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Mechanisms for Immune Escape in Epithelial Ovarian Cancer

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Abstract

Epithelial ovarian cancer (EOC) uses a variety of mechanisms to subvert the patient's immune system, however, a lot remains unknown regarding the cancer-immune system interplay. The aim of this thesis was to study tumor-mediated mechanisms for immune escape in EOC, with a focus on the role of cytokines and EOC-derived exosomes. Specifically, we studied: 1) the cytokine mRNA profile in the tumor microenvironment (TME) and peripheral blood of EOC patients, to elucidate its role in host immune suppression; 2) the correlation between cytokine mRNA and protein expression by EOC cells; 3) the composition and function of EOC-derived exosomes and their effect on the NKG2D cytotoxic pathway and 4) the influence of surgery on circulating EOC exosomes and the NKG2D cytotoxic pathway.

We found that proinflammatory and immunosuppressive cytokines promoting Treg cells dominate the cytokine mRNA expression locally in the EOC microenvironment and systemically in the peripheral blood mononuclear cells, compared to women with benign ovarian conditions and women with normal ovaries. The absence of an IFN- γ response together with systemically elevated IL-4 levels indicate deviation of the immune system from a cytotoxic to a humoral response. Comparing cytokine mRNA to protein expression, we found that cytokine mRNA signals were universally detected, and in some instances translated into proteins, but the protein expression levels depended on the material analyzed and the method used. Our results suggest that cytokine mRNA expression profiles can be used for some instances in studies of mechanistic pathways and in comparisons between patient groups, but cannot replace expression at the protein level. Studying the phenotype and function of EOC-derived exosomes, we found that the major cytotoxic NKG2D receptor-mediated pathway is suppressed by NKG2D ligand expressing EOC exosomes acting as decoys, downregulating the cognate receptor. In contrast, DNAM-1 ligands are seldom expressed and not associated with the exosomal membrane surface, leaving the accessory DNAM-1 cytotoxic pathway unaffected. Following these results, we studied NKG2D mediated cytotoxicity *in vivo* in EOC patients before and after surgery. We found that surgery of the primary EOC tumor has a beneficial effect on the anti-tumor cytotoxic immune response. One mechanistic explanation could be a decrease in circulating NKG2D ligand-expressing exosomes, thus improving the cytotoxic NK cell function.

In conclusion, our results contribute to the understanding of the mechanisms responsible for tumor immune escape in general, and in EOC patients in particular, and might be useful in developing novel antitumor treatments. Our studies highlight the prevailing immunosuppression in the local TME and the immunosuppressive role of EOC exosomes. Furthermore, they support the notion that cancer surgery is also a way of removing exosome-producing cells and reducing the serum concentration of immunosuppressive exosomes, thus boosting the patients' cytotoxic anti-tumor response.

Keywords

human, ovarian cancer, high-grade serous cancer, EOC, HGSC, HGSOC, tumor microenvironment, immune escape, immune suppression, cytokines, exosomes, NKG2D, MICA/B, ULBP1-3, DNAM-1, surgery

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