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The Early Stages of Intrauterine Infection result in Tissue Specific Fetal Inflammation in a Rhesus macaque Model of Choriodecidual Ureaplasma Infection

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Keywords

preterm birth, intrauterine infection, perinatal brain injury, neuroinflammation, Ureaplasma parvum

Abstract

Introduction: Intrauterine infection is associated with preterm labor and perinatal brain injury. Choriodecidual infection represents an early stage of ascending reproductive infection prior to microbial invasion of the amniotic cavity (MIAC). The present study examines the effects of intrauterine Ureaplasma infection on fetal inflammation and inflammasome activity.

Methods: Catheterized pregnant rhesus monkeys underwent choriodecidual inoculation at 118±1dGA (control and Ureaplasma, U.p. groups, n=4, repeated every 5d until fetal necropsy at 136±2dGA (~21days infection; Term=167d). Inflammasome, and inflammatory mediators were assessed in amniotic fluid (AF), membranes, fetal plasma, lung and brain by RT-qPCR, multiplex ELISA, western blot along with brain histopathology. Statistical significance ($P<0.05$) determined by Student's t-test /Mann-Whitney after Shapiro-Wilk test for normality.

Results: In U.p. animals, chorioamnionic membranes were positive for UP by culture/PCR. However, AF remained negative for UP and there were no differences in uterine activity or AF cytokines. Pro-inflammatory cytokines, including IL-18 were upregulated in fetal membranes and fetal lung with increased expression of IL-18, IL-18R1, and CASP-1 ($P<0.05$). This was accompanied by fetal membrane inflammasome activation (NLRP3, ASC, CASP1). U.p. fetuses also had elevated plasma IL-18 (26 vs. 134 pg/mL, $P=0.02$) and showed increased staining of astrocytes (GFAP, $P<0.01$), and oligodendrocytes (Olig2, $P=0.04$), but reduced mature myelin (MBP, $P=0.02$). However, IL-18 and inflammasome associated genes were significantly downregulated ($P<0.05$) in U.p. fetal brain cortex.

Conclusions: In our translational non-human primate model of intrauterine infection, we demonstrate the presence of membrane and systemic fetal inflammation prior to MIAC. In contrast, at this timepoint following chronic, localized choriodecidual infection, downregulation of inflammatory markers and inflammasome components in the fetal brain suggests the presence of a protective/pre-conditioning response. The balance and timing of pro- and anti- inflammatory responses has implications for the timing of diagnosis and administration of therapeutics.