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MicroRNAs regulating Toll Like Receptor inflammatory pathways in preterm and term placenta and cord blood

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Title:

MicroRNAs regulating Toll Like Receptor inflammatory pathways in preterm and term placenta and cord blood.

Abstract, no longer than 300 words. The box will 'expand' over 2 pages as you add text/diagrams into it: (Your abstract must use Normal style. Do not enter author details)

An immature ability to regulate the innate immune response may contribute to the high rates of morbidity seen in the preterm population. Placental inflammation *in-utero* may exacerbate this immaturity. Toll-like receptors (TLRs) play a key role in pathogen recognition and their activation initiates an intracellular signalling cascade resulting in pro-inflammatory cytokine transcription. TLR signalling is post-transcriptionally regulated by microRNAs (miRs). We have previously demonstrated increased Interleukin-6 in preterm compared to term cord blood following TLR2 and TLR4 stimulation. We now investigate the expression of miRs regulating TLR signalling in preterm and term placenta, and following stimulation in cord blood.

Cord blood and placentae were collected following term ($n=26$) and preterm delivery (<37 weeks, $n=19$). Cord blood was stimulated with TLR2 and TLR4 agonists, and collected at baseline and 6 hours. RNA was extracted and relative expression of *let7e*, *miR155*, *miR146a* and *miR106a*, and their respective mRNA targets: *TLR4*, *SOCS1*, *IRAK1* and *Interleukin-10* were quantified relative to *RNU48* and β -*actin*, respectively using qPCR.

No difference was observed between term and preterm placental miR or mRNA expression. In cord blood from term neonates, TLR stimulation increased *let7e* ($p=0.044$), *miR155* ($p=0.052$) and *miR106a* expression ($p=0.048$) compared to unstimulated blood. However, TLR stimulation in preterm cord blood did not increase the expression of any miR compared to baseline control.

While placental miR expression does not change between term and preterm placenta, these data suggest that increased cytokine production in preterm neonates following pathogen exposure may be driven by an inability to regulate this response by miRs that regulate TLR and SOCS1 expression. This may result in a pro-inflammatory-biased innate immune response. These novel findings are the first to suggest that differential miR expression in preterm compared to term neonates may contribute to a dysregulated neonatal innate immune response, predisposing to neonatal inflammatory morbidities.