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Immune modulation in serous epithelial ovarian cancer

Focus on the role of tumor-derived exosomes

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Hörsal D Unod T9, Norrland's Universitetssjukhus, fredagen den 15 September, kl. 9:00.
Avhandlingen kommer att försvaras på engelska.

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Abstract
Serous epithelial ovarian cancer (EOC) is a potent suppressor of the immune defense. Here, we studied interactions between EOC and the immune system that lead to escape from tumor immune surveillance. We explored: 1) tumor escape from cytotoxicity by exosome-mediated modulation of the NK-cell receptors NKG2D and DNAM-1; 2) cytokine mRNA profiles in the EOC microenvironment and peripheral blood and their role in the suppression of the anti-tumor immune responses; 3) expression of long non-coding (lnc) RNAs in EOC tumors and exosomes.

We found that EOC-secreted exosomes carried MICA/B and ULBP1-3, ligands of NKG2D, and could downregulate the NKG2D receptor and impair NKG2D-mediated cytotoxicity. In contrast, the DNAM-1 receptor ligands PVR and nectin-2 were seldom found in exosomes and were not associated with the exosomal membrane leaving the DNAM-1 receptor-mediated cytotoxicity intact. We compared cytokine mRNA expression in the tumor microenvironment and in immune cells of peripheral blood in EOC patients and patients with benign ovarian conditions. EOC patients were unable to mount an IFN-gamma mRNA response needed for tumor cell elimination. Instead, there was a significant up-regulation of inflammation and immune suppression i.e. responses promoting tumorigenesis and T-regulatory cell priming that suppress anti-tumor immunity. In addition, we studied lncRNAs in tissues and sera exosomes from EOC and benign ovarian conditions aiming to assess the lncRNA(s) expression profile and look for lncRNA(s) as possible marker(s) for early diagnosis. We found a deregulated lncRNAs expression in EOC tissues that correlated well with the lncRNAs expression in exosomes. Candidate lncRNAs with the highest expression and abundance were suggested for evaluation as EOC diagnostic markers in a future large cohort study. Our studies of EOC tissue and EOC exosomes highlight the immunosuppressive tumor microenvironment and the complex tumor exosome-mediated network of immunosuppressive mechanisms, and provide a mechanistic explanation of the observation that NKG2D-mediated cytotoxicity does not function in EOC patients and is partially replaced by the accessory DNAM-1 dependent cytotoxic pathway. The deregulated lncRNAs expression in EOC tissues and exosomes might serve for diagnostic purposes but could also be a potential risk of spreading tumor-derived lncRNAs in EOC exosomes to recipient cells throughout the body.

Keywords
Ovarian cancer, EOC, HGSC, exosomes, NKG2D, MICA/B, ULBP, DNAM-1, PVR, Nectin-2, lncRNAs, immune suppression, anti-tumor immunity, NK-cell cytotoxicity, cytokines, Th1, Th2, T regulatory response, inflammation, tumor microenvironment.

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