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Targeted attack: mechanisms by which ovarian cancers suppress the immune system

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Epithelial ovarian cancer (EOC) is the seventh most common cancer diagnosis among women worldwide and has the highest mortality rate of all gynecologic malignancies (1). In the United States, EOC is the fifth most common cause of cancer deaths among women (2). Despite improvements in treatment, 5-year survival rates of patients with advanced ovarian cancer remain less than 50% (3,4) because the majority of patients present with late stage disease (5). Thus, the identification of novel biomarkers and the development of innovative therapeutic approaches are urgently needed. It has been well established that evading immune surveillance is critical for tumor growth and metastasis, and other groups have shown that vascular endothelial growth factor (VEGF) expression is inversely correlated with survival in ovarian cancer patients (6,7). Therefore, we investigated the effects of ovarian cancer-associated VEGF on CD1d-mediated antigen presentation to natural killer T (NKT) cells (8). We found that inhibition of VEGF production by ovarian cancer cell lines led to a reduction in the expression of the immunosuppressive ganglioside GD3 and restored NKT cell activation. Thus, we identified a novel link between immunosuppressive ganglioside shedding and VEGF production by ovarian cancers.

The editorials by Bamias and Gavalas and Kinose *et al.* discuss our recent findings (8) and provide insight into potential future directions. The impact of angiogenic factors on the tumor microenvironment, reported by Bamias and Gavalas, underscore the effects of VEGF on immune cell responses. Importantly, they highlight studies that demonstrate the inhibitory effects of VEGF on dendritic cells and VEGF-mediated suppression of T cell responses. Bamias and Gavalas astutely note that future studies need to delineate the effects of VEGF on various T cell subtypes. Moreover, this group previously reported that VEGF levels inversely correlate with NKT-like cell numbers (6), which emphasizes the importance of evaluating the effects of VEGF on other immune cells. *In vitro*, primary lymphocyte subpopulations can be treated with recombinant VEGF and then the treated cells can be

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assessed both phenotypically and functionally. Various readouts of the cells' functionality, such as growth rate and cytokine production, can be evaluated following treatment. Clinically, it will be important to determine whether higher VEGF levels correlate with increased GD3 levels in tumor-associated ascites.

Kinose *et al.* also discuss another study (9), which showed that VEGF directly suppresses T cell activation, proliferation, and cytotoxic activity via VEGF receptor 2 (VEGFR-2). This study is important because it paves the foundation for future studies on the effects of VEGF on NKT cell function, particularly given the fact that NKT cells express VEGF receptor on their surface (unpublished data from our lab). Therefore, VEGF may directly inhibit NKT cell function. Given its pleiotropic effects on the immune system, Kinose *et al.* suggest that VEGF levels may be used as a prognostic factor to select patients likely to benefit from anti-angiogenic therapies. We concur and our data demonstrate that VEGF inhibition also abrogates the shedding of another immunosuppressive factor, GD3. However, more work is needed in this area. EOC is heterogeneous disease and another group identified a subset of high-grade serous cancers from the ICON7 trial in which antiangiogenic therapy might actually confer a worse progression-free survival (PFS) and overall survival (OS) when compared with chemotherapy alone (10).

Other unresolved questions that remain to be elucidated are what are the signaling events downstream of VEGF receptor that lead to alterations in the lipid repertoire and what key enzymes in the ganglioside synthesis pathway are affected by VEGF? Ultimately, future studies will identify these enzymes in the ganglioside synthesis pathway, which can be used as novel targets for therapeutic intervention. We are grateful for the interest our article has generated and are working to develop *in vitro* organoid model systems as well as utilize animal models to address these remaining questions, in an effort to eradicate this recalcitrant disease.

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References

1. Ataseven B, Chiva LM, Harter P, et al. FIGO stage IV epithelial ovarian, fallopian tube and peritoneal cancer revisited. *Gynecol Oncol.* 2016; 142:597–607. [PubMed: 27335253]
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013; 63:11–30. [PubMed: 23335087]
3. Chu CS, Kim SH, June CH, et al. Immunotherapy opportunities in ovarian cancer. *Expert Rev Anticancer Ther.* 2008; 8:243–57. [PubMed: 18279065]
4. Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet.* 2006 Nov; 95(Suppl 1):S161–92. [PubMed: 17161157]
5. Argento M, Hoffman P, Gauchez AS. Ovarian cancer detection and treatment: current situation and future prospects. *Anticancer Res.* 2008; 28:3135–8. [PubMed: 19031970]
6. Bamias A, Koutsoukou V, Terpos E, et al. Correlation of NK T-like CD3+CD56+ cells and CD4+CD25+(hi) regulatory T cells with VEGF and TNFalpha in ascites from advanced ovarian

cancer: Association with platinum resistance and prognosis in patients receiving first-line, platinum-based chemotherapy. *Gynecol Oncol.* 2008; 108:421–7. [PubMed: 18036640]

7. Rudlowski C, Pickart AK, Fuhljahn C, et al. Prognostic significance of vascular endothelial growth factor expression in ovarian cancer patients: a long-term follow-up. *Int J Gynecol Cancer.* 2006; 16(Suppl 1):183–9.
8. Tiper IV, Temkin SM, Spiegel S, et al. VEGF Potentiates GD3-Mediated Immunosuppression by Human Ovarian Cancer Cells. *Clin Cancer Res.* 2016; 22:4249–58. [PubMed: 27076627]
9. Gavalas NG, Tsiatas M, Tsitsilonis O, et al. VEGF directly suppresses activation of T cells from ascites secondary to ovarian cancer via VEGF receptor type 2. *Br J Cancer.* 2012; 107:1869–75. [PubMed: 23169339]
10. Gourley C, McCavigan A, Perren T, et al. Molecular subgroup of high-grade serous ovarian cancer (HGSOC) as a predictor of outcome following bevacizumab. *J Clin Oncol.* 2014; 32 abstr5502.