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Eutopic endometrium from women with endometriosis and chlamydial endometritis share immunological cell types and DNA repair imbalance: A transcriptome meta-analytical perspective

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ABSTRACT

The aim of this study was to identify the key similarities between the eutopic endometrium of women with endometriosis and chlamydia-induced endometritis taking into account tissue microenvironment heterogeneity, transcript gene profile, and enriched pathways. A meta-analysis of whole transcriptome microarrays was performed using publicly available data, including samples containing both glandular and stromal endometrial components. Control samples were obtained from women without any reported pathological condition. Only samples obtained during the proliferative menstrual phase were included. Cellular tissue heterogeneity was predicted using a method that integrates gene set enrichment and deconvolution approaches. The batch effect was estimated by principal variant component analysis and removed using an empirical Bayes method. Differentially expressed genes were identified using an adjusted p-value < 0.05 and fold change $= 1.5$. The protein-protein interaction network was built using the STRING database and interaction score over 400. The Molecular Signatures Database was used to analyse the functional enrichment analysis. Both conditions showed similarities in cell types in the microenvironment, particularly $CD4^+$ and $CD8^+$ Tem cells, NKT cells, Th2 cells, basophils, and eosinophils. With regards to the regulation of cellular senescence and DNA integrity/damage checkpoint, which are commonly enriched pathways, 21 genes were down-regulated and directly related to DNA repair. Compared to the endometriosis samples, some chlamydial endometritis samples presented a lack of enriched immune pathways. Our results suggest that both conditions show similar distributions of microenvironment cell types, the downregulation of genes involved in DNA repair and cell cycle control, and pathways involved in immune response evasion.

1. Introduction

Endometriosis is a gynaecological condition that affects 5 %–10 % of women of reproductive age (Cramer and Missmer, 2002; Giudice and Kao, 2004; Fuldeore and Soliman, 2017; Eisenberg et al., 2018). The disease is associated with a negative psychological and social impact, with repercussions on women's quality of life (Culley et al., 2013), impairs their productivity (Nnoaham et al., 2011), and has significant direct and indirect economic costs (Simoens et al., 2012; Soliman et al., 2017). Pain (non-cyclical pain, dysmenorrhoea, dyskinesia, dyspareunia) (Schliep et al., 2015) remains a leading symptom, as well as infertility, abnormal uterine bleeding, and ovarian mass (Sinaii et al., 2008). Despite all associations, there are no specific symptoms or clinical signs that are good predictors of the disease (Nnoaham et al., 2012; Surrey et al., 2017). In fact, because of the overlap of symptoms, endometriosis is often misdiagnosed as other conditions (Seaman et al., 2008). Two other noteworthy points are the lack of correlation between the severity of symptoms and the extent of the disease (Vercellini et al., 2007), and the presence of endometriosis in a reasonable number of asymptomatic women (Tissot et al., 2017).

Histologically, it is characterised by the presence of endometrial-like tissue outside the uterine cavity, usually represented by a peritoneal, ovarian, or deep infiltrative lesion (Nisolle and Donnez, 2019; Agarwal and Subramanian, 2010), although it also occurs in extra-pelvic sites

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more rarely (Andres et al., 2020). The cause of the disorder is unknown. Sampson's retrograde menstruation theory (Sampson, 1927) is the most widely accepted explanation for the origin of injuries, although there are other plausible theories or gaps that complete Sampson's theory (Sourial et al., 2014). On the other hand, as not all women with retrograde menstruation develop endometriosis (Halme et al., 1984), other factors must be involved in its genesis (Zondervan et al., 2018), such as genetic susceptibility (Rahmioglu et al., 2014), immunological tolerance dysfunction, such as autoimmunity and immune surveillance deficiency (Symons et al., 2018; Izumi et al., 2018; Vallvé-Juanico et al., 2019), and changes into the eutopic endometrium (Vinatier et al., 2000; Carvalho et al., 2011; Brosens et al., 2012). Some authors have also proposed a "bacterial contamination hypothesis", in which the outbreak of pathophysiological events that would culminate in endometriosis could be due to the colonisation of the intrauterine environment by microbes (Khaleque N. Khan et al., 2018). In fact, this concept of initial infection followed by sterile inflammation has been proposed previously (Kobayashi et al., 2014). These hypotheses are supported by studies showing an association between endometriosis and endometritis and lower genital tract infection (Ballard et al., 2008; Seaman et al., 2008; Cicinelli et al., 2017; Takebayashi et al., 2014; Tai et al., 2018; Lin et al., 2016), microbial contamination of the uterine cavity, or ectopic lesions by various agents (Khan et al., 2010, 2016; Khan et al., 2014; Leonardi et al., 2020), as well as by the association between endometriosis and more severe pelvic inflammatory disease (Elizur et al., 2014). Recently, the genetic-epigenetic theory has been postulated to jointly explain and understand all observations of endometriosis pathophysiology (Koninckx et al., 2019a,b). This theory has proposed that endometriosis could be triggered by a cumulative set of genetic-epigenetic alterations, and that infection could be a potential cofactor in this scenario (Koninckx et al., 2019a,b).

Among the potential pathogens, *Chlamydia trachomatis* (chlamydia) stands out for being the most common sexually transmitted bacterial infection in the USA, as well as globally (Wiesenfeld, 2017). It occurs more frequently among young women aged 14–19 years and has a high recurrence rate (repeated infections), ranging from 15 % after 4 months to 60 % after 18 months, mainly due to the resumption of sexual activity, although protective immunity may be acquired with age (Batteiger et al., 2010; O'Connell and Ferone, 2016). Chlamydia can also be transmitted to neonates during vaginal delivery, leading to infection of the urogenital tract (Schachter et al., 1979; Darville, 2005). As in endometriosis, chlamydia infection seems to be influenced by genetic predisposition (Mahdi, 2002; Ohman et al., 2011). In addition, chlamydia infection appears to be associated with an increased risk of ovarian cancer (Das, 2018), similar to endometriosis (Pearce et al., 2012). While acute infection is often asymptomatic, disease progression is uncertain. Some women have a protective immune response with bacterial clearance, while others have a pathological immune response with unfavourable outcomes, such as pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain, and infertility (Darville and Hiltke, 2010). Generally, patients with repeated infections were found to have a lower bacterial load in subsequent episodes, suggesting that prior exposure may restrict replication at the local site as a result of the activation of a specific adaptive response, but occurs only in the promotion of partial immunity (Gomes et al., 2006). However, the mechanisms responsible for this balance between protective and pathological immune responses remain poorly understood (Lijek et al., 2018).

Advances in molecular biology techniques in recent decades has provided important information that has led to a deeper understanding of several aspects of disease biology, including providing important insights into endometriosis. Recently, transcriptome meta-analysis demonstrated that, independent of the hormonal milieu and the severity degree of endometriosis, eutopic endometrium in women is associated with a unique tissue microenvironment, transcription patterns, and enriched pathways, suggesting a status of sustained stress and/or damage (Poli-Neto et al., 2020). In addition to quantifying the expression of a pre-selected number of probes/genes determined by certain platforms, and RNA sequencing incorporates high-throughput sequencing to identify all expressed sequences (Lowe et al., 2017), microarray techniques provide researchers with fast, cheap, and reproducible results when studying known genes (Chen et al., 2017). A number of studies using this technology have identified candidate genes and pathways involved in the pathogenesis of endometriosis (Kao et al., 2003; Burney et al., 2007; Ohlsson Teague et al., 2009; Wu et al., 2006), and only one using samples from women with chlamydia endometrial infection (Vicetti Miguel et al., 2013). Considering the evidence of a higher risk of endometriosis between patients with lower genital tract infection and the potential for endometrial infection to trigger the initial stages of endometriosis development, we proposed to explore these independent transcriptome data using a meta-analytical approach. We believe it is possible to infer key similarities between the eutopic endometrium of women with endometriosis or with chlamydia-induced endometritis from the point of view of tissue microenvironment heterogeneity, transcript gene profile, and enriched pathways. The information presented in this study will contribute to the understanding of the relationship between endometrial infection and endometriosis, direct further research, and could culminate in effective proposals for the prevention and/or treatment of endometriosis in the future.

2. Material and methods

2.1. Data acquisition and preparation

We conducted a meta-analysis by combining multiple microarray datasets from samples of eutopic endometria obtained from childbearing women. We performed a search in two public databases for the raw microarray data. The databases used included Array Express (http://www.ebi.ac.uk/arrayexpress/) from the European Bioinformatics Institute (EBI), and Gene Expression Omnibus (GEO) repository (http://ncbi.nlm.nih.gov/geo/) from the National Centre for Biotechnology Information (NCBI). We used datasets previously selected in our recent meta-analysis (Poli-Neto et al., 2020). As previously described, data were obtained from GSE4888 (Talbi et al., 2006), GSE6364 (Burney et al., 2007), GSE7305 (Hever et al., 2007), GSE7307 (GEO repository), and GSE51981 (Tamaresis et al., 2014). Raw data from E-MTAB 694 was also included (Sohler et al., 2013). GSE29981 was not selected because it included only the glandular component analysed after laser capture microdissection. We considered only studies that published raw data from samples containing both glandular and stromal components, due to the importance of the microenvironment in the pathophysiology of the disease (Ahn et al., 2016). All these studies used the GPL570 platform and high-density oligonucleotide Affymetrix GeneChip Human Genome U133 Plus 2.0 Array (Affymetrix, Santa Clara, CA), which covers over 47,000 transcripts and 21,000 genes.

An update of the search was performed using "chlamydia" or "endometritis" as additional search terms. Thus, we identified one additional dataset containing the transcriptome profile of endometrial tissue from women with genital chlamydia infection, GSE41075 (Vicetti Miguel et al., 2013). However, the authors used the GPL571 platform and Affymetrix GeneChip Human Genome U133A 2.0 Array (Affymetrix, Santa Clara, CA), which covers 18,400 transcripts and 14,500 well-characterized human genes. All these genes were identified using the GPL570 platform. To proceed with an equivalent analysis, we included an additional endometriosis study previously identified but not included in our previous meta-analysis using the GPL571 platform, GSE25628 (Crispi et al., 2013). Although cross-platform normalisation is possible, we may include critical batch effects that, when removed, may minimise the significance of the biological effect. Therefore, we included only studies that used Affymetrix platforms.

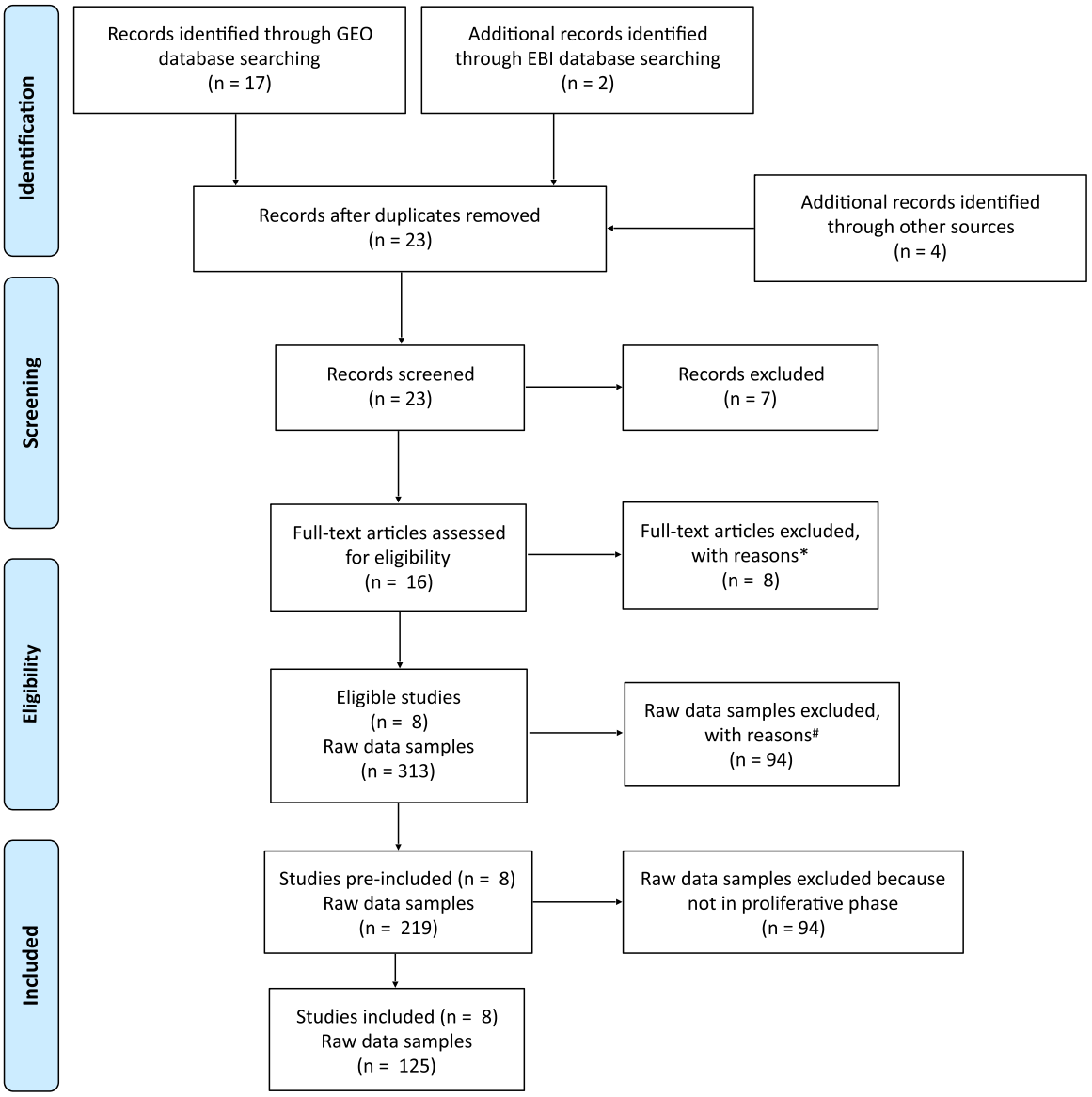
Healthy control samples were obtained from women without any reported pathological condition. Chamydial samples were obtained from women without symptoms of acute pelvic inflammatory disease

who had no other identified infection. The menstrual phase provides important phenotypic information owing to the significant molecular phenotypic differences presented by the eutopic endometrium in each phase (Talbi et al., 2006; Burney et al., 2007). The detailed selection of databases and samples is summarised in a flow diagram (Fig. 1).

For initial phenotype classification, we divided the endometriosis samples into two groups: stage I–II and stage III–IV. This division was based on evidences that early stages have a predominance of pro-inflammatory cytokines related to Th1 profile, while late stages present a Th2 profile, characterised by an immunosuppressive effect and tissue repair (Pizzo et al., 2002; Poli-Neto et al., 2020), as well as by evidence that the profile of genetic susceptibility is different among women with stage I-II or stage III-IV disease (Rahmiogluet al. 2014). We also focused on common alterations that occur throughout the eutopic endometria of women with endometriosis or chlamydial endometritis. All computational analyses were performed in R. The CEL format files containing the microarray experimental data were downloaded and processed using the robust multiarray average method (RMA) to allow for background correction, normalisation, and summarisation (Irizarry et al., 2003a,b). After pre-processing, the probe expression level was collapsed to the corresponding gene using the highest value (maximum) of expression in each sample.

2.2. Cell type prediction

The presence of numerous cell types within samples can influence



* GSE47577 - endometrial tissue of women with symptomatic uterine fibroids
* GSE32178 - myometrial biopsies
* GSE17025 - endometrioid and papillary serous histologic subtypes
* GSE12446 - endometrial tissue postmenopausal endometrium
* GSE7846 - endometrial endothelial cells
* GSE29981 - only glandular component was analysed by laser capture microdissection
* E-GEOD9511 - myometrial biopsies
* EGEOD6573 - deciduas, placentas and fat tissues of preeclamptic women
# GSE4888: not included samples from patients with adenomyosis, leiomyomata, ovarian cyst, pain, and prolapse reported; GSEA6364: not included samples from healthy patients because authors affirm that they were obtained from GSE4888; GSE7305: not included samples from ovary; GSE7307: not included samples from ovary; GSE51981: not included endometrium samples from women with "uterine pathology" reported.

Fig. 1. Flowchart of dataset selection and samples inclusion strategy.

the quality of microarray interpretations, affecting biological conclusions as a result (Venet et al., 2001). Based on this, we determined tissue cellular heterogeneity using the xCell package (Aran et al., 2017), a method that integrates gene set enrichment with deconvolution approaches to predict 64 immune and stromal cell types, and CIBERSORTx (Newman et al., 2015; Chen et al., 2018; Newman et al., 2019), a deconvolution gene signature-based approach, to estimate the abundance of cell types, among them, 22 immune cell subsets. The use of xCell allowed for comparability between samples, while CIBERSORTx generated a relative cell fraction score, which allows only an intra-sample comparison, although it has been extended to an "absolute mode", which provides a score that can be compared between samples. xCell initially computes individual cell scores (an arbitrary unit), and ultimately grouped these values into immune and stromal scores that comprise the overall microenvironment score. The Wilcoxon test was performed as a two-sided test to compare score outcomes.

2.3. Menstrual phase prediction

After generating these initial data, we unified the databases considering only genes present in both expression matrices, that is, the genes identified by the GPC571 platform. Then, since we had identified that the menstrual phases of eutopic endometria from women with Chlamydia infection were not known, we predicted them using a supervised learning approach, called prediction analysis of microarrays, provided by PAMR package (Hastie et al., 2019). This method provides a classification of gene expression data by the method of nearest shrunken centroids (Tibshirani et al., 2002). The algorithm overall error rate was 8 %; however, all the samples were predicted as proliferative phases with cross-validated probabilities near 100 %. Considering the need to remove potential non-biological experimental variation (batch effect), the absence of samples from women with chlamydia infection in the secretory phase posed a serious risk of removing true biological representation during this process. Therefore, only samples collected in the proliferative phase were considered.

2.4. Identification of differently expressed genes (DEGs)

After unifying our expression sets, we estimated the batch effects derived from combining multiple datasets by principal variant component analysis (PVCA) (Li et al., 2009),which is a hybrid approach that incorporates principal component analysis (PCA) and variance component analysis (VCA). After the identification, the batch effect was removed using ComBat, an empirical Bayes method (Chen et al., 2011).

Although low-expression gene filtering can improve the detection sensitivity of differentially expressed genes (DEGs) (Bourgon et al., 2010; van Iterson et al., 2010), we chose to analyse all 12,403 collapsed genes without filtering for gene expression. This decision was taken mainly owing to the heterogeneity of the number of samples between groups, which could result in unbalanced exclusions.

For DEG identification, we used the Limma package (Ritchie et al., 2015). First, we assessed the empirical array quality weights (Ritchie et al., 2006), as these values increase the statistical power to detect true differential expression without increasing the false discovery rate. As the values were heterogeneous, we used them in the linear model analysis. All comparisons were performed between the experimental samples (endometritis and endometriosis) and the control samples (healthy). The following criteria were considered for selection of DEGs: fold change of 1.5, and false discovery rate (adjusted p value) of 5%. After a preliminary analysis of the pathways highlighted in the network, we selected genes related to DNA repair for further analysis. To this end, we used data from Errol et al. (2006), and Lange et al. (2011), which were recently actualized and are available (https://www.mdanderson.org/documents/Labs/Wood-Laboratory/human-dna-repair-genes.html#Human%20DNA%20Repair%20Genes; including the activity linked to the Online Mendelian Inheritance in Man database®). We used the STRING database to summarise the protein-protein interaction (PPI) network. The PPI network was constructed using up- and down-regulated genes found simultaneously in all conditions studied. In order to reduce the complexity of the interaction network, we select genes using more stringent cut-offs at 1 % for an adjusted p-value and at 2.0 for fold change. For the results and discussion, we considered only interactions with scores higher than 400 (Szklarczyk et al., 2015).

2.5. Gene set enrichment analysis

Prior to gene set enrichment analysis, we searched for patterns or relationships in the expression data using hierarchical unsupervised clustering. For this, we plotted a heatmap using the complexHeatmap package (Gu et al., 2016) with the Ward D2 method, and used the Euclidean distance as the measurement of distance between two points. Visual criteria and statistical methods were used to choose the best number of clusters (Tibshirani et al., 2001; Yuan and Yang, 2019). Then, we performed functional enrichment analysis using all genes pre-ranked by a signal-to-noise ranking metric without filtering. The analysis was performed using GSEA Software 4.0 (Subramanian et al., 2005), considering and the Molecular Signatures Database (MSigDB 7.0 released), which possesses a wide collection of annotated gene sets (Liberzon et al., 2011). There are other excellent tools for enrichment analysis (Maere et al., 2005; Reimand et al., 2019), but we believe that the method employed could overcome two common limitations in this type of analysis, allowing us to: (1) include the complete list of genes in the analysis, thus avoiding the use of arbitrary thresholds for gene selection; (2) identify key pathways in a concise, non-redundant manner to facilitate the interpretation of the results. We initially applied GSEA to the hallmark gene sets to summarise the well-defined biological conditions of the original founder sets to reduce both variation and redundancy (Liberzon et al., 2015) from numerous pathway/gene set databases, such as BioCarta (Nishimura, 2001), Kyoto Encyclopaedia Genes Genomes (KEGG) (Kanehisa et al., 2008), Reactome (Fabregat et al., 2018), Gene Ontology (GO) (Ashburner et al., 2000), miRBase (Kozomara and Griffiths-Jones, 2014), and others (Xie et al., 2005; Zeller et al., 2003; Schaefer et al., 2009; Brentani et al., 2003; Su et al., 2004; Ramaswamy et al., 2001; Segal et al., 2004; Godec et al., 2016; Naba et al., 2012; Newman and Weiner, 2005). We used the following parameters: 1000 permutations, weighted enrichment statistics (p value = 1), and the exclusion of gene sets with sizes larger than 500 genes and smaller than 15 genes. For interpretation, a stringent false discovery rate (FDR) q-value of $\leq$ 1% was considered significant, as suggested by the authors. The enrichment scores (ES) reflected the degree to which the genes in a gene set were overrepresented. Positive and negative signals in the ES indicated a correlation with the gene set enrichment at the top or the bottom of the ranked list, that is, up- or down-regulated genes. The ES were adjusted for variations in gene set size, and represented by normalised enrichment scores (NESs). More details can be obtained by consulting the documentation (http://www.gsea-msigdb.org/gsea/index.jsp).

3. Results

3.1. General

Our dataset selection and sample inclusion strategy is presented in a PRISMA flowchart (Fig. 1). The overall gene expression before and after batch effect removal is presented in Fig. 2. Our study was composed of 54 samples obtained from healthy women, 12 obtained from women with chlamydial endometritis, and 59 samples obtained from women with endometriosis (16 stage I–II and 43 stage III–IV) (Table 1).

3.2. Microenvironment

Fig. 3 shows a graphical comparison using normalised average xCell

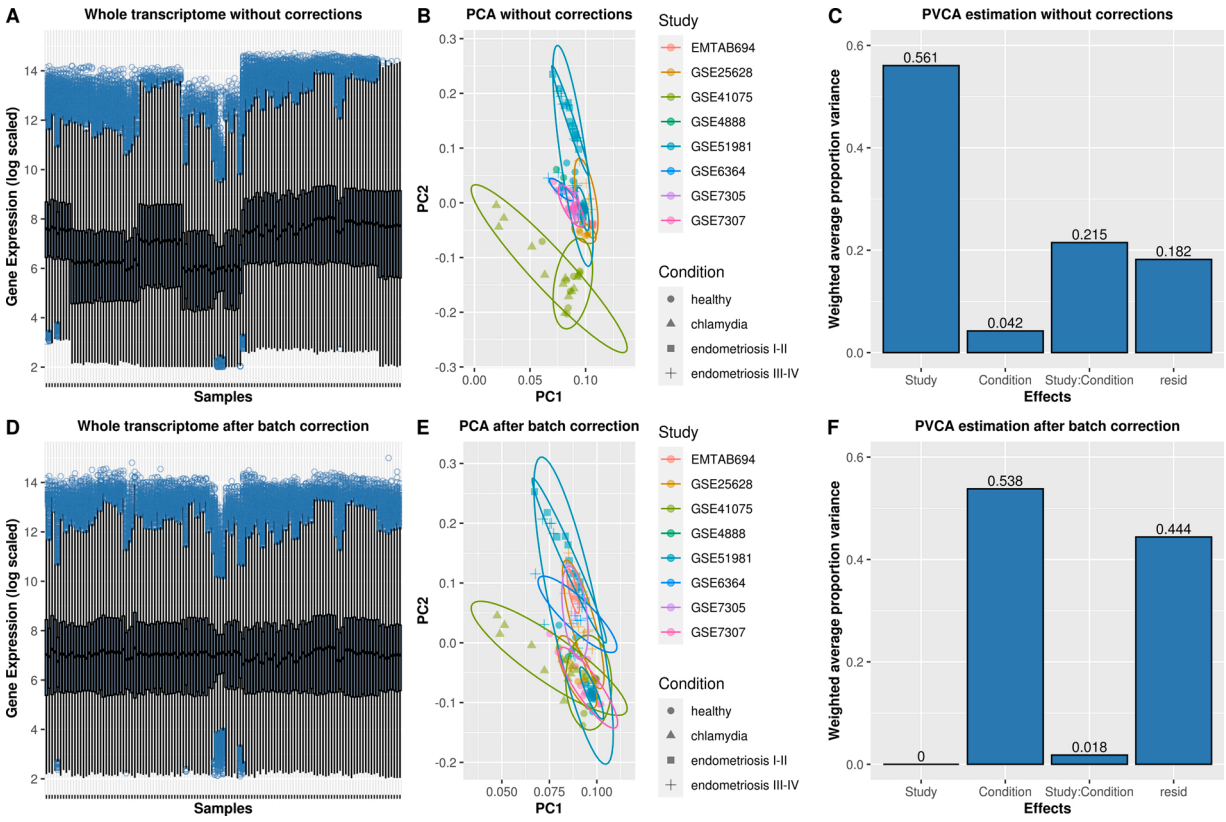


Fig. 2. Gene expression after combining data from datasets, identification and removal of the batch effect.
Notes: Boxplots show the intensity of the log2-transformed gene expression before (A) and after (D) batch effect removal. Scatterplots show PCA analysis of normalised gene expression data before (B) and after (E) batch effect removal by Combat; ellipse underlying assumptions about the distribution of the data were drawn considering a multivariate t-distribution and a confidence level of 0.95. bar charts show the proportion of batch effect by PVCA estimation from possible sources before (C) and after (F) batch correction. ComBat with parametric adjustment was used to remove the estimated batch effect.

Table 1
Datasets and samples selected by searching in Pubmed and GEO repository.

GEO series / Study	Reference	Samples	Eutopic endometrium from women condition
GSE4888	Talbi 2006	3	Healthy
GSE6364	Burney 2007	6	Endometriosis III-IV
GSE7305	Hever 2007	8	Endometriosis III-IV
GSE7307	GEO repository	16	Healthy
GSE25628	Crispi 2013	15	Healthy (n = 6) Endometriosis III-IV (n = 9)
GSE41075	Vicetti Miguel 2013	21	Healthy (n = 9) Chlamydial endometritis (n = 12)
GSE51981	Tamaresis 2014	48	Healthy (n = 20) Endometriosis I-II (n = 11) Endometriosis III-IV (n = 17)
E-MTAB-694	Sohler 2013	8	Endometriosis I-II (n = 5) Endometriosis III-IV (n = 3)

scores of the cell types differentially predicted in at least one condition regarding healthy control samples. Among these, some cell types are highlighted, namely $CD4^+$ and $CD8^+$ Tem cells, NKT cells, Th2 cells, basophils, and eosinophils. The full list of scores for all specific cell types is presented in the Supplementary datasets (Dataset 1). CIBERSORTx was less consistent in identifying differences in the immune landscape among samples from endometritis and endometriosis in healthy eutopic endometrium. A total of 53.8 % of Pearson's correlation coefficients comparing the original mixture with the estimated mixture were below 0.70.

3.3. DEGs

The full list of up-regulated and down-regulated genes that were differentially expressed between healthy control and chlamydial endometritis (1464/1245), stage I-II (2817/3787), and stage III-IV endometriosis (1008/2318) are provided in the Supplementary datasets (Datasets 2A-C). Overall, 74 and 464 genes were found to be commonly up- and down-regulated, respectively across all conditions (Fig. 4) (Datasets 3A-B). Additionally, to show statistical significance (adjusted p value) versus magnitude of change (fold change) we have presented some volcano plots (Fig. 5). In these plots we also displayed the genes used for building the PPI network considering more stringent criteria (adjusted p-value = 0.01, fold change = 2.0).

The estimated PPI network showed important interactions among genes that were commonly up- and down-regulated (Fig. 6). As said before, for avoiding high complexity, we have chosen a more stringent list of genes (up-regulated genes: *APOD*, *CFD*, *CTSW*, *GPX3*, *MUC5B*, *SST*; down-regulated genes: *ADAMTS6*, *ASPM*, *BRIP1*, *BUB1B*, *CCNA2*, *CCNB1*, *CCNE2*, *CDKN3*, *CENPF*, *CENPU*, *CEP55*, *CKAP2*, *DHFR*, *DLGAP5*, *DONSON*, *DTL*, *ECT2*, *FAM208B*, *FBXO5*, *GGH*, *GRB14*, *HMMR*, *KIF11*, *KIF15*, *KIF18A*, *KIF20A*, *KMO*, *MAD2L1*, *NCAPG*, *NDC80*, *NUSAP1*, *P2RY14*, *PBK*, *POSTN*, *PRC1*, *PRSS12*, *RAD51AP1*, *SHCBP1*, *SPAG5*, *TCERG1*, *TOP2A*, *ZWILCH*"). The expected number of edges was 35, the number of edges found was 461, and the PPI enrichment p-value was < 1.0e-16. Functional enrichments in this network showed more frequent pathways related to regulation of cell cycle, cellular senescence, DNA integrity/damage checkpoint (including DNA double-strand break repair), response to stress, folate biosynthesis, and antifolate resistance. A full list of functional enrichments is presented in the Supplementary datasets (Dataset 4A-F).

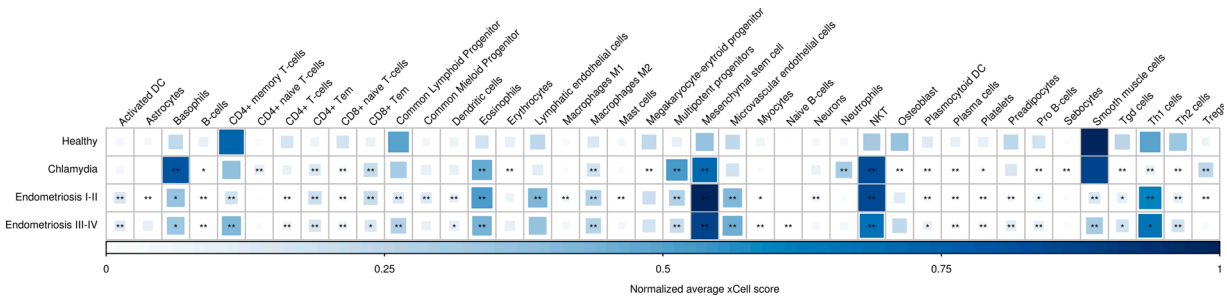


Fig. 3. Graphical comparison among normalised average xCell scores of the cell types differently predicted in eutopic endometrium from healthy, chlamydia-induced endometritis and endometriosis.
Notes: To construct the plot, first we chose cell types in which xCell scores were significantly different in at least one condition considering $p < .01$ (**). Once this condition was satisfied, we have also added to the plot xCell scores at $p < .05$ (*).

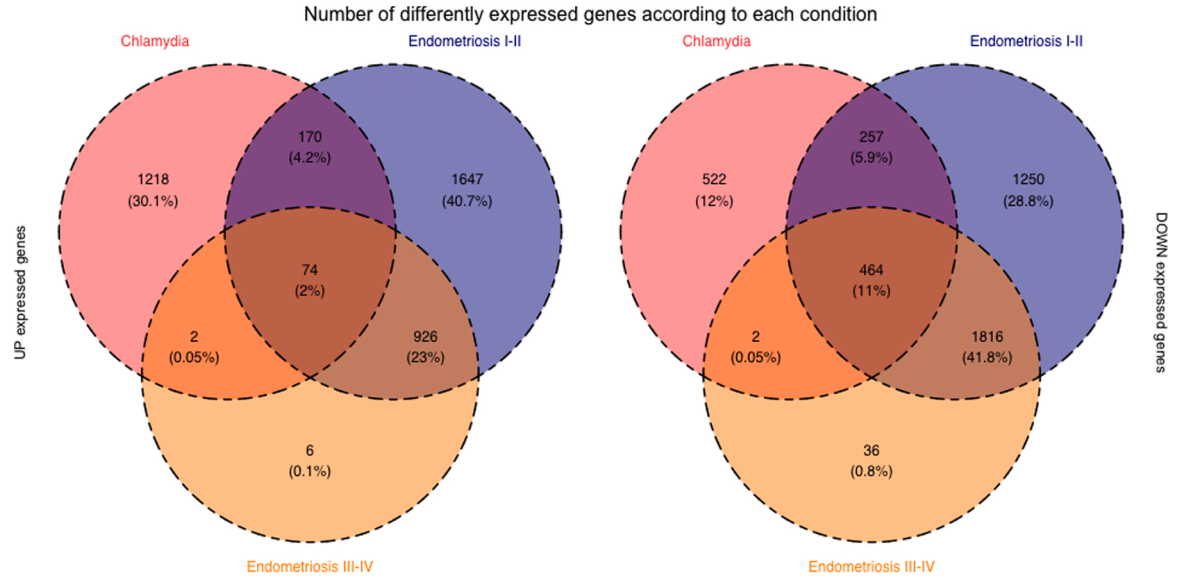


Fig. 4. Venn diagram showing the number of differentially expressed genes per comparison across conditions and the overlap between each set of genes.

The most commonly down-regulated genes were directly related to DNA repair functions: base excision repair (*NEIL3*), poly ADP ribose polymerase enzymes that bind to DNA (*PARPBP*), mismatch excision repair (*MSH2*, *MSH6*), nucleotide excision repair (*RPA1*), homologous recombination (*PDS5B*, *PAXIP1*, *SMC6*), Fanconi anaemia DNA repair (*FANCI*, *BRIP1*, *FANCL*), non-homologous end joining (*PRKDC*), DNA polymerases (*POLA1*, *POLE2*, *REV1*, *POLI*), editing and processing nucleases (*FEN1*, *EXO1*), ubiquitination and modification (*USP1*), chromatin structure and modification (*ATRX*), and other conserved DNA damage response genes (*PCNA*). Fig. 7 shows the expression of these genes across all the conditions.

3.4. Unsupervised clustering

Our analysis suggests that two is the optimal number of clusters, as shown in Fig. 8. Chlamydial endometritis-associated samples were located in both clusters. The first (subcluster A) was predominantly composed of samples from healthy controls (85.2 %, 46 from 54 samples), but also samples of chlamydial endometritis (58.3 %, 7 from 12 samples), while the second (subcluster B) was predominantly composed of samples from women with endometriosis (94.9 %, 56 from 59 samples) and chlamydial endometritis (41.7 %, 5 from 12 samples). Thus, we refined the groups for gene set enrichment analysis as follows: healthy, healthy endometrium specimens grouped in subcluster A (n = 46); chlamydia A, chlamydial endometritis specimens grouped into subcluster A (n = 7); chlamydia B, chlamydial endometritis specimens grouped in subcluster B (n = 5); endometriosis associated specimens grouped in subcluster B (n = 16 for endometriosis I—II, and n = 43 for endometriosis III-IV).

3.5. Gene set enrichment analysis

Numerous pathways are commonly dysregulated among chlamydial endometritis and eutopic endometrium associated with endometriosis: myogenesis, UV response, fatty acid metabolism, oxidative phosphorylation, protein secretion, E2F targets, G2M checkpoint, mitotic spindle, MYC targets, androgen response, KRAS signalling, and MTORC1 signalling. Specimens of chlamydial endometritis grouped in subcluster A (the same as in healthy specimens), different from other conditions studied, showed enrichment for multiple immune pathways (allograft rejection, coagulation, complement, IL6 JAK STAT3 signalling, inflammatory response) and signalling pathways (IL2 STAT5 signalling, and TNFA signalling via NFkB). Further relevant information is presented in Fig. 9. All enriched pathways are presented in the Supplementary datasets (5A[1-4], 5B[1-4], 5C[1-4], and 5D[1-4], representing Hallmark, Gene Ontology, KEGG, and Reactome, respectively).

4. Discussion

The results of our meta-analysis indicate that the eutopic endometrium of women with Chlamydia infection, despite certain particularities, shares common characteristics with the eutopic endometrium of

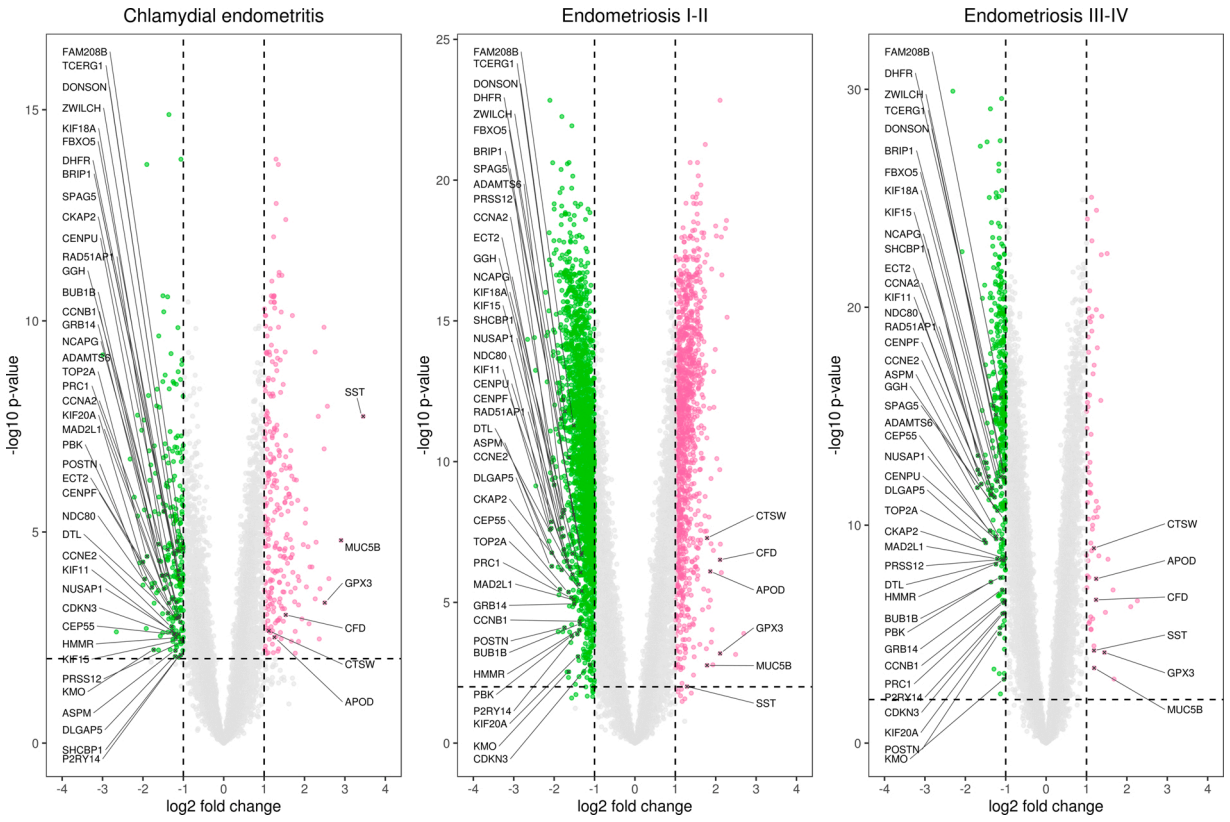


Fig. 5. Volcano plots showing differently expressed genes in eutopic endometrium from each condition.
Notes: Horizontal and vertical dashed lines represent adjusted p value (.05) and fold change (2.0), respectively. Black marks represent commonly DEGs identified in both conditions, considering adjusted $p < .05$ and $FC > 2.0$ (logFC>1.0).

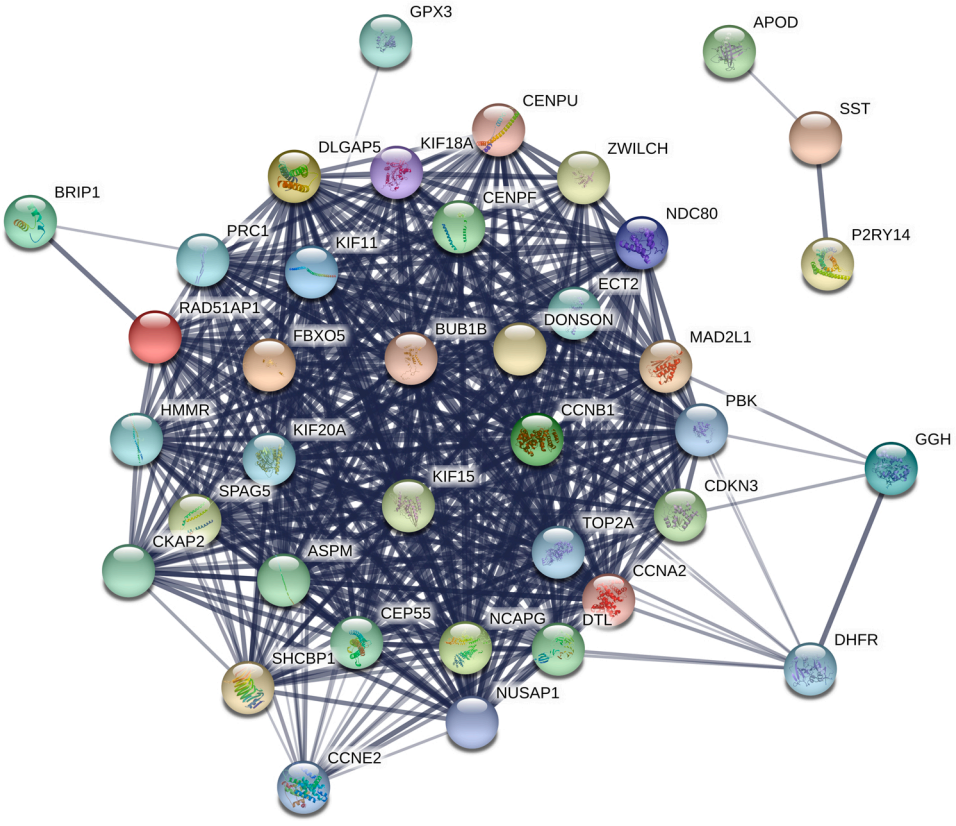


Fig. 6. Protein-protein interaction network (STRING DB) showing dysregulated genes found simultaneously in all conditions.
Notes: Network edges mean confidence, that is, the thickness of the line indicates the strength of the data support. We considered a minimum required interaction score of 0.40 (medium confidence) and hidden disconnected nodes in the network. Expected number of edges: 35, number of edges found: 461, PPI enrichment p-value: < 0.001 (< 1.0e-16).

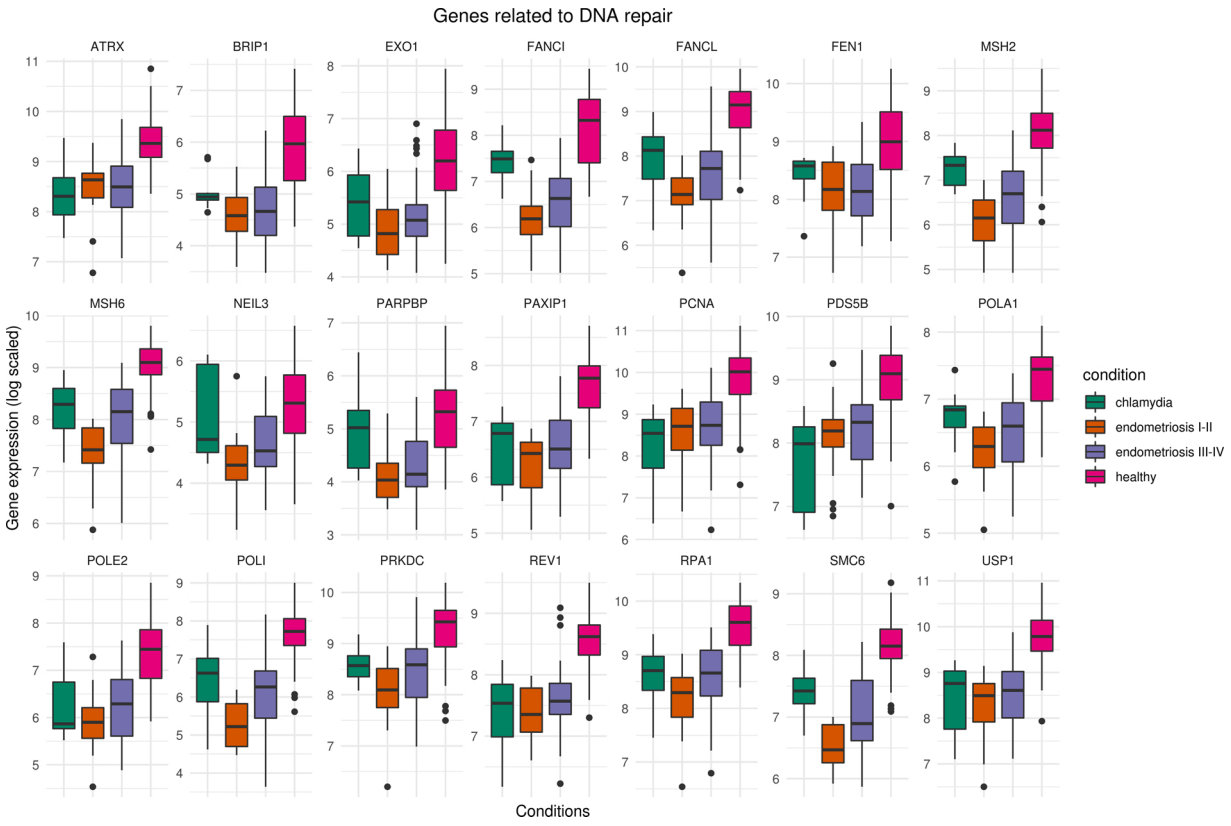


Fig. 7. Barplots representing commonly down-regulated genes related to DNA repair in all conditions.

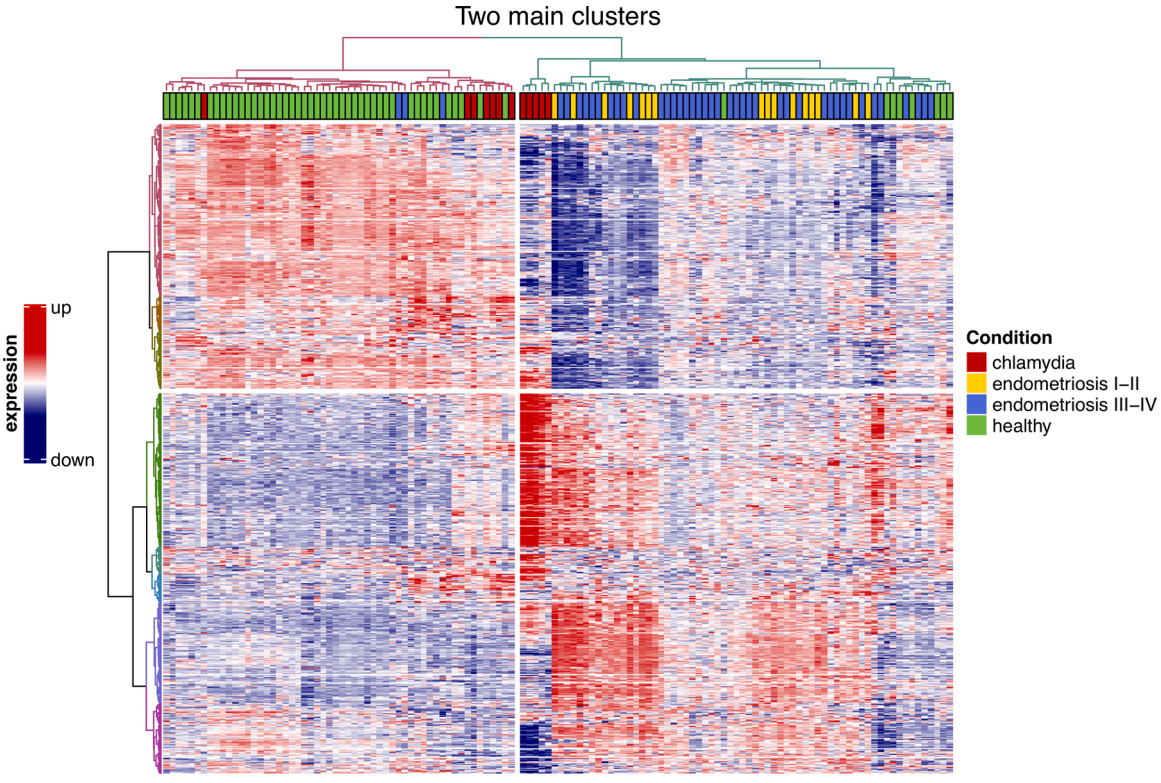


Fig. 8. Heatmap showing the two main clusters obtained by hierarchical clustering of gene expression levels.

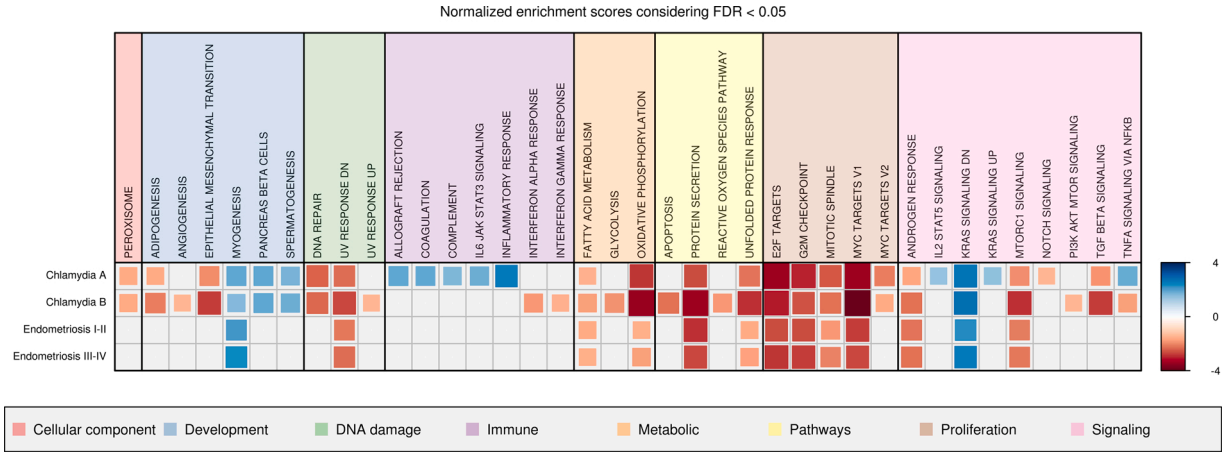


Fig. 9. Functional pathways identified by gene set enrichment analysis in each condition after selection according heatmap classification.

women with endometriosis, both from the perspective of cell types in the microenvironment as well as in terms of the dysregulated genes and pathways involved. Two findings are of particular relevance, since they reinforce the hypothesis of the association between chlamydia infection and endometriosis: (i) the profile of immune cells in the microenvironment and (ii) the common downregulation of multiple genes related to DNA damage repair. In addition, our meta-analysis also suggested that the eutopic endometrium of women with chlamydia-induced endometritis can present at least two distinct transcriptomic profiles. In the first, we did not observe robust activation of immune pathways, as in the eutopic endometrium specimens of women with endometriosis, suggesting a potential evidence for immune evasion.

4.1. Implication of cell types in microenvironment

After acute infection is resolved, it is followed by the promotion of an effector adaptive immune response; however, this only provides partial protection against reinfection (Batteiger et al., 2010). The immunopathogenesis of chlamydial infections has two possible hypotheses: the "immunological hypothesis", which relates to the adaptive immune cells inducing immunopathology (Brunham and Rey-Ladino, 2005), and the "cellular hypothesis", which identifies infected cells as the initiators or modulators of pathology (Stephens, 2003). According to our data, we observed a similar profile of upregulation of effector memory CD8 T cells in the endometrium of women with chlamydia-induced endometritis and endometriosis I-II, and to a lesser extent in III and IV. Two subgroups of memory T cells, comprised of central memory and effector memory T cells, were initially identified with differential marker expression and the distinct ability to migrate to secondary lymph organs or peripheral tissues, respectively. CD8 T cells were found to migrate to sites of chlamydial infection and induce protective immunity via a mechanism dependent on IFN-γ production (Wizel et al., 2008). However, evidence obtained from the chlamydial infection models implicates CD8 + T cells in chlamydial pathogenesis, since CD8 + T cell deficiency significantly reduced oviduct pathology, and reconstitution with wild-type CD8 + T cells restored tissue damage. Additionally, a previous study found that TNF-α deficient mice exhibited the same phenotype, suggesting that CD8 + T cells cause genital pathogenesis via TNF-α production (Murthy et al., 2011).

Previous studies using experimental models and humans have demonstrated that Th1-type CD4 + T cells exert a protective role against acute infection and reduce the development of chronic disease (O'Meara et al., 2014). In addition, chlamydia persistence occurs due to low levels of various stressor factors, such as IFN-γ produced by Th1 lymphocytes, hypoxia, and antimicrobial products, which are not able to destroy microorganisms and convert them into their resting state (Bavoil, 2014). In our study, we observed a reduced Th1 cell response in women with endometritis, suggesting that a defective Th1 response may be associated with disease progression. However, we also observed a marked increase in this cell subtype, especially in endometriosis I-II, suggesting that the proinflammatory Th1 response is more active in the early stages of disease. Interestingly, an increase in M1 macrophage numbers was only observed in women with endometriosis I-II, highlighting the prevalence of macrophages with a proinflammatory profile, potentially mediated by IFN-γ produced by Th1 lymphocytes. Our findings suggest that a differential profile of activation is responsible for the cellular immune response mediated by Th1 lymphocytes and M1 macrophages during endometritis and endometriosis. Since endometriosis can be triggered by chlamydia infection, we hypothesized that the divergent profile of this cellular Th1 response may be attributed to different disease phases (acute and chronic), or different clinical forms of endometritis.

Notably, we observed a similar decrease in the number of Th2 lymphocytes in the endometrium of women with endometritis or endometriosis. Th2 lymphocytes mainly secrete IL-4 and anti-inflammatory IL-10 cytokines. A recent study found that IL-10 deficiency enhances the effector Th1 response and chlamydial clearance and alleviated tissue damage (Marks et al., 2007). In addition, T cells that secreted higher amounts of IL-10 were found in infertile women, suggesting a pathogenic role of IL-10 in endometrial dysfunction. In addition to Th2 lymphocytes, regulatory T cells (Tregs) also secrete IL-10 and TGF-β cytokines (Kinnunen et al., 2002). In this context, we observed an elevated Treg number in women with endometritis, but a depletion in women with endometriosis (Sakaguchi et al., 2010). In their study, Moore-Connors et al. (2013) studied the depletion of Treg anti-CD25 prior to *C. muridarum* genital infection and observed an attenuated inflammation, decreased neutrophil recruitment, and lower oviduct pathology as a result. Interestingly, Treg lymphocytes are also able to convert into Th17 lymphocytes (Moore-Connors et al., 2013). The production of IL-17 is primarily driven by Th17 lymphocytes, which modulate granulopoiesis and neutrophil migration through the production of chemokines by epithelial cells and fibroblasts in the mucosal surfaces (Weaver et al., 2007; Aujla et al., 2007; Pérez et al., 2019). In parallel, increased neutrophil numbers were only detected in the endometrium of women with endometritis, indicating that the prevalence of this cell subtype is mediated by acute chlamydia infection.

Another marked difference was the increased number of NKT cells observed in the endometrium of women with chlamydia infection or endometriosis, which was most evident in stages I-II than III-IV. A recent article published by our group found higher numbers of NKT cells in stage I-II endometriosis compared to those in healthy controls (Poli-Neto et al., 2020). NKT cells recognise lipids and glycolipids present in class I non-classical MHC molecules, also known as CD1. In addition, NKT cells express markers characteristic of natural killer cells (NK) and T

lymphocytes, such as αβ T cell receptors, with very limited diversity. Additionally, NK and NKT cells share various activating and inhibitory receptors to recognise alterations in infected cells (Lanier, 2005; Heller et al., 2018)., such as the NKG2D activating receptor. In patients with endometriosis, the levels of MICA, a ligand for NK2G2D, were significantly elevated compared to healthy women and correlated with disease severity (González-Foruria et al., 2015). Another study verified that MICA is upregulated in uterine macrophages in the endometrium after TLR3 stimulation and activates local NK cells, resulting in the production of IFN-γ (Basu et al., 2009). Since we observed increased NKT and M2 macrophage numbers in the endometrium of women not only with endometritis, but also women with endometriosis, we hypothesized that the crosstalk between these cells may contribute to immune evasion mechanisms and disease progression. However, this will require further analysis.

There are two main macrophage phenotypes: (1) classically activated, interferon gamma (IFNγ)/LPS-induced (M1) macrophages, and (2) alternatively activated, IL-4-induced (M2) macrophages. A previous study demonstrated that M2 macrophages are more permissive to chlamydia intracellular survival, while M1 macrophages are more able to control infection mediated by IFN-γ (Gracey et al., 2013). Additionally, IL-4 activated and infected macrophages produce IL-10, suggesting that this cytokine may act in an autocrine manner to maintain the alternative activation phenotype. As already mentioned, a similar shift to M2 polarisation was observed in the endometrium of women with endometritis or endometriosis III-IV without alteration in M1 macrophages. One plausible explanation is that factors released by the microenvironment after persistent infection by chlamydia may favour M2 macrophage polarisation, which contributes to endometriosis onset and/or outcome. Indeed, other studies have reported that the infection promoted by this microorganism is associated with at least two important events observed in endometriosis: (1) epithelial mesenchymal transition induction, fibrosis (Igietseme et al., 2015, 2017), and (2) evading immune system surveillance (Wong et al., 2019).

It is worth mentioning that our data also revealed a marked increase in granulocytes, such as basophils and eosinophils, in both pathological conditions. In fact, a large number of eosinophils were previously found to infiltrate the endometrium of women with endometriosis (Blumenthal et al., 2000). Similarly, eosinophils have been more commonly observed in the endometrium of women with chronic endometritis than in healthy women (Adegboyega et al., 2010; Perlman et al., 2016). Using a murine model of genital *C. trachomatis* infection, earlier studies confirmed that IL-4-secreting eosinophils are essential for endometrial stromal cell proliferation and tissue repair after infectious stimulus (Vicetti Miguel et al., 2017). Since both clinical conditions are correlated with tissue regeneration (Evans et al., 2016; Karin and Clevers, 2016), it is reasonable that endometrial eosinophils present in the endometrium play an essential role in the repair of endometrial tissue. Interestingly, a higher increase in basophil numbers was observed not only in the endometrium of women with endometritis, but also in endometriosis at either the I-II or II-IV stages. Recently, a study used mass cytometry analysis to identify rare immune populations in the peritoneal cavity associated with endometriosis, such as mast cells and basophils (Guo et al., 2020). Despite recent evidence of the upregulation of these cell subtypes in endometriosis, their respective functions remain unexplored and will require further investigation.

4.2. Implication of commonly DEGs identified

Regarding DEGs, we did not identify a strong network of interactions between the most commonly upregulated genes (*APOD*, *CFD*, *CTSW*, *GPX3*, *MUC5B*, *SST*), with the exception of *APOD* and *SST*. *APOD* encodes a protein called apolipoprotein D. The regulation of its expression is complex and is modulated by multiple processes, including immune response, oxidative stress, and inflammatory stress (Do Carmo et al., 2007). Progesterone and arachidonic acid are potential ligands (Muffat and Walker, 2010). *SST*, in turn, encodes the somatostatin protein, a peptide hormone involved in multiple processes, including the endocrine system, neurotransmission, and cell proliferation (O'Toole and Sharma, 2019). It is likely that its endometriosis-associated expression is a consequence of the presence of inflammatory mediators in the microenvironment (Zhao et al., 2018).

On the other hand, the interaction network between down-regulated genes was broad. Additionally, over-representation analysis performed using STRING, an approach used to determine whether known biological functions or processes are over-represented (enriched) in an experimentally derived gene list, as a list of DEGs, showed that the regulation of the cell cycle and DNA integrity checkpoint could be affected. Indeed, we observed that a significant number of genes directly related to DNA repair were commonly down-regulated in chlamydia-induced endometritis and endometriosis-associated eutopic endometrium. Our data provide evidence that damage to DNA repair is a potential outcome induced by pathogens, in this case chlamydia, which can favour or even determine conditions for the development of endometriosis.

Replication in the eutopic endometrium of women with endometriosis occurs without a DNA damage response (Hapangama et al., 2009), and higher DNA damage and lower DNA repair could be related to the progression of endometriosis (Carvalho et al., 2013). Likewise, recent studies have also shown that genes related to double-strand breaks can be reduced in the endometrium of women with endometriosis (Choi et al., 2018), and polymorphisms in nucleotide excision repair genes can be associated with the risk of developing endometriosis, as well as the development and progression of endometriosis-related ovarian cancer (Shen et al., 2019). However, the primary events underlying these mechanisms have yet to be identified.

In turn, chlamydia infection is also associated with host DNA damage and proliferation without an adequate DNA repair response (Chumduri et al., 2013), including impaired base excision (Gulve et al., 2019) and homologous recombination repair (Mi et al., 2018). Interestingly, even cells that are cleaned from pathogen infection present a persistent and increased resistance to DNA damage-induced apoptosis (Padberg et al., 2013). Thus, given that chlamydia is the key agent responsible for the development of inflammatory disease of the lower genital tract, as well as the fact that this condition results in an increased risk of endometriosis, that the host DNA damage promoted by it can be persistent even after cleared infection, and that is may be heritable in host cells, it is plausible to hypothesize that infection promoted by chlamydia in the eutopic endometrium may trigger facilitating or determining initial events that culminate in endometriosis. Additionally, numerous bacterial pathogens are known to modify the chromatin architecture of host cells (Hamon and Cossart, 2008), some of which are related to the initiation of endometriosis, such as shigella (Kodati et al., 2008), mycoplasma (Campos et al., 2018), and Escherichia (Martin and Frisan, 2020).

4.3. Implication of commonly enriched pathways identified

As shown in the results section, we refined the enrichment analysis using groups identified by unsupervised clustering. This was important since there could be an overlap between the conditions, even if discrete. In other words, it was not possible to know, based on clinical data from the baseline studies, whether women with endometriosis were previously tested for chlamydia, or vice versa. Despite this, we obtained an interesting result, namely the fact that the endometrium of women with chlamydia endometritis had a heterogeneous transcriptomic profile, indicating that it behaves more similarly to the endometrium of women with endometriosis compared to the endometrium of healthy women. The immune response category of pathways seems to be the main difference. The endometrium of some patients with chlamydia and the absolute majority of samples from women with endometriosis did not show a significant enrichment of immunological pathways. This could

be evidence of impairment in immune surveillance. In fact, it is known that evading immunosurveillance is essential for the pathogenesis of endometriosis (Leavy, 2015), and it is important for certain strains of chlamydia to escape from the host's immune response (Geisler, 2010). However, the contributing factors associated with chlamydial and endometriosis evasion of the immune system are not yet fully understood. The best studied mechanism involves the involvement of chlamydial proteasome/protease-like activity factor (CPAF), which can inhibit anti-chlamydial immunity by degrading certain transcription factors related to proinflammatory mediator production, such as nuclear factor-kappa B (NF-kB) (Zhong et al., 2001). In addition, this factor can inhibit the expression of major histocompatibility complex (MHC) molecules (Rödel et al., 1998) by degrading RFX5 and USF-1, or by inducing IFN-β (Witkin et al., 2017). It has also been previously reported that the class I/II major histocompatibility complex is suppressed by chlamydia to avoid immune response detection (Reimand et al., 2019). In parallel, the upregulation of HLA-G, an important mediator of immune cell inhibition, seems to be related to advanced stages and potentially endometriosis progression (Rached et al., 2019). Indeed, chlamydia could use many ways to evade the immune system (Christodoulakos et al., 2007; Wong et al., 2019), as well as endometriosis. Another overlap between the pathophysiology of these diseases is the involvement of oestrogen receptor beta in the immune evasion of endometriosis (Han et al., 2015) and chlamydial infection (Berry and Hall, 2019). However, on the other hand, our study does not allow us to conclude whether this change is inherent to the individual or non-immunogenic phenotype induced by different strains of chlamydia or whether it represents a transition phase of a dynamic process of immunosurveillance and immune evasion, as observed in tumor immunoediting (Mittal et al., 2014).

4.4. Strengths and limitations

Meta-analysis is a very valuable tool for the compilation and interpretation of biological data related to the transcriptome. However, we need to reflect on some points, including its limitations. First, although we only used data from studies that had used an Affymetrix platform, the platforms were not identical. Second, the initial preparation of the raw data, mainly the computational removal of batch effects, can culminate in a minimisation or even removal of real biological differences (Nygaard et al., 2015). The third point relates to the characterisation of the studied population. It was not possible to know whether women with endometriosis also had chlamydia-induced endometritis, nor whether women with endometritis had endometriosis; there may be an overlap between these patients. We attempted to minimise this effect by selecting cases using hierarchical clustering and "super"-selecting samples for further analysis. Fourth, although the PAMR prediction algorithm correctly predicted more than 90 % of the samples regarding the phase of the menstrual cycle, we may have misclassified some cases and, consequently, included or excluded them inappropriately. A fifth point to be mentioned relates to the inclusion of samples of eutopic endometrium in the proliferative phase, which makes it impossible to study possible variations in cell subpopulations, transcribed genes, and enriched pathways during the entire length of the menstrual cycle. This was important to guarantee the reliability of the meta-analysis. We also recognise that endometriosis is a heterogeneous disease and that staging, although it does reflect the extent of the disease, does not correlate with the symptoms manifested. Thus, despite clustering the samples into I-II (early) and III-IV (late) stages, it seems reasonable that, against the evidence of sharing similar pathophysiological processes among them, there may be peculiar differences among stages potentially not identified in this meta-analysis. Another question relates to the methodology used to identify the genes themselves. Although the use of RNA sequencing is superior to microarray platforms from different points of view, the latter are cheaper, valid, and reproducible for the analysis of genes and known pathways (Mantione et al., 2014). In addition, the casuistry available in the literature is wider. In any case, these methodological challenges must be addressed in the future.

In conclusion, the eutopic endometrium from women with chlamydia-induced endometritis and endometriosis shares characteristics in terms of the cell type distribution, the downregulation of genes involved in DNA repair and cell cycle control, and the expression of pathways involved in immune response evasion. Taken together, our findings indicate that it is plausible that these could be key mechanisms to understand the potential causal relationship between chlamydia infection and endometriosis. Additionally, we think that at least three questions need to be investigated in further studies: (1) could *Chlamydia trachomatis* be a causative factor of endometriosis by damaging and impairing DNA repair in eutopic endometrium lining?; (2) is immune "deficiency" induced by the pathogen or is it inherent to the individual?; (3) what is the role of polymorphism in susceptibility to chlamydia infection and/or endometriosis?

Author contributions

Omero Benedicto Poli-Neto: Conceived and designed the analysis, Acquired of the data, Performed the computations, Supervised the computational simulations, Analysed and interpreted the data, Drafted, and revised the article, Final approval.

Daniela Carlos: Interpreted the data, Drafted and revised the article, Final approval.

Aureo Favaretto Junior: Acquired the data, Performed computational simulations.

Julio Cesar Rosa-e-Silva: Conceived and designed the analysis, Revised the article, Final approval.

Juliana Meola: Conceived and designed the analysis, Interpretation of data, Revised the article, Final approval.

Daniel Tiezzi: Acquisition of the data, Performed the computations, Supervised the computational simulations, Analysed and interpreted the data, Revised the article, Final approval.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jri.2021.103307.

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