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P-792  Stem cells association to the immune cell populations of the human endometrium during the window of implantation

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Study question: Are endometrial stem cells associated with endometrial immune cell populations during the window of implantation?
Summary answer: Endometrial stem cells are associated with the presence of macrophages and B-cells, but do not correlate to T-cells and natural killer (NK) cells.

What is known already: The endometrial stem cells are essential for the periodic uterine regeneration. Besides their role in tissue remodeling it has been recently shown that they exert immunomodulatory and anti-inflammatory effect on the components of the immune system. A well known fact is that the immune cell composition of the endometrium during the window of implantation is pivotal for the successful embryo implantation. There are only a few publications that study the association of the endometrial stem cells with the immune cells with regard to the window of implantation.

Study design, size, duration: Single center prospective study analyzing the cell composition of endometrial samples from women undergoing IVF. A total of 109 patients without endometrial pathologies were recruited for endometrial biopsy between March 2020 and January 2022. Endometrial samples were obtained on day 7 after LH peak in the presumed window of implantation and processed to formalin-fixed, paraffin-embedded slices for immunohistochemical analysis. This study received the approval of the hospital’s medical ethics committee.

Participants/materials, setting, methods: Tissue sections were immunohistochemically stained for CD117 and NOTCH1 as stem cell markers as well as for immune cells with CD3 (T-cells), CD8 (T-killers), CD4 (T-helpers), CD56 (NK cells), CD68 (Macrophages), CD14 (Macrophages) and CD79a (B-cells) antibodies. The percentage of positively stained stromal cells was evaluated by Image-J software in the same tissue area for each sample. Statistical analysis: Spearman correlation, $p < 0.05$ was considered significant.

Main results and the role of chance: Immunohistochemical analysis showed that NOTCH1 and CD117 positive stem cells are present in all samples with mean 0.133±0.029% and 0.034±0.004%, respectively, and they were significantly correlated ($R = 0.397$, $p < 0.001$). The presence of CD3+ T-cells, CD4+ T-helpers, CD8+ T-killers, CD56+ NK cells, CD79a+ B cells, CD68+ macrophages, CD14+ macrophages was also confirmed with mean 1.133±0.259%, 0.374±0.058%, 0.074±0.013%, 0.883±0.184%, 0.188±0.060%, 1.018±0.202% and 1.309±0.257%, respectively.

Spearman analysis revealed significant positive correlation between NOTCH1 positive stem cells and CD79a+ B-cells ($R = 0.211$, $p = 0.029$), CD14+ macrophages ($R = 0.231$, $p = 0.017$), but no relation to the other studied immune cell types was observed ($p > 0.05$).

Significant positive correlation between CD117 positive stem cells and CD79a+ B-cells ($R = 0.211$, $p = 0.029$), CD14+ macrophages ($R = 0.262$, $p = 0.007$), CD68+ macrophages ($R = 0.216$, $p = 0.025$) and no relation to the other studied immune cell types was observed ($p > 0.05$).

When the immune cells ratios were evaluated and analysed for correlation with stem cells, it turned out that only CD117 positive stem cells are significantly correlated to CD8+ T-killers/CD68+ macrophages ratio ($R = -0.274$, $p = 0.007$).

Limitations, reasons for caution: In this study only immunohistochemical analysis was used. In future studies flowcytometrical quantification of the studied cells will be used. Also more immune cell subtypes should be included in the analysis to further characterise the stem cells association to the immune cell populations.

Wider implications of the findings: During the window of implantation the endometrial stem cells are associated to the macrophages distribution. In contrast to NOTCH1+, CD117+ stem cells relate to the endometrial B-cells. These findings confirm the role of the endometrial stem cells in the fine tuning of the immune behavior during the window of implantation.

Trial registration number: Not Applicable