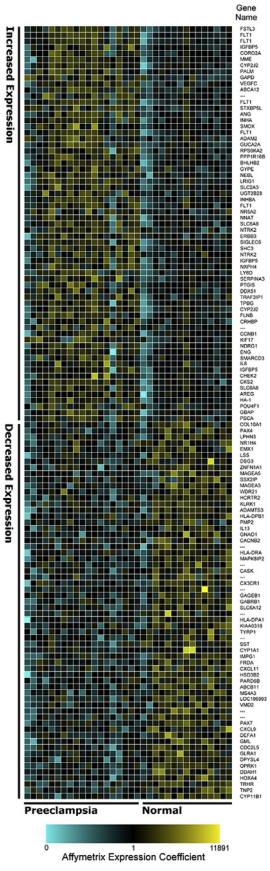
# Discovery of antiangiogenic factors in the pathogenesis of preeclampsia



TO THE EDITORS: We report here the historic transcriptomics data that led to the discovery and characterization of antiangiogenic factors in the pathogenesis of preeclampsia. In 2001 and 2002, to identify novel secreted factors playing a pathologic role in preeclampsia, we performed gene expression profiling of placental tissue from 19 women with preeclampsia and 15 normotensive pregnant women using Affymetrix U95A microarray chips (Affymetrix, Santa Clara, California). Among the preeclamptic women, 89% were nulliparous compared with 19% among the normotensive women. The data were analyzed using Bayesian Analysis of Differential Gene Expression (BADGE method, version 1.0), a computer program implementing a Bayesian approach to identify differentially expressed genes across experimental conditions.[1] We identified a gene set of 127 genes; 65 of them were up-regulated and 62 were down-regulated, at a false positive rate of 1% (Supplemental Table). The Figure depicts the heatmap of the up- and down-regulated genes, many of which code for proteins regulating angiogenesis and metabolism. Among the most up-regulated transcripts were the endogenous inhibitor of vascular endothelial growth factor (VEGF) signaling, referred to as fms-like tyrosine kinase 1 (FLT1 or VEGFR1) and its soluble isoforms (sFLT1 or sVEGFR1). We characterized the sFLT1 pathway and noted that in animals, sFLT1 was sufficient to induce hypertension and proteinuria, and phenocopied several features of preeclampsia.[2] Taken together with the findings that anti-VEGF drugs were inducing preeclampsia-like phenotypes in cancer patients,[3] we hypothesized that excess sFLT1 was responsible for the maternal syndrome of preeclampsia.[2,4] Soluble endoglin, a second antiangiogenic protein in this list, was also further characterized by our group to play a synergistic role in the pathogenesis of preeclampsia.[5] Nearly 20 years after the initial transcriptomic studies, the characterization of these antiangiogenic protein pathways have led to an improved understanding of the pathophysiology of preeclampsia, new biomarkers for early detection of the disease, and new therapeutic targets for this condition.[6] Further characterization of other gene products described in the Supplemental Table may lead to a better understanding of the processes leading to preeclampsia. ■

**FIGURE**
**Heatmap of up-regulated and down-regulated genes in preeclampsia**




Colormap of the predictive gene set for placental mRNA expression in normal vs preeclampsia patients. The *rows* represent the predictive genes for preeclampsia, whereas the *columns* represent the expression levels for a given patient relative to the average gene expression. Significantly up-regulated genes include those coding for the fms-like tyrosine kinase 1 family of mRNAs and follistatin-related protein, whereas the significantly down-regulated genes include those coding for cytochrome P450 (CYP11B1). Genes with no names are left blank. However, their gene accession IDs are included in the Supplemental Table.

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S.A.K. is listed as a coinvestigator on patents held by Beth Israel Deaconess Medical Center for the use of biomarkers in the prediction and treatment of preeclampsia. He has financial interest in Aggamin Pharmaceuticals, has served as consultant to Roche Diagnostics and Thermo Fisher Scientific, and reports receiving research funding from Thermo Fisher Scientific and Siemens. T.L. reports no conflict of interests.

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