Transcriptomic profile of the maternal-fetal interface may reveal potential protective effects against miscarriage after COVID-19 vaccination

yiyuan qu¹, chengcheng zhu¹, tao sun¹, jianqiu jiang¹, ying gu¹, linping jin¹, xujia huang¹, bingbing wu¹, jian xu¹, and xiuying chen¹

¹Zhejiang University

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Abstract

Background: Concerns of COVID-19 vaccine safety from pregnant women still widespread. We used transcriptomic profile analysis to study changes of the maternal-fetal interface after vaccination and explore the possible protective effects from vaccination against miscarriage. Methods: We collected decidual tissuesafter uterine curettage from pregnant women in the first trimister with (n = 6) and without a COVID-19 vaccination (n = 6) and performed RNA-sequencing. Furthermore, we ananlyzed our transcriptome datas of samples and other datasets about maternal-fetal interface and miscarrige to analyze the potential link by bioinformatics tools. Results: We identified 879 different expressed genes from pregnant women who received vaccination and found that the COVID-19 vaccine could alter some hazardous RSA-related genes, such as CXCL11, FOS, FOSB, LY96, MMP10, and NCF2. Vaccination also changed some hazardous RSA-related signaling pathway. These molecules induced the transformation of M2 macrophages and promoted the balance of Th1/Th2 immune responses. Finally, these effects on the immune microenvironment of the maternal-fetal interface also showed corresponding positive changes. Conclusion: Many RSA-related signaling molecules were reversed after COVID-19 vaccination, indicating that the vaccine did not cause RSA, and these molecules ultimately may have protective effects on miscarriage by influencing the immune microenvironment at the maternal-fetal interface.

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Fold enrichment









synaptic vesicle budding from presynaptic endocytic zone GO:0016185 membrane

BP GO:0061025 membrane fusion

4.95E-09 6.94E-07 10.29 49.57

BP	GO:0031623	receptor internalization	10.29	1.87E-08	40.04	2.10E-06
CC	GO:0098844	postsynaptic endocytic zone membrane	7.35	4.52E-10	311.82	5.88E-08
CC	GO:0044327	dendritic spine head	7.35	8.86E-08	111.36	5.76E-06
CC	GO:0005854	nascent polypeptide-associated complex	5.88	2.99E-07	249.45	1.30E-05
CC	GO:0031966	mitochondrial membrane	11.76	5.31E-07	16.30	1.72E-05
CC	GO:0031410	cytoplasmic vesicle	10.29	5.59E-04	6.72	1.25E-02
MF	GO:0008017	microtubule binding	11.76	3.58E-05	8.58	6.66E-03
MF	GO:0005262	calcium channel activity	7.35	1.04E-04	20.17	9.67E-03
MF	GO:0072345	NAADP-sensitive calcium-release channel activity	4.41	1.73E-04	143.24	1.02E-02
MF	GO:0003924	GTPase activity	11.76	2.19E-04	6.42	1.02E-02
MF	GO:0005261	cation channel activity	5.88	4.04E-04	27.28	1.45E-02
KEGG	hsa04961	endocrine and other factor-regulated calcium reabsorption	4.41	2.73E-02	11.33	7.84E-01
KEGG	hsa05100	bacterial invasion of epithelial cells	4.41	5.39E-02	7.80	7.84E-01
KEGG	hsa04060	cytokine-cytokine receptor interaction	7.35	5.43E-02	3.39	7.84E-01
KEGG	hsa04721	synaptic vesicle cycle	4.41	5.52E-02	7.70	7.84E-01
KEGG	hsa04662	B cell receptor signaling pathway	4.41	6.03E-02	7.32	7.84E-01



A

Ε







Category	Number	Term	%	PValue	Fold Enrichment	FDR
BP	GO:0045944	positive regulation of transcription from RNA polymerase II promoter	23.38	1.94E-06	3.89	7.51E-04
BP	GO:0032496	response to lipopolysaccharide	10.39	2.21E-06	13.23	7.51E-04
BP	GO:0006357	regulation of transcription from RNA polymerase II promoter	25.97	1.48E-05	3.03	3.37E-03
BP	GO:0051591	response to cAMP	6.49	2.95E-05	27.79	5.02E-03
BP	GO:0000122	negative regulation of transcription from RNA polymerase II promoter	18.18	6.37E-05	3.76	8.66E-03
CC	GO:0090575	RNA polymerase II transcription factor complex	18.18	6.31E-16	30.67	1.04E-13
CC	GO:0000785	chromatin	28.57	1.39E-10	5.55	1.14E-08
CC	GO:0035976	transcription factor AP-1 complex	5.19	4.81E-07	213.82	2.63E-05
CC	GO:0005667	transcription factor complex	9.09	2.28E-04	8.00	9.35E-03
CC	GO:0032993	protein-DNA complex	5.19	6.55E-04	23.24	2.15E-02
MF	GO:1990837	sequence-specific double-stranded DNA binding	24.68	3.34E-12	8.60	6.35E-10
MF	GO:0003700	transcription factor activity, sequence-specific DNA binding	20.78	3.17E-09	7.27	2.60E-07
MF	GO:0003677	DNA binding	24.68	2.78E-06	3.59	8.82E-05
MF	GO:0000976	transcription regulatory region sequence-specific DNA binding	11.69	4.13E-06	9.53	1.12E-04
MF	GO:0008134	transcription factor binding	10.39	1.75E-05	9.65	4.16E-04
KEGG	hsa04668	TNF signaling pathway	10.39	2.52E-06	12.47	3.76E-04
KEGG	hsa05031	amphetamine addiction	7.79	3.81E-05	15.18	2.84E-03
KEGG	hsa04380	osteoclast differentiation	9.09	7.20E-05	9.55	3.58E-03
KEGG	hsa04926	relaxin signaling pathway	7.79	7.27E-04	8.12	2.51E-02
KEGG	hsa05418	fluid shear stress and atherosclerosis	7.79	1.02E-03	7.54	2.51E-02

D



C1orf162 FOS FOSB KCNE3 LY96 MMP10 MNDA MTUS1 NCF2 SMIM3 CCND2

dS2

dS1

EVT

LC3

0





	0.6
	0.4
	0.2
	0
	-0.2
	-0.4
	-0.6
1000	

Figure legends

Figure 1-1. Identification of differentially expressed genes of early pregnant women's decidual tissue after vaccine.

A. The heatmap shows differentially expressed genes;

B. The volcano plot shows differentially expressed genes;

C. Principal Component Analysis of differentially expressed genes

Figure 1-2. Function enrichment of the genes in early pregnant women's decidual tissue after vaccine.

D. Bubble chart showing the BP of the up-regulated genes;

E. Bubble chart showing the MF of the up-regulated genes;

F. Bubble chart showing the CC of the up-regulated genes;

G. Bubble chart showing the KEGG of the up-regulated genes;

H. Bubble chart showing the BP of the down-regulated genes;

I. Bubble chart showing the MF of the down-regulated genes;

J. Bubble chart showing the CC of the down-regulated genes;

K. Bubble chart showing the KEGG of the down-regulated genes

Figure 2. Systematical analysis of the connection between covid-19 placenta genes and early pregnant women's decidual genes.

GSEA analysis helps find the gene set with the same differential expression trend from the expression matrix of all genes. Positive enrichment score indicated that this gene was enriched in the experimental group of the reference gene set, while the negative score showed the enrichment in the control group.

A. The GSEA plot shows the enrichment of up-regulated covid-19 placenta gene set was concentrated in the experimental group of our RNA-seq data set.

B. The GSEA plot shows the enrichment of down-regulated covid-19 placenta gene set was concentrated in the control group of our RNA-seq data set.

C. The protein-protein interaction of the up-regulated core-enrichment covid-19 placenta genes in the GeneMANIA database;

D. The protein-protein interaction of the down-regulated core-enrichment covid-19 placenta genes in the GeneMANIA database;

E. The table shows target enrichment forms performed on core-enrichment covid-19 placenta genes.

Figure 3. Systematical analysis of the connection between RSA women's decidual genes and early pregnant women's decidual genes.

GSEA analysis helps find the gene set with the same differential expression trend from the expression matrix of all genes. Positive enrichment score indicated that this gene was enriched in the experimental group of the reference gene set, while the negative score showed the enrichment in the control group.

A. The GSEA plot shows the enrichment of up-regulated RSA decidual gene set was concentrated in the control group of our RNA-seq data set.

B. The GSEA plot shows the enrichment of down-regulated RSA decidual gene set in our RNA-seq data set of vaccinated decidual.

C. The protein-protein interaction of the up-regulated core-enrichment RSA decidual genes in the GeneMANIA database;

D. The protein-protein interaction of the down-regulated core-enrichment RSA decidual genes in the GeneMANIA database;

E. The table shows target enrichment forms performed on core-enrichment RSA decidual genes.

Figure 4-1. Analysis of the functional gene sets of the maternal-fetal interface.

A. The GSVA analysis shows the expression of immune infiltration gene set.

B. The GSVA analysis shows the expression of angiogenesis gene set.

C. The GSVA analysis shows the expression of trophoblast cell migration gene set.

D. The PCA analysis shows the expression of immune infiltration gene set.

E. The PCA analysis shows the expression of angiogenesis gene set.

F. The PCA analysis shows the expression of trophoblast cell migration gene set.

Figure 4-2. The link between core-enrichment genes and maternal-fetal interface.

G. The heatmap shows the expression of core-enrichment covid-19 placenta genes in the maternal-fetal interface associated cells at the single-cell level.

H. The heatmap shows the expression of core-enrichment RSA decidual genes in the maternal-fetal interface associated cells at the single-cell level.