



IL-6 and VEGF-A, novel prognostic biomarkers for ovarian cancer?

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Epithelial ovarian cancer (EOC) is the deadliest gynecological cancer in the Western world with a 5-year survival rate of <30% (1). One reason for the EOC high mortality is related to its unusual mechanism of dissemination. Cells detach from the primary tumor site and then aggregate to form free-floating multicellular spheroids. Spheroids are transported at distant sites in peritoneal fluid and seed onto the peritoneal lining where secondary tumor nodules occur (2). Because this process is clinically silent, most women (~70%) present with metastasis throughout the peritoneal cavity and large amount of ascites, highlighting the need to develop new diagnostic modalities, and ultimately make diagnoses earlier. EOC encompasses five distinct pathological subtypes including high-grade serous carcinoma (HGSC), which is, by far, the most common subtype encountered in the clinic (3,4). Despite advances in cancer therapy, the first-line treatment for EOC continue to be, particularly for HGSC subtypes, debulking surgery and platinum-based chemotherapy (5,6). Although most patients respond to this treatment, the development of resistance to chemotherapy commonly occurs, contributing to the low survival rate.

The improvement of EOC survival will require the development of new diagnostic, prognostic and drug resistance biomarkers. Indeed, the identification of new EOC biomarkers is a major women health issue worldwide as 5-year survival has not significantly changed over last three decades. The early detection of EOC remains clinically difficult because the lack of symptoms and the lack of sensitive and specific marker. Reliable markers that identify patients at more curable stages are urgently needed. Even discriminating between benign gynecological conditions and EOC may be clinically problematic because

of the lack of specific marker. Another issue where progress needs to be made is the development of prognostic marker for intrinsic drug resistance. Up to 30% of patients with EOC will be resistant to initial first-line standard chemotherapy (6). Yet, all patients initially received the standard platinum-based therapy. Currently, patients with intrinsic resistance can only be identified after they experienced early relapse to therapy. The stratification of these patients at the time of the initial debulking surgery would substantially decrease morbidity by decreasing their exposure to toxic and inefficient treatments. Although serum CA125 has been the mainstay marker for EOC assessment and management since the early 1980's (7-9), its clinical utility as a diagnostic, prognostic and even as a drug resistance marker has been limited. However, there is a very good correlation between serum CA125 rising and falling levels and EOC progression and regression (10-12). Indeed, CA125 is the only biomarker currently recommended for the monitoring of therapy and for the detection of recurrent diseases. Nonetheless, given the limitations of CA125, there is an urgent need for new biomarkers for EOC.

Patients with HGSC will often present with large amount of ascites, which constitutes a unique form of tumor environment. Cell-free ascites contains a variety of survival factors, including cytokines, chemokines, growth factors, and extracellular matrix (ECM) fragments that change over the course of the disease and promote chronic inflammation (13,14). Chronic inflammation, in turn, contributes to EOC progression by creating a proliferative, migrating, angiogenic and pro-survival environment (15,16). Cell-free ascites constitutes a valuable fluid for the identification of new biomarker as it can be obtained through a simple

puncture. Biofluids such as ascites are valuable as potential sources of markers relative to serum as they reflect events in ovarian tumorigenesis earlier than in peripheral blood circulation. In addition, the ascites soluble factor levels are several orders of magnitude higher relative to serum, which increases the likelihood of detecting low abundance proteins such as cytokines and chemokines. Interleukin-6 (IL-6) is among the most abundant pro-inflammatory cytokine in EOC ascites (12). IL-6 is secreted in ascites by tumor cells, peritoneal mesothelial cells and tumor-associated macrophages (TAMs). Several important roles have been reported for IL-6 signaling including regulation tumor cell proliferation, invasion and angiogenesis (17-19). Angiogenesis is an important process that promotes the growth, invasion, and metastasis of EOC and contributes to the formation of ascites. The vascular endothelial growth factor (VEGF) belongs to the VEGF/PDGF group and has been shown to play a critical role in pathways involved in pathological angiogenesis. VEGF and its related glycoproteins regulate angiogenesis and vascular permeability through binding with their receptors. Bevacizumab, a recombinant humanized monoclonal IgG antibody that targets VEGF-A, is being evaluated for OC treatment. Thus, there is a strong rationale to exploit ascites in search for new biomarkers.

In a recent manuscript, Dalal and colleagues investigated the prognostic potential of ascites IL-6 and VEGF-A for EOC (20). The publication of this manuscript provides additional evidence for moving forward the paradigm of IL-6 and VEGF-A as biomarkers for EOC. In this study, ascites levels of IL-6 and VEGF-A were determined prospectively for thirty newly diagnosed and untreated EOC patients. Ascites were obtained at the time of the initial debulking surgery. Controls included fifteen patients with benign ovary pathology. The results showed, without surprise, that EOC patients had significantly higher ascites levels of IL-6 and VEGF-A relative to controls. In addition, patients with advanced diseases also had higher levels as compared to patients with stage I/II diseases, which is in line with the concept that peritoneal inflammation increases with EOC progression. Using receiver operating curves (ROC), the authors showed an excellent predictive value (sensitivity 100%, specificity 100%) of both markers for discriminating between OC cases and benign diseases, which is consistent with previous studies (21). Although they demonstrated an association between high IL-6 and VEGF-A levels in ascites and shorter progression-free survival, the number of events was very limited (6 total) and

thus these data must be interpreted with caution. A longer follow-up of this cohort would be required to confirm these data. Presumably for the same reason, IL-6 and VEGF-A were not found to be independent prognostic factors in a univariate analysis.

Although this study supports the potential of IL-6 and VEGF-A as diagnostic and prognostic markers for EOC, it has some limitations, which includes the small number of EOC patients, the limited number of events and the inclusions of different subtypes. It is well recognized now that different EOC subtypes represent different diseases from a molecular standpoint. As VEGF-A secretion, for example, may be subtype specific (22), the inclusion of various subtypes may affect the outcome.

Sensitive and specific markers that are independent from clinical parameters are urgently needed to improve EOC diagnostic, prognostic and management. The study of Dalal and colleagues is another step toward this goal. However, there is still a long way to go before any of these biomarkers can be routinely used in clinic. The process of biological and clinical validation along with the demonstration of clinical utility is a long and uncertain journey (23). Nonetheless, studies such as Dalal and colleagues are important to identify potentially new markers that could provide the basis for future validation research in order to achieve significant clinical impact.

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