The Role of Toll-Like Receptors and TNF-Alpha in Neonatal Host Defense

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Human neonates are uniquely susceptible to bacterial infections. The neonatal immune response is blunted due in part to the naivety of the neonate’s innate and adaptive immune responses. The mechanism of this increased susceptibility is poorly understood. Toll-Like Receptors (TLRs) have been described as having a central role in innate immune responses. TLRs are a family of pattern recognition receptors that recognize pathogen-associated molecular patterns (PAMPs). Tumor Necrosis Factor Alpha (TNF-alpha) is a proinflammatory cytokine which contributes to host defense. Here we examine the expression of TNF-alpha in cord blood after stimulation with ligands for TLRs 1–7 and compare the response to an adult control.

Whole blood was obtained from healthy adults and umbilical cord blood from healthy term deliveries. TNF-alpha production was measured using Lumines multi-analyte technology. The following TLR ligands were utilized: TLRs-1&2 (PAM3CSK4), TLRs-2&6 (Zymosan), TLR-3 (Poly I:C), TLR-4 (LPS), TLR-5 (Flagellin) and TLR-7 (Lipoxorbin).

Adult and cord blood produced similar amounts of TNF-alpha in response to TLRs-1&2, TLRs-2&6, TLRs-3, TLRs-5, and TLR-7. The TNF-alpha production in response to LPS, the ligand for TLR-4, however, was significantly lower in cord blood (450 pg/mL) than in adult blood (733 pg/mL) (p=0.025). While the highest overall production of TNF-alpha was through TLR-4, peak concentrations were significantly lower than adults. We speculate that this deficiency in TLR-4 signaling may significantly contribute to the immaturity of the neonatal immune response and their increased susceptibility to infections.