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Commentary

Plasma free cell RNA profiling for the prediction of preeclampsia

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Pre-eclampsia is characterized by the onset of new hypertension and proteinuria after 20 weeks of gestation or the development of new hypertension and end-organ dysfunction, with or without proteinuria. Its early onset, rapid progression, and susceptibility to multiorgan dysfunction induction make it a leading cause of maternal and perinatal morbidity and mortality. However, the heterogeneity and complexity of preeclampsia make it challenging to identify at-risk pregnancies through pathophysiologic methods before clinical symptoms appear, posing a significant hurdle for the accurate prediction and precise treatment of preeclampsia. Plasma free RNA (cfRNA) encompasses various RNA molecules carrying unique information about human tissues, rendering it a potent tool for noninvasive monitoring of maternal, placental, and fetal conditions during pregnancy.

Zhou et al. [1] investigated cfRNA profiles in 715 healthy pregnant women and 202 pregnant women with preeclampsia before symptom onset. They identified 77 differentially expressed genes, comprising 44% messenger RNA and 26% microRNA, distinguishing mothers with preterm preeclampsia from healthy counterparts before symptoms emerged. These genes also play a crucial functional role in the physiology of preeclampsia. Two classifiers were developed using 13 cfRNA features and two clinical features (in vitro fertilization and mean arterial pressure) to predict preterm and early onset preeclampsia before diagnosis. In the independent validation cohort, the preterm preeclampsia prediction model achieved an 81% area under the curve and a 68% positive predictive value (preterm, n=46; control, n=151). Additionally, in the external validation cohort, the premature preeclampsia prediction model demonstrated an 88% area under the curve and a 73% positive predictive value (premature preeclampsia, n=28; control, n=234).

Moufarrej et al. [2] analyzed cfRNA levels in 404 blood samples obtained from 199 pregnant mothers at different time points: before 12 weeks, from 13 to 20 weeks, after 23 weeks, and post-delivery for each participant. Comparing cfRNAs from preeclamptic and normotensive mothers, they identified a total of 544 differentially expressed genes (DEGs) that underwent alterations during pregnancy and postpartum. Notably, the majority of these DEGs (92%) were protein-coding genes, while only 8% (43 DEGs) belonged to other types, such as mitochondrial transfer RNAs and long-chain non-coding RNAs. The changes in gene expression were most significant before 20 weeks of gestation. Subsequently, the researchers developed a logistic regression model with an AUROC (Area under the receiver operating characteristic curve) of 0.99, specificity of 85%, and sensitivity of 100%, enabling the identification of pregnant women at risk of developing preeclampsia at or before 16 weeks of gestation. The model was successfully validated on validation group 1 and two other independent cohorts.

Rasmussen et al. [3] analyzed cfRNA in 2,539 plasma samples obtained from 1,840 pregnant women across eight independent cohorts. These samples represented a diverse range of ethnicities, nationalities, geographic locations, socioeconomic backgrounds, and gestational

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ages, resulting in the most extensive and diverse gestational transcriptome dataset collected to date. The analysis unveiled the potential to predict fetal gestational age and reflect the physiological state of pregnancy progression by examining the cfRNA transcriptome in maternal plasma. Seven differentially expressed genes - CLDN7, PAPPA2, SNORD14A, PLEKH1, MAGEA10, TLE6, and FABP1 - were identified. Notably, four of these genes (CLDN7, PAPPA2, TLE6, and FABP1) have demonstrated associations with preeclampsia or placental development. Leveraging the known characterization of these genes, a logistic regression model was developed to predict the probability of preeclampsia. The model's predictive performance was thoroughly evaluated, demonstrating its effectiveness in predicting preeclampsia with a sensitivity of 75%, a positive predictive value of 32.3%, and an AUC of 0.82.

Munchel et al. [4] conducted a study involving the collection and sequencing of blood samples from 40 pregnant women diagnosed with pre-eclampsia, with an additional 73 women serving as controls. Their aim was to identify RNA changes that could potentially predict the onset of preeclampsia. Through their investigation, they discovered over three dozen abnormalities in placental RNA associated with the development of preeclampsia. Subsequently, they developed a model for predicting preterm preeclampsia with an accuracy ranging from 85% to 89%, validated at 72%.

In summary, cfRNA testing opens up a new set of tools that can be used to address problems that arise early in life. The use of this new method for early disease prediction will open up the possibility of developing relevant therapies.

Disclosure of conflict of interest

None.

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References

[1] Zhou S, Li J, Yang W, Xue P, Yin Y, Wang Y, Tian P, Peng H, Jiang H, Xu W, Huang S, Zhang R, Wei F, Sun HX, Zhang J and Zhao L. Noninvasive preeclampsia prediction using plasma cell-free RNA signatures. Am J Obstet Gynecol 2023; 229: 553.e1-553.e16.

[2] Moufarrej MN, Vorperian SK, Wong RJ, Campos AA, Quaintance CC, Sit RV, Tan M, Detweiler AM, Mekonen H, Neff NF, Baruch-Gravett C, Litch JA, Druzin ML, Winn VD, Shaw GM, Stevenson DK and Quake SR. Early prediction of preeclampsia in pregnancy with cell-free RNA. Nature 2022; 602: 689-694.

[3] Rasmussen M, Reddy M, Nolan R, Camunas-Soler J, Khodursky A, Scheller NM, Cantonwine DE, Engelbrechtsen L, Mi JD, Dutta A, Brundage T, Siddiqui F, Thao M, Gee EPS, La J, Baruch-Gravett C, Santillan MK, Deb S, Ame SM, Ali SM, Adkins M, DePristo MA, Lee M, Namsaraev E, Gybel-Brask DJ, Skibsted L, Litch JA, Santillan DA, Sazawal S, Tribe RM, Roberts JM, Jain M, Høgdall E, Holzman C, Quake SR, Elovitz MA and McElrath TF. RNA profiles reveal signatures of future health and disease in pregnancy. Nature 2022; 601: 422-427.

[4] Munchel S, Rohrback S, Randise-Hinchliff C, Kinnings S, Deshmukh S, Alla N, Tan C, Kia A, Greene G, Leety L, Rhoa M, Yeats S, Saul M, Chou J, Bianco K, O'Shea K, Bujold E, Norwitz E, Wapner R, Saade G and Kaper F. Circulating transcripts in maternal blood reflect a molecular signature of early-onset preeclampsia. Sci Transl Med 2020; 12: eaaz0131.