48 A ROLE FOR CXCL13 IN THE HOST RESPONSE TO INTRA-AMNIOTIC INFECTION

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OBJECTIVE: CXCL13 is a novel chemokine produced by mature and recently recruited macrophages to sites of inflammation, which has anti-microbial and anti-angiogenic properties. A role for CXCL13 has been proposed in placental malaria. However, little is known about this chemokine in normal pregnancy, as well as in those associated with bacterial infection. The purpose of this study was to determine whether CXCL13 is present in amniotic fluid (AF) and if its concentration changes with intra-amniotic infection/inflammation (IAI).

STUDY DESIGN: A cross-sectional study was performed including patients in the following groups: 1) midtrimester (n=65); 2) term not in labor (n=22); 3) term in labor (n=47); 4) preterm labor (PTL) with term delivery (n=55); and 5) PTL leading to preterm delivery with (n=42) and without (n=68) IAI. CXCL13 concentrations were determined by ELISA. Non-parametric statistics were used for analysis.

RESULTS: 1) CXCL13 is a physiologic constituent of AF, as it was present in 99% of samples (295/299); 2) The concentration of CXCL13 in AF did not change with gestational age (p=0.11); 3) Patients with PTL and IAI had a significantly higher median concentration of CXCL13 than those without IAI [327.5 pg/mL (59.9-11608) vs 190.7 pg/mL (50.5-13663.6), respectively; p=0.02] and those who delivered at term [145.2 pg/mL (46.3-798.7), respectively; p<0.001]; 4) Spontaneous labor did not result in a change in the median AF concentration of CXCL13 [labor: 86.9 pg/mL (0-450) vs no labor: 77.8 pg/mL (36.0-317.7); p=0.75].

CONCLUSION: 1) We report for the first time the presence of CXCL13 in AF and that its concentrations are dramatically increased in intra-amniotic infection/inflammation; 2) Unlike other chemokines (IL-8), CXCL13 concentrations did not change with spontaneous parturition; 3) In addition to participating in the host response against infection, CXCL13 participates in the homing of regulatory T cells, which have been implicated in the tolerance of the fetal allograft.

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49 A POLYMORPHISM IN A GENE CODING FOR THE NALP3-INFLAMMASOME IS ASSOCIATED WITH PRETERM PREMATURE RUPTURE OF THE MEMBRANES

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OBJECTIVE: A cytoplasmic structure called the inflammasome has recently been demonstrated to regulate the production and release of interleukin-1beta (IL-1beta). A key structural component of the inflammasome is a protein called NALP3, a product of the CIAS1 gene. A polymorphism in the CIAS1 gene results in altered gene expression and variations in IL-1beta production. We hypothesized that, since IL-1beta is a prime trigger of preterm labor, a womans CIAS1 genotype may influence susceptibility to an adverse pregnancy outcome.

STUDY DESIGN: Buccal swabs were collected from women with preterm (n=92) and term delivery (n=121). DNA was extracted and tested by polymerase chain reaction for a length polymorphism in intron 4 of the CIAS1 gene. Clinical outcomes were obtained only after completion of all testing.

RESULTS: Homozygosity for the 12 unit repeat was strongly associated with a term birth (P<.0001). Conversely, homozygosity or heterozygosity for the 6, 7 or 9 unit repeats was associated with preterm birth (P=.01). Differentiating the preterm birth patients into those with preterm premature rupture of membranes (pPROM, n=21), spontaneous preterm birth (n=21) or indicated preterm birth (n=83) revealed that only in the women with pPROM was the frequency of allele 12 homozygosity decreased from women with term deliveries (P<.0001). The absence of the 12 repeat was more frequent in women who delivered at <32 weeks (18.4%), at 32-34 weeks (30.8%) and at 35-36 weeks (29.4%) as compared to women who delivered at >36 weeks (10.7%) (P<.05). The absence of the 12 repeat was also more frequent in women who delivered a low birth weight infant (23.5%) as compared to those who delivered an infant >2500 g (10.9%) (P=.02).

CONCLUSION: The absence of homozygosity for the 12 unit repeat in the CIAS1 gene coding for the NALP3-inflammasome is a risk factor for pPROM.

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50 NUCLEATED RED BLOOD CELLS (NRBC) ARE A DIRECT RESPONSE TO MEDIATORS OF INFLAMMATION IN NEWBORNS WITH EARLY ONSET NEONATAL SEPSIS (EONS)

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OBJECTIVE: The mechanism responsible for an elevated fetal NRBC count is still unknown. We propose that independent of hypoxia or fetal stress, inflammation plays an important role in modulating fetal erythroblastosis. We sought to determine if fetal inflammation is associated with an increased NRBC count in pregnancies complicated by intra-amniotic inflammation (IAI).

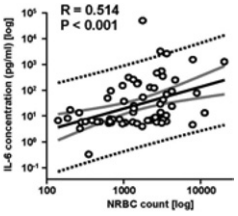
STUDY DESIGN: The relationship between peripheral NRBC count, histological chorioamnionitis (HCA), umbilical cord interleukin-6 (IL-6), erythropoietin (EPO), cortisol and acid-base status were analyzed in 61 consecutive preterm singletons, born to mothers who had an amniocentesis to rule out infection. Proteomic profiling of the amniotic fluid identified the presence of IAI according to established parameters. NRBC counts were assessed within 1h of birth. EONS was established based on hematological and microbiological indices. IL-6, EPO and cortisol were measured by sensitive immunoassays. Acid-base status was determined within 10 min. of delivery. Parametric or nonparametric analysis was employed as indicated.

RESULTS: 1) Fetuses with EONS were delivered at an earlier GA (p=0.001) and more often by mothers with IAI (p=0.022) and HCA (p<0.001); 2) Neonates with EONS had higher absolute NRBCs (p=0.015) (Table); 3) There was a direct relationship between NRBC count and cord blood IL-6 (Figure); 4) NRBC had no relation to EPO, acid-base status or cortisol regardless of EONS. These relationships remained following correction for GA, diabetes, IUGR and steroid exposure.

CONCLUSION: In the setting of inflammation-associated preterm birth and in the absence of hypoxia, we demonstrate that the fetal erythropoeitis is a direct response to inflammatory mediators.

Variables	No EONS (n=49)	EONS (n=19)
GA at delivery, *wks*	29.6 ± 2.7	27.1 ± 2.8 *
NRBC count, *cells/mm³*	1,330 [665-2,630]	3,020 [1,388-4,558] *
IL-6, *pg/mL*	7.4 [5.8-33.1]	90.2 [17.9-407.5] *
EPO, *mIU/mL*	6.6 [4.0-15.2]	11.3 [3.7-30.8]
Cortisol, *ng/mL*	73.2 ± 34.8	70.9 ± 37.1
pH vein	7.35 [7.33-7.39]	7.38 [7.34-7.40]
pH artery	7.32 [7.27-7.33]	7.33 [7.31-7.36]
pO2 vein, *mmols/L*	30.8 [26.1-37.7]	38.7 [30.3-49.6]
pO2 artery, *mmols/L*	23.6 [18.4-28.0]	31.2 [22.0-38.0]
base deficit vein, *mmols/L*	3.5 [2.2-4.7]	3.9 [2.1-5.4]
base deficit artery, *mmols/L*	4.3 [2.4-5.4]	4.2 [2.5-5.5]

* *P < 0.05*



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