A comparison of immunoregulatory protein profile in plasma between women with and without histologic chorioamnionitis in preterm premature rupture of membranes

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Introduction

Importantly, several studies indicated that patients complicated by histologic chorioamnionitis (HCA) are at increased risk for maternal and neonatal complications, including impending preterm delivery and neonatal sepsis, neurologic morbidity, and death. Therefore, a more accurate and earlier prenatal diagnosis of subclinical HCA, especially by using non-invasive methods, is clinically important for deciding on the treatment strategy and for counseling patients with preterm premature rupture of membranes (pPROM).

We aimed to compare the profiles of immune-regulatory proteins in plasma of women with pPROM and HCA with those without HCA, and to identify novel plasma biomarkers for HCA.

Materials and Methods

A case-control study was conducted using a membrane-based human cytokine microarray technology (RayBio Custom Human Cytokine Array)

Plasma samples were obtained <72 hours before delivery from 14 women with pPROM and HCA (case subjects) and 14 women with pPROM without HCA (control subjects matched by gestational age).

We screened and compared the plasma profiles of 507 immuno-regulatory proteins in women with and without HCA, using antibody microarray.

To validate the antibody array results, plasma levels of IL-6, IL-8, MMP-9, Pref-1, angiopoietn-2, S100 A8/A9, M-CSF, TIMP-1, CXCL14, and IGFBP-2 were further quantified by ELISA in twenty-eight samples of the exploratory study with additional 11 plasma samples (5 women with HCA and 6 women without HCA).

Results

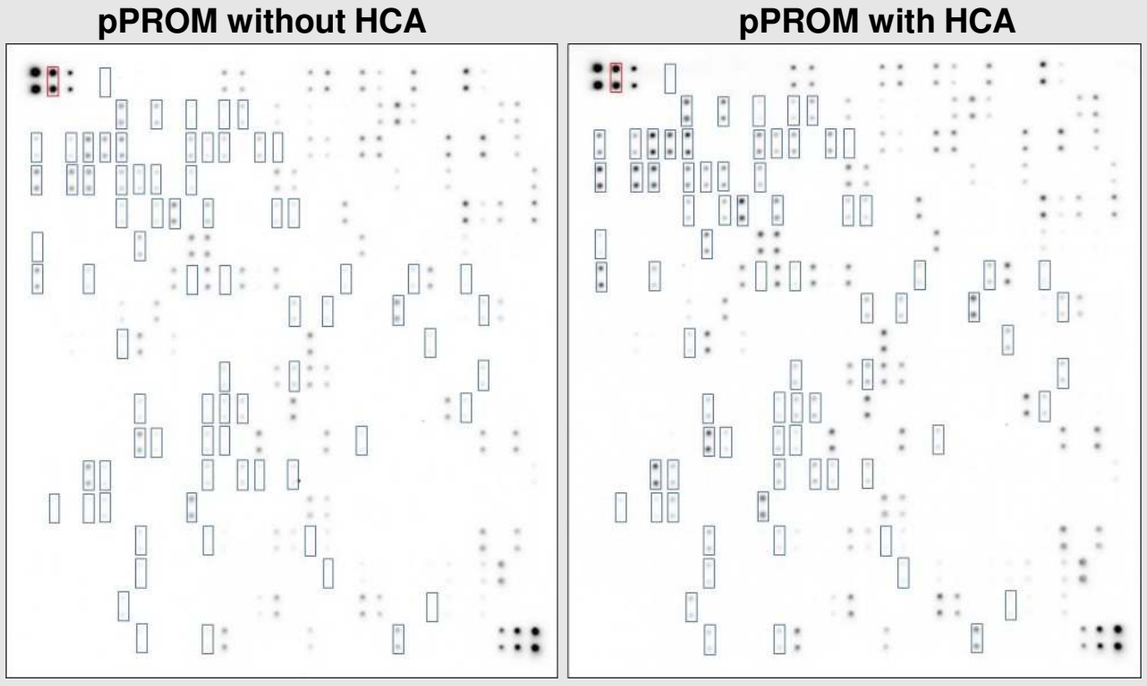

Figure 1. Expression levels of 507 immunoregulatory proteins in the plasma of pPROM women in HCA versus non-HCA groups. The pooled plasma samples in each group (14 women with HCA, 14 gestational age-matched control subjects) were assayed using the RayBio human antibody array. Using a 2-fold change as the threshold, 77 differentially up-regulated proteins in HCA relative to non-HCA women are presented in rectangles. pPROM, preterm premature rupture of membranes; HCA, histologic chorioamnionitis.

Results

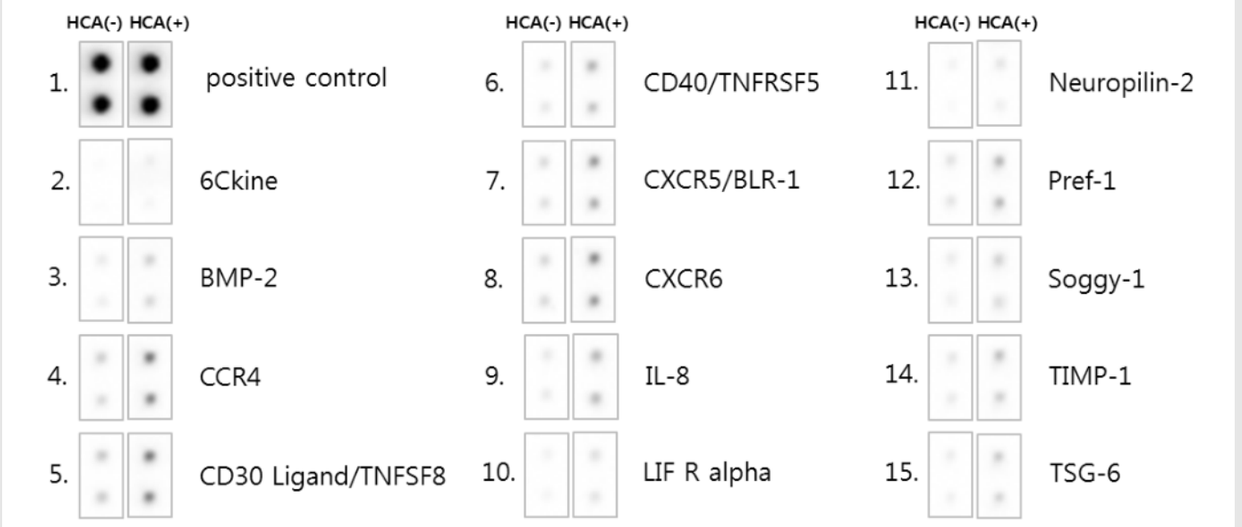

Figure 2. A list of the molecules with significantly different levels of expression in the plasma of pPROM women in HCA versus non-HCA groups. Fourteen proteins exhibited higher expression in pPROM women with HCA. pPROM, preterm premature rupture of membranes; HCA, histologic chorioamnionitis.

Table 1 Comparison of demographic and plasma levels of immuno-regulatory proteins measured by ELISA in women with and without HCA

	pPROM with HCA (n=20)	pPROM without HCA (n=19)	P-value
Maternal age (years)	32.1	31.7	0.667
Nulliparity	45%	58%	0.421
Gestational age at sampling (weeks)	32.8	30.2	0.001
Gestational age at delivery (weeks)	33.0	20.8	0.002
Plasma Il-6 (pg/mL)	3.62	12.40	0.016
Plasma IL-8 (pg/ml)	5.46	6.07	0.478
Plasma MMP-9 (ng/ml)	182.5	337.7	0.003
Plasma Pref-1 (ng/mL)	5.82	7.57	0.297
Plasma Angiopoietin 2 (ng/mL)	5.11	5.01	1.000
Plasma S100 A8/A9 (ng/mL)	290.2	515.8	0.014
Plasma M-CSF (pg/mL)	111.6	269.0	0.343
Plasma TIMP-1 (ng/ml)	166.6	165.9	0.989
Plasma CXCL14 (ng/ml)	1.17	1.11	0.569
Plasma IGFBP-2 (ng/mL)	98.7	76.9	0.513

pPROM, preterm premature rupture of membranes; HCA, histologic chorioamniontis; IL, Interleukin; MMP, matrix metalloproteinase; Pref-1, Preadipocyte factor 1; S100 A8/A9, S100 calcium-binding protein A8/A9 complex; M-CSF, macrophage colony-stimulating factor; TIMP, tissue inhibitors of matrix metalloproteinases; CXCL, chemokine (C-X-C motif) ligand; IGFBP-2, insulin-like growth factor-binding protein 2

Conclusions

The protein expression pattern in the plasma is significantly altered between pPROM women with HCA and those without HCA. The increased levels of IL-6, MMP-9, and S100 A8/A9 in plasma of pPROM women with HCA indicated that maternal systemic inflammatory response in the maternal plasma compartment is involved in the pathogenesis of HCA, and suggest candidates of potential new biomarker for HCA.

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