immunity impairment. Thus, cytokine antagonism may be an essential factor in the treatment of ovarian cancer. Based on the increased knowledge on the role of the immune system in ovarian cancer, major improvements are to be expected of immunotherapy based treatment of this disease. This article aims to summarize the current literature views on the evidence for a role for chronic inflammation with a specific focus on anti-inflammatory cytokines.
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***Corresponding author:**
Slawomir J Terlikowski, Department of Obstetrics
Gynecology and Maternity Care, Medical University of Bialystok
Szpitalna 37, 15-295 Bialystok, Poland
Tel.: +48856865036; Fax.: +48856865037; e-mail: sterlikowski@gmail.com

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INTRODUCTION

Epithelial ovarian cancer (EOC) appears to be associated with inflammation, and the growth, differentiation, and signaling of these tumors is tought to be regulated via cytokines to be regulated by cytokines [1,2]. The growth and progression of EOC may be due to local cytokine-induced immunosuppression, which may lead to a state of immune privilege in the site of the tumor, allowing tumor development as an escape mechanism.

In EOC ascites, increased levels of IL-6 and IL-10 were found, which suggests an immunosuppressive tumor environment in patients with EOC where TH2 inhibitory immune response is favored [3]. Another mechanism believed to be implemented by EOC to escape from immune elimination is up-regulation of immune inhibitory cytokines such as IL-10, C-C motif chemokine 22 (CCL22), and transforming growth factor β (TGFβ) in the tumor microenvironment [4]. IL-10 and TGFβ are strong repressors of an ongoing immune response. TGFβ is a potent inhibitor of cell proliferation for epithelial, endothelial, and hematopoietic cells and plays a prominent role in epithelial-mesenchymal transition believed to be involved in carcinogenesis [5].

Cytokines are polypeptides or glycoproteins with a molecular weight usually below 30 kDa that provide growth, differentiation and inflammatory or anti-inflammatory signals to different cell types. Cytokines are most often released during a defined period in response to a stimulus, and the extent of their action is short-lived due to their limited half-life in the blood circulation. As a result, cytokines normally exert an autocrine or paracrine effect [6]. For an anticancer immune response to lead to effective killing of cancer cells, a series of stepwise events must be initiated and allowed to be processed.

The objective of understanding the inherent immune biology related to EOC is to better define strategies to harness the human immune response against cancer. What is more, to achieve to durable responses and/or complete elimination of ovarian cancer cells. The complexity of the cytokinic network present in the ascitic fluid constitutes a very large field to investigate in order to define new diagnostic methods, combinations of prognosis factors, and novel treatments in EOC.

While the role of immune cells in EOC surveillance has long been known, recent results show that many tumor cell types secrete immunosuppressive cytokines such as IL-2, IL-10 and Transforming Growth Factor-B (TGFβ) that can also recruit cells that negatively regulate immunity such as T-regulatory cells, myeloid suppressor cells, NK cells and macrophage subsets [7,8].

The aim of this article is to summarize the current literature views on the evidence for a role for chronic inflammation with a specific focus on above-mentioned cytokines in EOC.

Interleukin 2 (IL-2)

Interleukin-2 (IL-2) is a T-cell growth factor that plays a critical role in T cell-dependent immunity and is believed to be important in anti-tumor immunity, although the *in vivo* IL-2-mediated mechanisms are not yet fully defined. IL-2 is a cytokine mainly released by activated T cells and acts as a T cell growth factor, enhancing the cytotoxic activity of previously activated T cells. It also stimulates growth and differentiation of B-lymphocytes and natural killer (NK) cells thas, may act as a chemoattractant for eosinophils. Noteworthy is to mention that human eosinophils express functional IL-2 receptors [9].

The use of the intraperitoneal route for administration of immune biologics, including IL-2, in ovarian cancer, has not been extensively studied. However, intravenous administration of IL-2 as monotherapy or in association with immunotherapy has been tested in several clinical trials, demonstrating a 15-20% response rate in melanoma and metastatic renal cancer. In addition, significant activities of this cytokine have been found in other neoplasms such as lymphoma as well as lung, colorectal, gastric and pancreatic cancers [10]. The infusion of this cytokine at high doses is currently approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma. However, the systemic administration of this cytokine at the recommended dose is hampered by its toxic profile, which includes frequent grade 3 and 4 adverse effects [6].

Interleukin 10 (IL-10)

Interleukin 10 (IL-10) is known to be a potent anti-inflammatory cytokine. Almost all immune cells, including T cells, B cells, monocytes, macrophages, mast cells, granulocytes, dendritic cells, and keratinocytes, produce IL-10. Tumor cells can also secrete IL-10, as can tumor-infiltrating macrophages [11].

Several studies have indicated that IL-10 has both pro- and anti-tumoral effects. IL-10 inhibits NF-κB signaling; therefore, it can downregulate pro-inflammatory cytokine expression and act as an anti-tumoral cytokine. Moreover, IL-10 can exert anti-tumoral activity in ovarian carcinomas, through a mechanism involving MHC-I downregulation, thus inducing NK-mediated tumor cell lysis [12]. There have been several reports of increased IL-10 expression in ovarian cancer [13-16]. Zhou et al. [17] assessed the expression of IL-10 in primary ovarian carcinoma, and as compared with benign and normal controls the tissue level of this cytokine was

significantly higher in ovarian cancer. Furthermore, the malignant cases have also showed significantly high IL-10 levels in the serum and ascitic fluid. IL-10 was expressed in the ascites of most untreated primary advanced cancer patients, but nearly absent in ascites at recurrence. These results suggest that ovarian carcinoma cells are able to synthesize and secrete IL-10, which might assist in promoting the development and progression of this cancer. The tumor microenvironment differs between benign, malignant and non-neoplastic tumors, indicating a role of cytokines in tumor progression. This is supported by the analysis of cystic fluid [18].

Transforming Growth Factor β (TGF-β)

The Transforming Growth Factor (TGFβ) family controls different cellular responses in the development and cell homeostasis. Disruption of TGFβ signaling has been implicated in many cancers, including EOC. TGFβ superfamily ligands bind to TGFβ receptors type I (TGFβRI) and type II (TGFβRII), transmembrane serine-threonine kinases specific for each ligand and is a fundamental component of a key signaling pathway in normal ovarian cells that could also be important in EOC when it is dysregulated. TGFβ shifts from tumor-suppressing in early-stage cancer to tumor-promoting in advanced disease. TGFβ inhibits cell growth in benign cells while promoting progression in certain cancers, described as the TGFβ paradox [19]. It is widely believed, that TGFβ switches its role from tumor suppressor in normal cells to tumor promoter in advanced cancers, favoring invasiveness and metastasis depending on the tumor stage [20]. While TGFβ blocks cell growth in normal ovarian epithelial cells, in 40% of ovarian carcinomas TGFβ loses its cytostatic effect but its mesenchymal transition induction and extracellular matrix production is maintained [21]. TGFβ signaling seems seems to be a tumor promoter that controls proliferation in EOC [22].

Plewka et al. [2] demonstrated that the immunoreactivity of TGFβ in ovarian cancer depended on the histological tumor subtype and the degree of malignancy differentiation. In the case of serous tumors, the highest level of TGFβ immunoreactivity was observed in the borderline tumors suggesting a possible role of this growth factor in the pathogenesis of this type of ovarian lesions. This observation with finding of enhanced expression of TGFβ immunoreactivity in mucinous borderline and malignant tumors suggests that pro-oncogenic activities of TGFβ predominate over its tumor suppressor actions and that overexpression of TGFβ can enhance and stimulate tumor growth and malignant progression of ovarian cancer.

Tas et al. [23] evaluated the serum concentration of TGFβ1 in patients of all clinical OC stages and showed that a trend to significant relationship was found between the serum levels of TGFβ1 and the stage of the disease. The elevated serum TGFβ1 level was associated with metastatic disease. In contrast, serum values, serum values of TGFβ1 were not correlated with known disease-related variables. Similarly, neither serum TGFβ1 concentration had a prognostic value in both PFS and OS. Only the chemotherapy-unresponsive patients had significantly higher serum TGFβ1 levels compared with responsive ones. It was suggested suggested, that although the serum level of TGFβ1 has no diagnostic and prognostic role, its predictive value was found in EOC patients.

CONCLUSIONS

Cytokines are soluble proteins that mediate cell-to-cell communication and are powerful but complex immune mediators. Target cells expressing the corresponding sets of receptors integrate the information derived from the concentration and timing of exposure to different cytokines. Synergy or antagonism among different cytokines is a common characteristic, with high degrees of variability. Thus, cell and monoclonal antibody-based therapies in EOC might become partners in the new therapeutic strategies, whose antitumor efficacy in the future will reveal.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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