Interleukin-33 Driven Group 2 Innate Lymphoid Cell - Regulatory T Cell Axis in Endometriosis Pathophysiology

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Introduction/Background

The alarmin interleukin-33 (IL-33) contributes to endometriosis lesion alterations (fibrosis, angiogenesis, immune infiltration). These changes are largely driven by group 2 innate lymphoid cells (ILC2s), which orchestrate type 2 immune response. Regulatory T-cells (Treg) can temper this response, yet how both cell types shape the endometriotic lesion microenvironment remains unknown.

Materials and Methods

IL-33 (1ug) was administered every other day for one week via intraperitoneal injection to syngeneic mice (C57Bl6) with or without endometriosis induction (uterine biopsy engraftment). Endpoints include cytokine analysis of the peritoneal microenvironment, immunoprofiling of endometriosis associated tissues (spleen, peritoneal fluid (PF), uterus, lesion) by flow cytometry, and bulk RNA sequencing of fluorescence-activated cell sorted ILC2s and Tregs from the PF and lesion. Cell types were defined by canonical markers: Tregs (CD4+CD25+FOXP3+) and ILC2s (Lin-CD90+GATA3+).

Results

Preliminary experiments demonstrate that IL-33 drives increases in both ILC2 and Treg cell populations in the localized peritoneal microenvironment. Expression of the IL-33 receptor ST2, compliments these findings, whereby ST2 expression on Tregs and ILC2s was significantly higher in endometriosis mice treated with IL-33. These findings highlight the increased receptivity of both ILC2s and Tregs to IL-33 in endometriosis and suggest their involvement in mediating the associated type 2 inflammation, as confirmed through detection of type 2 cytokines (IL-5, IL-9, IL-13) in the peritoneal microenvironment. Through bulk RNA sequencing (in progress) we look to identify potential ligands and receptors enriched in ILC2s and Tregs to provide insight into mechanisms of cell interaction and whether they are tissue specific.

Conclusion

Our findings unravel the interplay between ILC2s and Tregs and their influence on the endometriosis lesion microenvironment, suggesting a potential role for Tregs in maintaining control over the ILC2 mediated type 2 immune response. These findings provide insight as to how dysregulation of the ILC2-Treg axis could exacerbate endometriosis pathophysiology.

Key words

Group 2 innate lymphoid cells, regulatory T-cells, interleukin-33