Role of endometrium in preeclampsia: A molecular signature Supported Vector Machine (SVM) based model for endometrial maturation prediction

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Background Preeclampsia (PE) is a hypertensive syndrome peculiar to human pregnancy. The disease is thought to arise from deficient placentation occurring in early gestation. Our previous work suggested that deficient endometrial maturation (or decidualization) beginning during the late secretory endometrium (LSE) and continuing after implantation might contribute to this placental defect [1]. However, the critical endometrial genes underlying insufficient endometrial maturation when they become dysregulated have not been identified. Therefore, the objective of this work was to identify a molecular signature of gene expression in the LSE that is able to predict optimal endometrial maturation.

Methodology and Results The R software was employed to re-analyze publically available microarray datasets from the GEO database: chorionic villous samples (GSE12767, n=12) obtained from women that developed PE (PE-CVS) and normal pregnancy (NP-CVS), and endometrial samples obtained at the different phases of the menstrual cycle: from the proliferative endometrium (PrE) through the LSE (GSE4888 and GSE6364, n=24). Data were imported with the affy package and normalized with MAS5. First, a t-test (limma package) was employed to determine differentially expressed genes (DEG, \( p < 0.05 \)) between PrE and LSE, and PE-CVS and NP-CVS. Then, the DEG were compared using Venn Diagrams to observe overlapping DEG. Similarity between overlapping genes was measured with Euclidean distance, clustered with complete linkage method and visualized in a heat map (Cluster 3.0). Clusters with similar expression in samples from PrE, early secretory endometrium (ESE) and PE-CVS (suboptimal endometrial maturation), and from middle secretory endometrium (MSE), LSE and NP-CVS (optimal endometrial maturation) were selected yielding a total of 37 DEG (Figure 1). The expression of these DEG was used to construct a model using SVM as classifier (package e1071). Finally, this model was tested on 3 external datasets: GSE6364 (n=43) and GSE299 (n=19) consisting of menstrual cycle samples obtained from healthy women, and GSE26787 (n=10) containing samples obtained in the LSE from fertile women and women with implantation failure. For the first 2 datasets, the model was able to correctly predict suboptimal endometrial maturation in samples from PrE or ESE and optimal endometrial maturation in samples from MSE or LSE. For GSE26787, the model predicted optimal endometrial maturation in samples from fertile women, and suboptimal endometrial maturation in 4 out of 5 samples from women with implantation failure.

Conclusion Expression of a cluster of 37 core genes could represent a molecular signature that, if dysregulated, may preclude optimal endometrial maturation, thereby predisposing to implantation failure and preeclampsia.

References