Dissecting Secretory Endometrial Immunity in Reproductive Failure: A Meta-Analysis of Gene Expression in Recurrent Pregnancy Loss and Recurrent Implantation Failure

Bui AH (1), Vargas E (2,3), Andrés-León E (4), Blanco-Rodríguez L (5), Leonés-Baños I (6,3), Altmäe S (6,3), Aghajanova L (1)

(1) Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Stanford University School of Medicine, Palo Alto, CA, USA;
(2) Systems Biology Unit, Department of Experimental Biology, Faculty of Experimental Sciences, University of Jaen, Jaen, Spain;
(3) Instituto de Investigación Biosanitaria ibs. GRANADA, Granada, Spain;
(4) Institute of Parasitology and Biomedicine López-Neyra, Spanish National Research Council. IPBLN-CSIC, Granada, Spain;
(5) Department of Obstetrics and Gynecology, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia;
(6) Department of Biochemistry and Molecular Biology, Faculty of Sciences, University of Granada, Granada, Spain.

INTRODUCTION

Recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF) are often evaluated and treated similarly in the clinical setting. It is believed that endometrial immune cell perturbations play a role in both conditions. However, there is limited understanding regarding how the immunologic profiles of these two conditions compare.

OBJECTIVE

To compare endometrial gene expression profiles of immune cell types between subjects with RPL, RIF, and healthy controls.

METHODS

- A meta-analysis of gene expression studies was conducted. Whole tissue microarray and RNA sequencing (RNA-seq) studies of secretory endometrial biopsies from subjects with RPL, RIF, and healthy controls were compiled from the Gene Expression Omnibus database (1).
- Microarray intensities and log-transformed RNA-seq counts were normalized, and batch effects were corrected using empirical Bayes methods (2-4).
- Bulk tissue cell type decomposition was performed to estimate relative immune cell type abundances within each sample using a human endometrium single-cell RNA-seq database as reference (5,6).
- Zero-inflated beta regression was then performed to compare individual immune cell type proportions between the RPL, RIF and control groups.
- All analyses were performed using R version 4.5.1.

RESULTS

Figure. Bulk Tissue Deconvolution. Immune Cell Proportions by Sample

Table. Immune Cell Average Proportions and Ratios by Phenotype

Cell Type	Proportion of Immune Cells (%)			Ratio of proportions (95% CI)	
	Control	RIF	RPL	RIF	RPL
B cell	1.29	1.53	0.76	1.04 (0.87, 1.24)	0.8 (0.6, 1.07)
cDC1	2.9	3.39	2.05	1.06 (0.91, 1.23)	0.91 (0.72, 1.15)
cDC2	6.7	5.98	8.11	1.08 (0.92, 1.25)	**1.32 (1.09, 1.6)**
eM1	3.62	2.91	2.94	0.85 (0.7, 1.03)	0.87 (0.67, 1.12)
eM2	21.11	22.17	19.21	1.08 (0.99, 1.18)	0.95 (0.85, 1.08)
eM2 cycling	6.77	6.19	7.11	1.12 (0.89, 1.4)	1.08 (0.8, 1.45)
ILC3	2.97	3.42	2.71	0.97 (0.78, 1.2)	0.94 (0.7, 1.26)
Monocyte	1.36	1.76	1.57	1.06 (0.88, 1.27)	1.01 (0.8, 1.29)
pDC	0.89	0.77	0.8	0.97 (0.77, 1.23)	1.12 (0.82, 1.53)
Peripheral lymphocyte	3.3	2.93	3.53	0.96 (0.8, 1.15)	1.01 (0.79, 1.29)
Plasma B cell	0.78	0.84	1.23	0.88 (0.71, 1.1)	1.18 (0.9, 1.55)
T cell CD4	1.56	1.28	1.45	0.94 (0.78, 1.13)	1.04 (0.81, 1.33)
T cell CD8	2.43	1.71	1.28	**0.72 (0.59, 0.87)**	**0.57 (0.43, 0.76)**
T Reg	1.85	2.12	1.21	0.94 (0.79, 1.13)	**0.69 (0.52, 0.92)**
uNK1	19.59	13.02	23.05	**0.65 (0.54, 0.78)**	1.2 (0.96, 1.5)
uNK1 cycling	11.8	13.56	10.77	**1.19 (1, 1.42)**	0.94 (0.73, 1.21)
uNK2	8.28	12.96	8.79	**1.31 (1.08, 1.59)**	1.16 (0.88, 1.54)
uNK3	2.79	3.46	3.43	**1.23 (1.04, 1.46)**	1.17 (0.94, 1.47)

- A total of 170 control, 165 RIF, and 64 RPL samples were compiled from six microarray and five RNA-seq databases for this analysis.
- Compared to controls, endometrial samples from subjects with RIF contained lower proportions of CD8 T cells (RR 0.72, p<0.001) and NK1 cells (RR 0.65, p<0.001), and higher proportions of NK2 (RR 1.31, p=0.005) and NK3 (RR 1.23, p=0.02) cells.
- Compared to controls, endometrial samples from subjects with RPL had lower proportions of CD8 T cells (RR 0.57, p<0.001) and regulatory T cells (RR 0.69, p=0.001).

CONCLUSION

Differences in immune cell concentrations between RPL and RIF may be indicative of different immunologic mechanisms contributing toward the development of these conditions. These findings warrant further investigation into differences in cell-type interactions between each condition.

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