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Correspondence

Epithelial ovarian cancer inherent resistance: May the pleiotropic interaction between reduced immunosurveillance and drug-resistant cells play a key role?

Dear Editor,

We read with great interest the paper by Giannakeas et al. (2016) about a novel mathematical model to describe ovarian cancer progression, based on the assumption that a small proportion of ovarian cancer cells are chemoresistant from the beginning. We truly appreciated accuracy of the reported information, which stimulated us to further to point out several elements, hoping to trigger a constructive debate. As appropriately stated by the Authors, slow-growing cancer stem cells may have inherent chemoresistance which allows an indefinite expansion, although limited due to the tendency for stem cells to undergo asymmetric self-renewal. Nevertheless, numerous important steps of epithelial ovarian cancer (EOC) initiation and progression may depend, at least in part, by the interaction between different types of committed stem cells within the ovary and the surrounding microenvironment. To date, accumulating evidence (Smolikova et al., 2012) suggests a pivotal role of several immune cells, including mast cells, T-cells, neutrophils and macrophages, in the remodeling processes after the ovulation. In this regard, the possible role of ovarian stem cells in the initiation and progression of EOC is getting growing attention: as widely reviewed by Thompson and Mok (2009), the typical up-regulation of pro-inflammatory cytokines during ovulation may generate a local microenvironment which induce the transformation of normal ovarian epithelial cells within in the ovary; subsequently, these transformed ovarian epithelial cells may undergo an immunoediting process which orchestrates the interaction between the infiltrating immune cells and ovarian stromal microenvironment toward the progression of EOC.

The notion that the immune system not only protects the host against tumor formation but also shapes tumor immunogenicity is the basis of the cancer immunoediting hypothesis, which stresses the dual host-protective and tumor-promoting actions of immunity on developing tumors. As summarized by Schreiber et al. (2011), this mechanism proceeds sequentially through three distinct phases termed "elimination" (the innate and adaptive immune systems work together to detect the presence of a developing tumor and destroy it before it becomes clinically apparent), "equilibrium" (rare tumor cell variants may survive the elimination phase and enter the equilibrium phase, in which the adaptive immune system prevents tumor cell outgrowth and also sculpts the immunogenicity of the tumor cells) and "escape" (tumor cells that have acquired the ability to circumvent immune recognition and/or destruction emerge as progressively growing, visible tumors). Corroborating this view, it was already demonstrated that high presence of intraepithelial $CD8^+$ tumor-infiltrating lymphocytes (TILs) (Zhang et al., 2003), low presence of $FoxP3^+$ T regulatory cells (Tregs) TILs (Barnett et al., 2010) and high CD8 +/Treg ratio (Sato et al., 2005) correlate with improved survival in EOC.

In addition, tumor-associated macrophages (TAM) seem to be crucial in the "immunoescaping" of EOC cells: according to recent data (Deng et al., 2015), M2 macrophages produce a selective cytokine pattern which address toward the immunosuppression respect to the M1 counterpart. Not surprisingly, it was recently evidenced that ovarian cancer drug-resistant cells promote the M2 polarization of macrophages through the proliferator-activated receptor γ (PPARγ)/nuclear factor-κB (NF-κB) pathway (Deng et al., 2015). From the clinical point of view, patients affected by EOC usually undergo satisfactory response to the initial surgical cytoreduction and chemotherapy, although most of them have drug-resistant recurrence later in time, that is conceivably due to the ability of ovarian cancer drug-resistant cells to escape first-line chemotherapy (Laganà et al., 2015).

Recent data suggest that platinum- and taxane-based chemotherapy for EOC can enhance anti-tumor immunity through immunogenic cell death, resulting in increased T cell activation and tumor infiltration: such effects could potentially sensitize tumors to immunotherapies, including checkpoint blockade. In particular, neoadjuvant chemotherapy was associated with increased densities of cytotoxic ($CD3^+$, $CD8^+$, $CD8^+$TIA-1^+, PD-1^+ and $CD20^+$) TILs (Lo et al., 2016), suggesting a possible key role for immunotherapy after the "canonical" chemotherapy in order to target drug-resistant EOC cells.

In conclusion, we appreciate the mathematical model proposed by Giannakeas et al. (2016) and we solicit future studies about the topic in order to clarify the role of ovarian cancer drug-resistant cells in the initiation and progression of the disease, taking into account the role of immune system and surrounding microenvironment and addressing toward a tailored immune target-therapy.

Declaration of interest

All authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company. The authors alone are responsible for the content and writing of the paper. No specific funding was obtained.

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