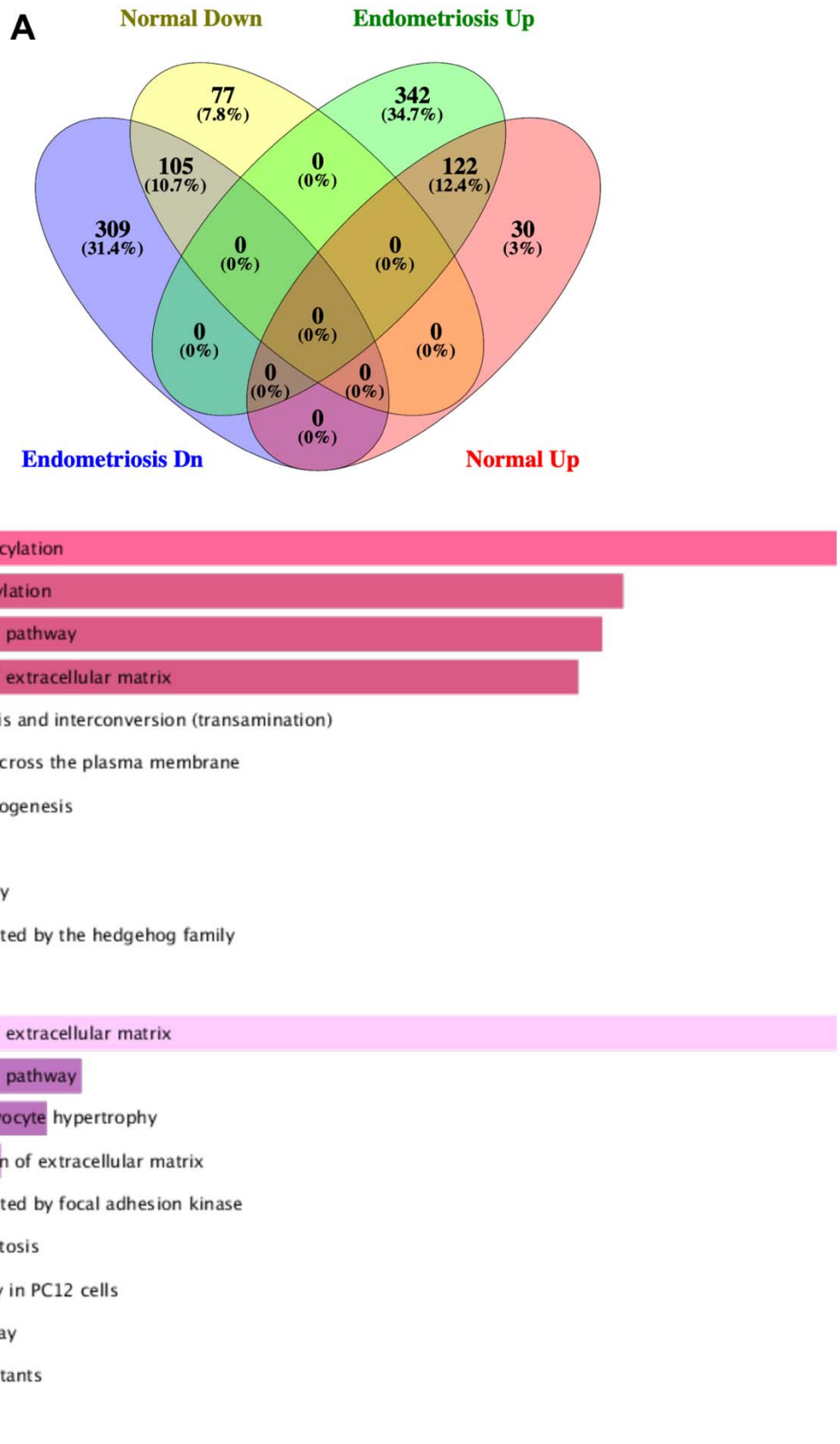
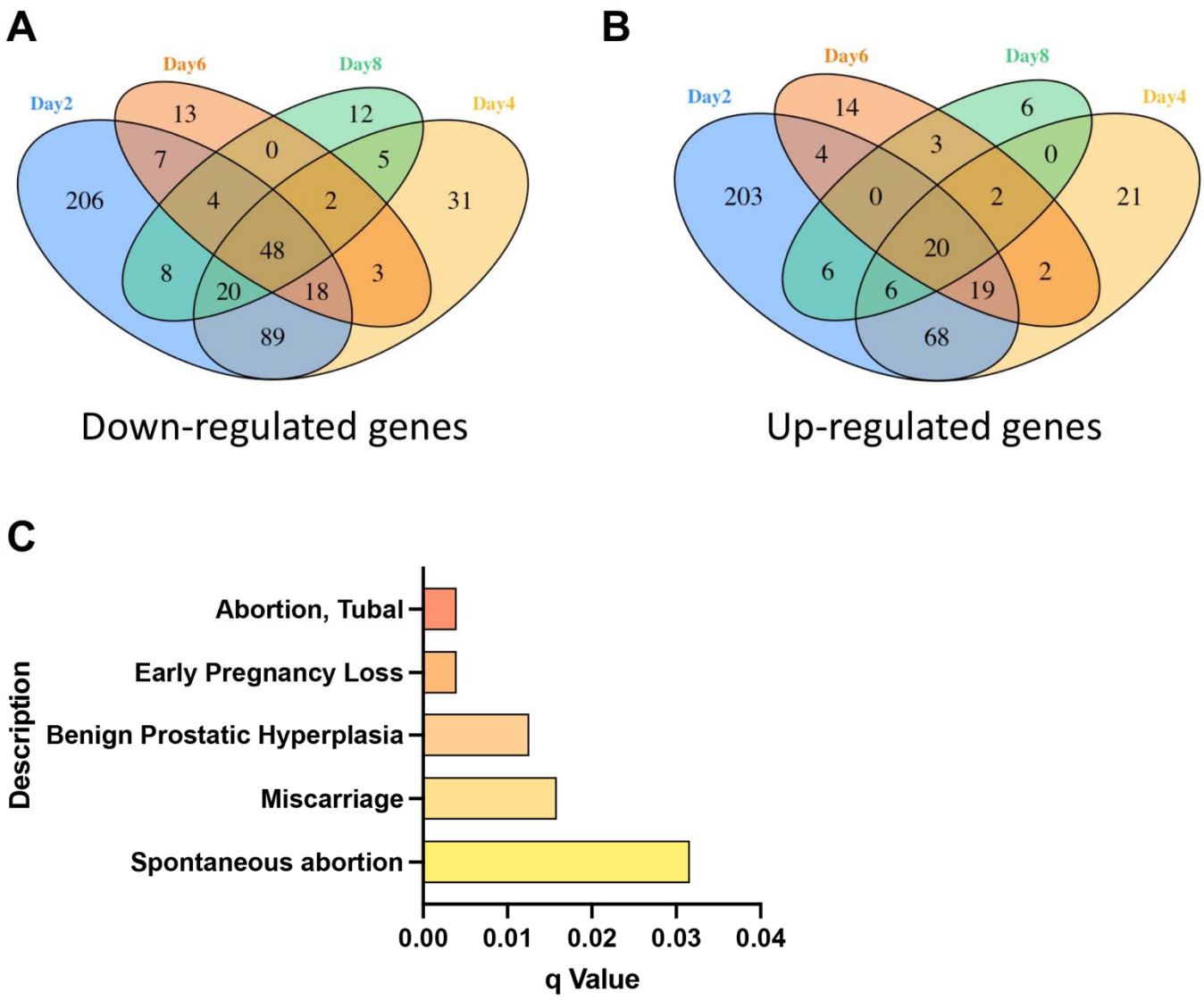
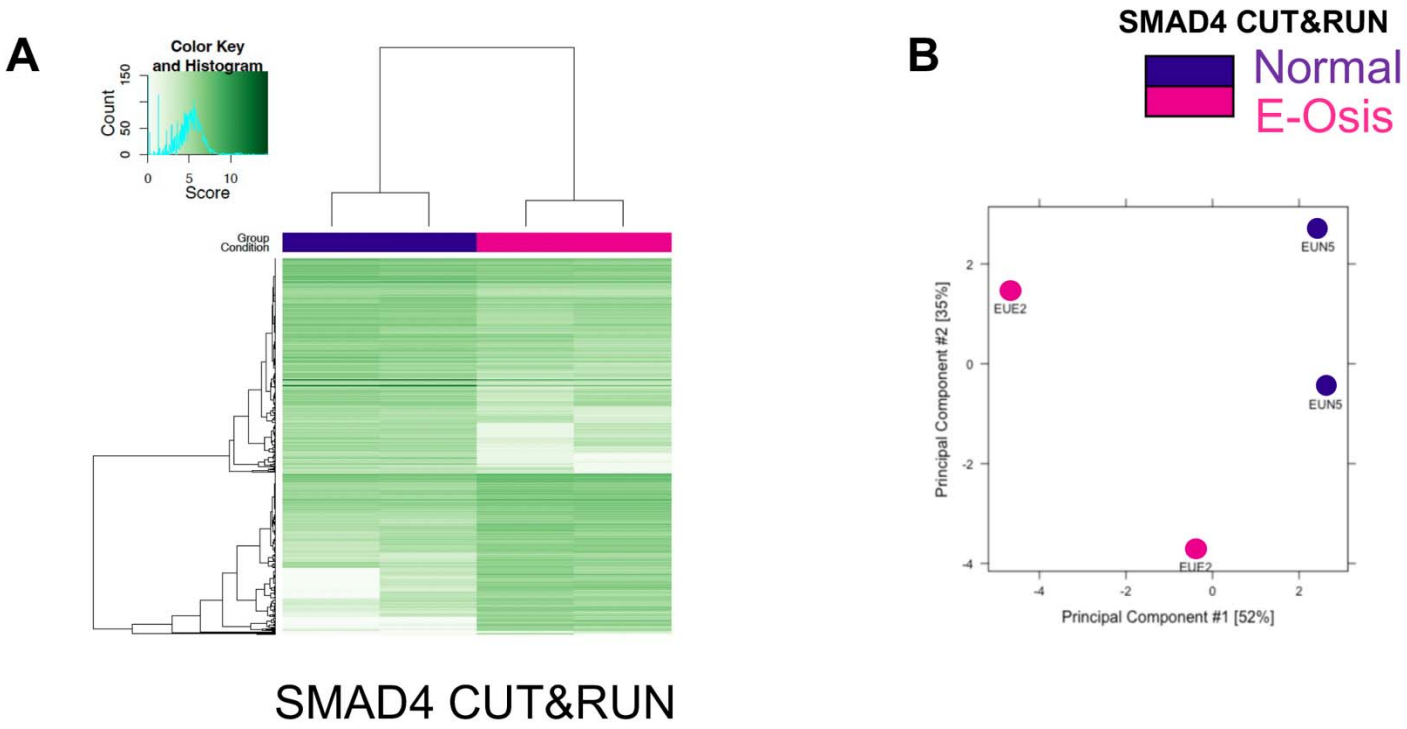
SUPPLEMENTARY INFORMATION



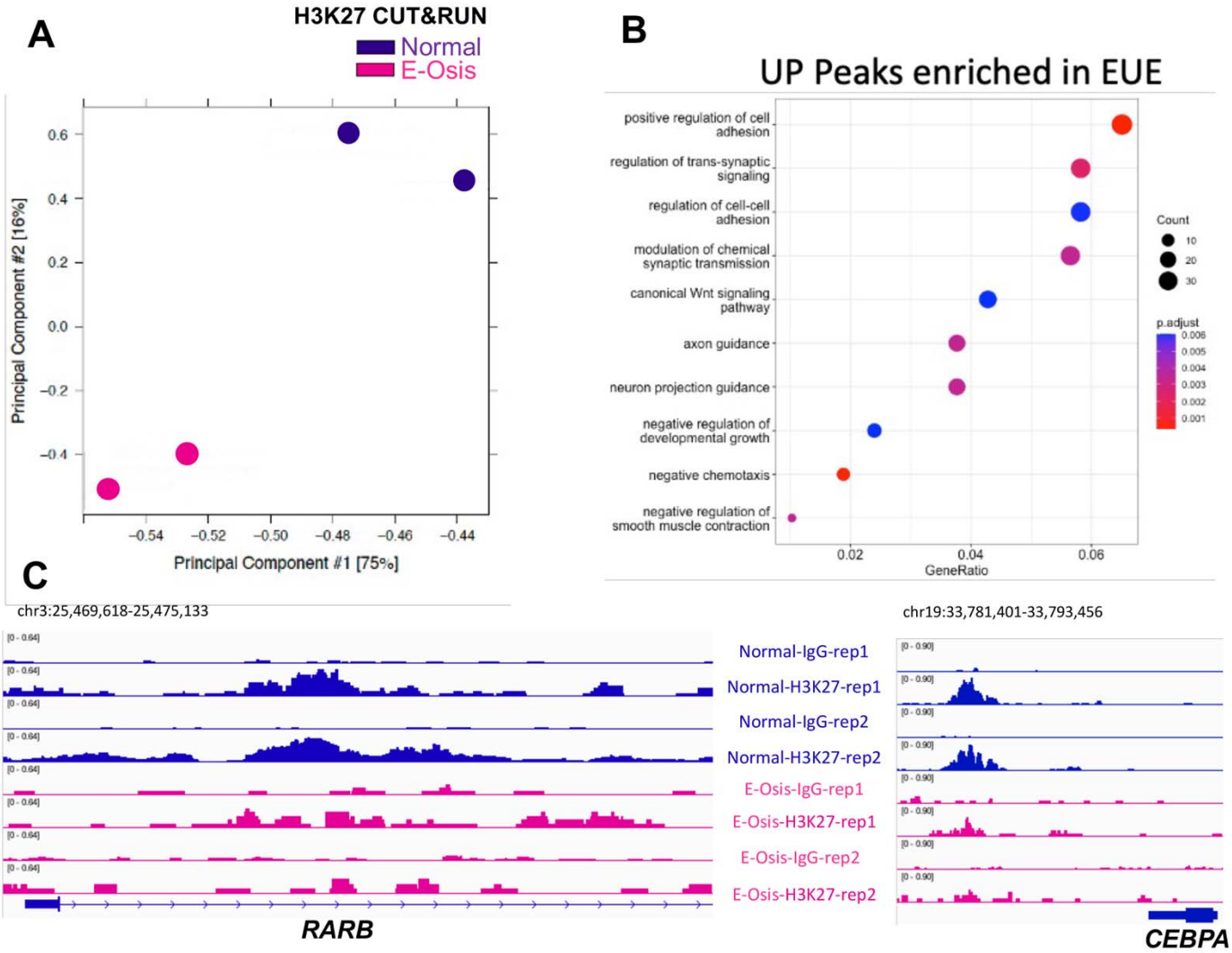
Supplemental Figure 1. Transcriptomic and gene ontology analysis of the time course decidualization datasets. A) A Venn diagram was used to display the number of conserved genes between the normal and endometriosis groups during the time course decidualization program. Genes that showed a significant change on Day 8 of decidualization were used (>1.4, <0.4-fold change, FDR < 0.05). B-C) Gene ontology analysis of the genes that showed a significant change (>1.4, <0.4-fold change, FDR < 0.05) on Day 8 of decidualization in the normal (B) or endometriosis (C) groups.



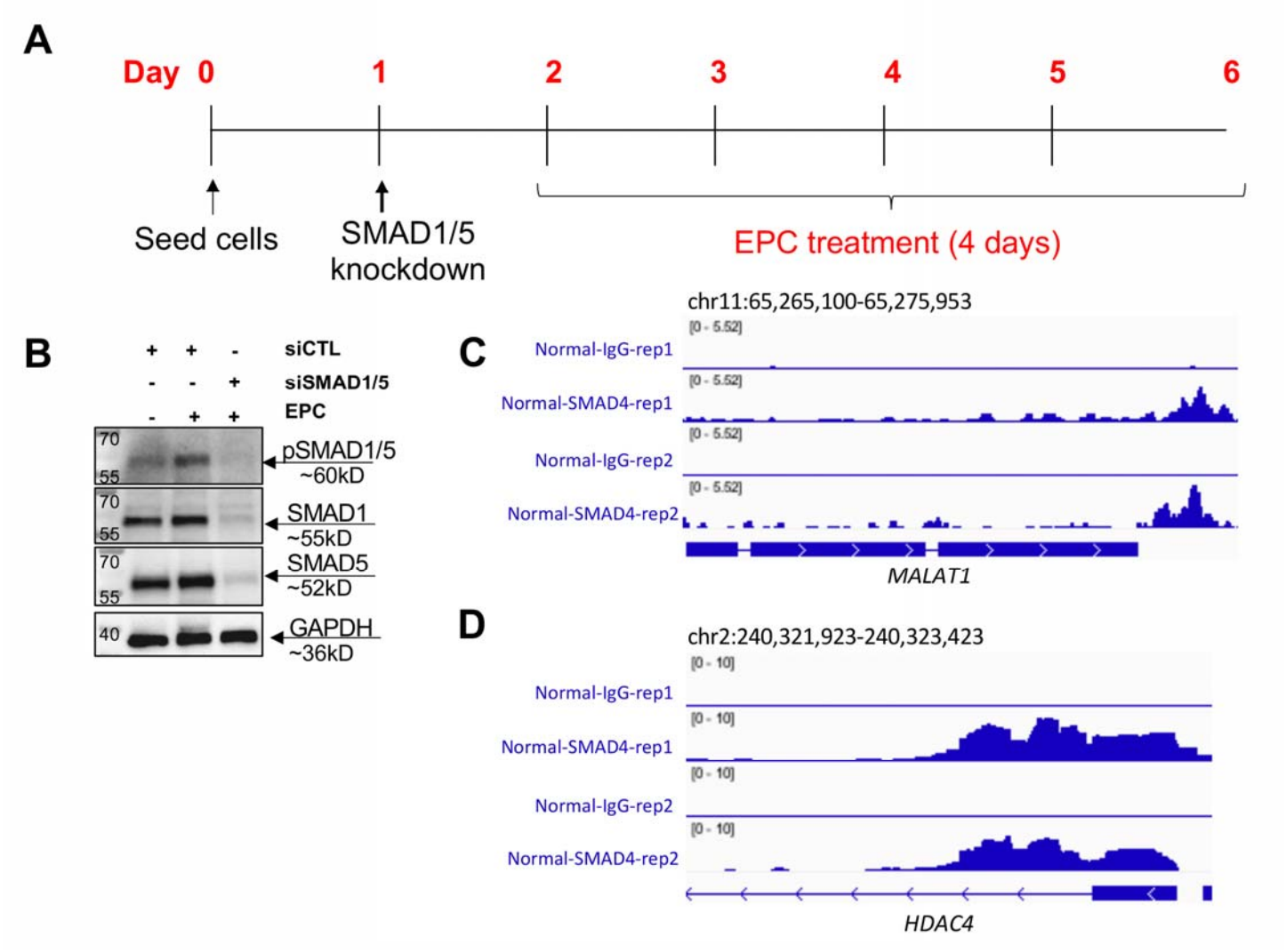
Supplemental Figure 2. Transcriptomic and classification of genes involved in the decidualization of endometrial stromal cells from individuals with and without endometriosis. A-B) A Venn diagram was used to display the number of conserved downregulated (A) and upregulated (B) genes in the time course decidualization of endometrial stromal cells from individuals with endometriosis. The analysis identified that 48 genes were consistently down-regulated (A) and 20 genes were consistently up-regulated (B) regardless of the EPC treatment length. C) DisGeNET analysis for the 48 genes that were consistently down regulated in the stromal cells from individuals with endometriosis relative to individuals without endometriosis during the time course decidualization treatment.



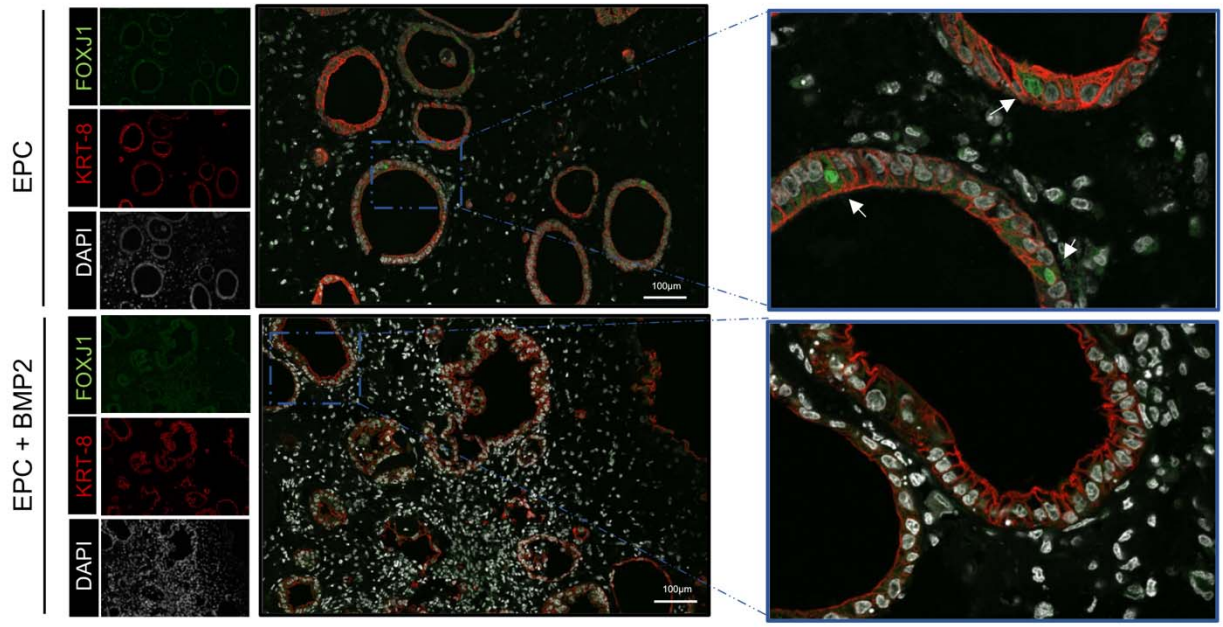
Supplemental Figure 3. Patient-specific distribution of SMAD4 binding analysis during decidualization. A) SMAD4 CUT&RUN in endometrial stromal cells from individuals with and without endometriosis (E-Osis) after 4 days of EPC treatment. Differential peak signals obtained for the genome-wide SMAD4 distribution in normal versus endometriosis. B) PCA plot of the SMAD4 binding signals comparing the normal versus endometriosis sample replicates.



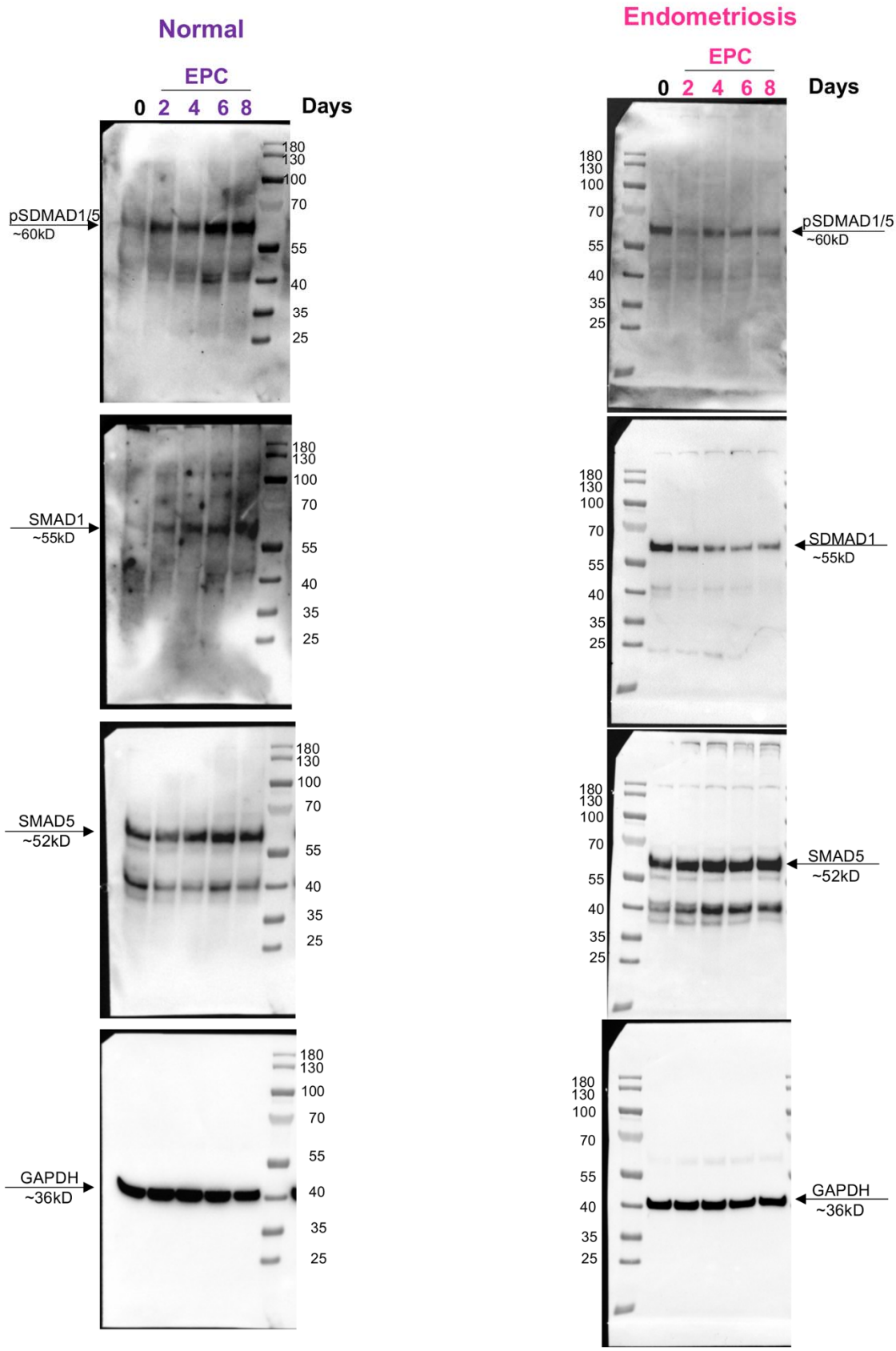
Supplemental Figure 4. Analysis of H3K27ac in the decidualizing stromal cells of individuals with and without endometriosis. A) PCA plot for H3K27ac replicates of normal and endometriosis stromal cells, showing that the replicates are reproducible. B) Gene ontology classification of the H3K27ac peaks increased in endometriosis stromal cells, showing that categories related to the regulation of cell adhesion were overrepresented. C) Genome track views for the distribution of H3K27ac peaks in the promoter regions of *RARB* and *CEBPA,* showing increased peak density in the endometrial stromal cells from individuals without endometriosis.



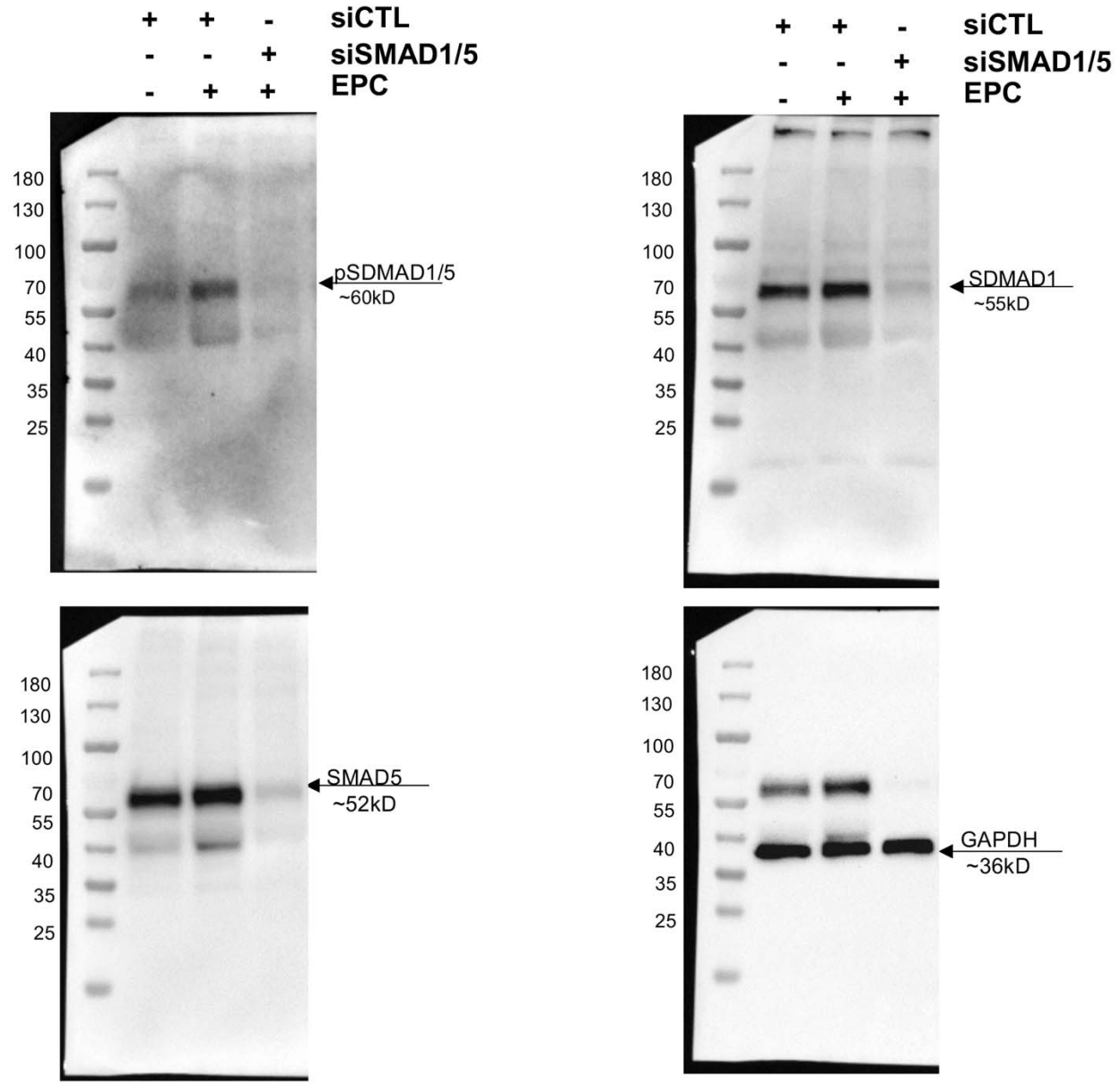
Supplemental Figure 5. siRNA knockdown of SMAD1 and SMAD5 perturbs decidualization. A) Experimental layout showing the time points at which endometrial stromal cells were plated, transfected with SMAD1/SMAD5 siRNAs, and induced to decidualize with 35nM estradiol, 1µM medroxyprogesterone acetate and 50µM cAMP (EPC) for 4 days. B) Western blot of endometrial stromal cells treated with non-targeting siRNAs (siCTL) or siRNAs targeting SMAD1 and SMAD5 and EPC. Membranes were probed with pSMAD1/5, total SMAD1, total SMAD5 and GAPDH antibodies to confirm knockdown of SMAD1/5 was successful. C-D) Genome track views of the *MALAT1* and *HDAC4* genes showing enrichment of the SMAD4 peaks.



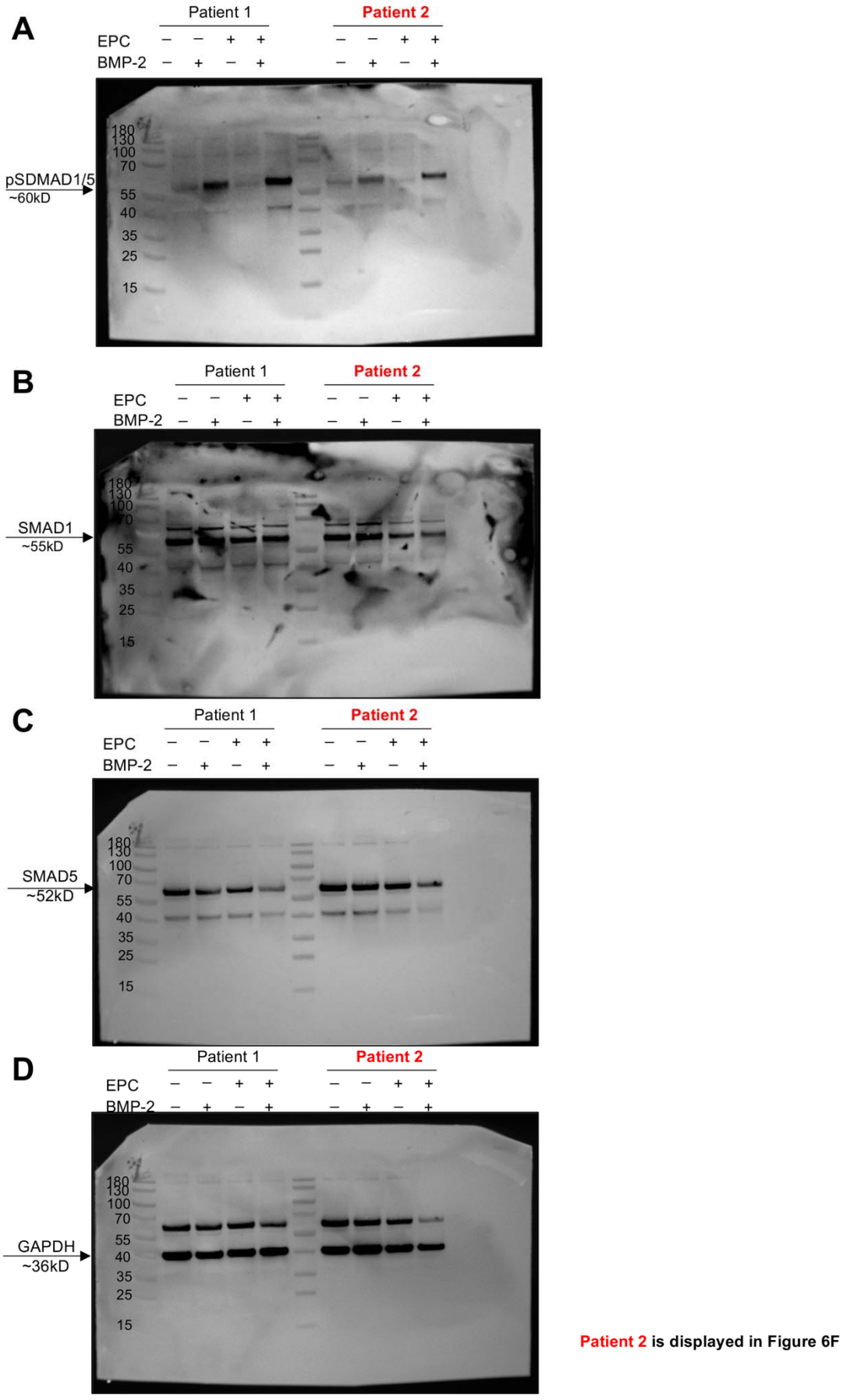
Supplemental Figure 6. Analysis of the ciliated cell marker, FOXJ1, in decidualizing 3D endometrial assembloids. Immunostaining of the ciliated cell marker, FOXJ1 (green), the epithelial cell marker (cytokeratin 8, KRT-8, red) and DAPI (white) in endometrial assembloids treated with EPC or EPC + BMP2, the hormonal stimuli.



Supplemental Figure 7. Uncropped western blot images corresponding to Figure 3.



Supplemental Figure 8. Uncropped western blot images corresponding to Supplemental Figure 5.



Supplemental Figure 9. Uncropped western blot images corresponding to Figure 6.

SUPPLEMENTAL TABLES

Supplemental Table 1. Differentially expressed genes in endometrial stromal cells from individuals with and without endometriosis during the time course decidualization treatment compared to baseline Day 0.

Supplemental Table 2. Gene ontology classification of differentially expressed genes in the endometrial stromal cells from individuals with and without endometriosis during time course decidualization compared to baseline Day 0.

Supplemental Table 3. Transcription factor regulators determined by EnrichR analysis from the genes that were differentially expressed during decidualization in endometrial stromal cells from individuals with and without endometriosis relative to baseline Day 0.

Supplemental Table 4. Complete gene expression matrix comparing endometrial stromal cells from individuals with and without endometriosis at each time point during decidualization and the DisGeNET analysis on the 48 consistently down regulated genes.

Supplemental Table 5. SMAD4 peak annotations in endometrial stromal cells from individuals with and without endometriosis treated with EPC for 4 days.

Supplemental Table 6. Peak annotation of H3K27ac in endometrial stromal cells from with and without endometriosis treated with EPC for 4 days.

Supplemental Table 7. Genes that are differentially regulated following EPC treatment and SMAD1/5 siRNA knockdown (siCTL + EPC vs. siSMAD1/5 + EPC).

Supplemental Table 8. PCR primer sequences.

Supplemental Table 9. List of antibodies and dilutions.