Immunosuppressive Mechanisms In Endometriosis

A focus on the role of exosomes

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Betula, målpunkt L0, by 6M, plan 0, Norrlands Universitetssjukhus, fredagen den 14 juni, kl. 09:00. Via länk: https://umu.zoom.us/j/66602646970

Avhandlingen kommer att försvaras på svenska.

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Abstract

Aberrant immunological mechanisms are suggested to be involved in the pathogenesis of endometriosis. However, much remains unknown regarding the interplay between endometriosis and the immune system. This thesis aimed to investigate immunological mechanisms in endometriosis, focusing on the role of exosomes. Specifically, we studied: 1) to assess cytokine mRNA profiles in endometriotic tissue, endometrium, and blood from endometriosis patients compared to healthy controls; 2) the immunosuppressive potential of endometriotic tissue-secreted exosomes via the NKG2D-mediated cytotoxic pathway and FasL/TRAIL-induced apoptosis; 3) NK-cell subpopulations in the blood of untreated endometriosis patients before and after surgery and/or medical treatment; 4) the role of circulating exosomes and the NKG2D-mediated cytotoxic pathway in patients with epithelial ovarian cancer (EOC), before and after surgery.

We found a downregulation of mRNA for cytokines mediating cytotoxicity in the endometriotic lesions. At the same time, inflammatory and T-regulatory cytokines were upregulated, and T-regulatory cells were also abundant in the endometriotic lesions. These findings suggest that the increased inflammation and priming of adaptive T regulatory cells result in impaired cytotoxicity. Furthermore, we found that endometriotic lesions produce high amounts of exosomes. The exosomes carry the NKG2D ligands MICA/B and ULBP1-3 and the proapoptotic molecules FasL and TRAIL. We showed that these exosomes downregulate the main activating NK receptor NKG2D on CTL and NK cells, reduce the killing ability of lymphocytes, and induce apoptosis of lymphocytes through the FasL/Fas pathway. The results show that endometriotic lesions secrete immunosuppressive exosomes that inhibit cytotoxicity and promote apoptosis of lymphocytes. A higher amount of CD56<sup>bright</sup> cells in serum was observed in one-third of endometriosis patients. Levels were normalized after surgical and/or medical treatment. Untreated patients had a lower expression of NKG2D receptors on their NK cells compared to treated patients and healthy controls. This could be due to endometriotic tissue-derived exosomes downregulating the receptor. Studying serum exosomes isolated from EOC patients we found that they carry the NKG2D ligands MICA/B and ULBP1-3 on their surface. EOC exosomes downregulated the expression of the NKG2D receptor and subdued NKG2D-mediated cytotoxicity in lymphocytes. Surgery of the primary EOC tumor had a beneficial effect, alleviating the exosome-mediated suppression of NKG2D-mediated cytotoxicity. Thus, exosome-mediated immunosuppression is revealed as a common mechanism of action for immune escape in endometriosis and cancer.

The results of this thesis provide novel and important insights into the immune system's function in endometriosis and provide new evidence as to why ectopic endometrial tissue persists and proliferates outside the uterine cavity. Furthermore, the results of this thesis might be useful in finding biomarkers for endometriosis and developing new therapies.

Keywords

endometriosis, immune suppression, immune privilege, NK cells, cytokines, regulatory T cells, exosomes, NKG2D, MICA/B, ULBP1-3, FasL, TRAIL