Review Article
Infection-Induced Vulnerability of Perinatal Brain Injury

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A growing body of evidence demonstrates that susceptibility and progression of both acute and chronic central nervous system disease in the newborn is closely associated with an innate immune response that can manifest from either direct infection and/or infection-triggered damage [2]. A common feature of these diseases is the systemic exposure of the neonate to bacterial infections that elicit brain inflammation. In recent years, the importance of innate immune receptors in newborn brain injury, the so-called Toll-like receptors, has been demonstrated. In this paper we will discuss how neonatal sepsis, with particular emphasis on Escherichia coli, coagulase-negative staphylococci, and group B streptococcal infections in preterm infants, and Toll-like receptor-mediated inflammation can increase the vulnerability of the newborn brain to injury.

1. Introduction
Perinatal brain injury represents a significant clinical problem [1]. A growing body of evidence demonstrates that susceptibility and progression of both acute and chronic central nervous system (CNS) disease is closely associated with an innate immune response that can manifest from either direct infection and/or infection-triggered damage [2]. A common feature of these diseases is the systemic activation of inflammatory mediators, which via the blood can disrupt the blood-brain barrier, affect the circumventricular organs in the brain (which lack a blood-brain barrier), or interact with the brain endothelium, thereby eliciting brain inflammation [3]. Furthermore, the presence of activated inflammatory cells derived from systemic circulation or from dormant brain resident populations is a key feature of many CNS diseases. More recently, the importance of innate immune receptors in CNS injury, the so-called Toll-like receptors (TLRs), has also been emphasized. In this paper we will focus on how neonatal sepsis and TLR-mediated inflammation increase the vulnerability of the newborn brain.

2. Neonatal Sepsis and Brain Injury
Infants with sepsis have an increased incidence of cerebral palsy [4] and white matter abnormalities [5–11]. In a large study of 6093 extremely low birth weight (<1000 g) infants, those who were infected (including early-onset sepsis, suspected sepsis (culture negative), and had necrotizing enterocolitis (NEC)) were more likely to have cerebral palsy than children who did not have a neonatal infection [12]. In another recent large sample-size study involving 1155 infants born at 23 to 27 weeks gestation, it was found that children who had both late bacteremia (positive blood culture result after the first postnatal week) and surgical NEC were more likely to have cerebral palsy than children who did not have a neonatal infection [13]. Moreover, by comparing outcomes of 150 infants with periventricular leukomalacia (PVL) with controls matched for gestational age, it was found that infants with bacterial sepsis were twice as likely to develop PVL, and those with meningitis were almost four times as likely to develop white matter disease [14]. Similar findings were noted in a smaller case-control study, where
associations between cerebral palsy, clinical chorioamnionitis and sepsis were demonstrated [15]. Moreover, there was an increased incidence of Gram-negative bacterial and fungal infections in a very low birth weight population, and these infants were at significantly increased risk for moderate to severe cerebral palsy and neurodevelopmental impairment at 18 months of age [16].

2.1. Bacterial Pathogens in Neonatal Sepsis. Escherichia coli is one of the main pathogens causing early-onset infections in preterm neonates, accounting for up to 40% of the cases of bacteremia among very low birth weight preterm infants (<1,500 g) [17]. Cerebral white matter injury has been found by MRI following Escherichia coli meningitis in human newborn infants [18]. Furthermore, Escherichia coli induce brain damage in a number of antenatal rabbit and rodent models [19–26]. Also, in a recent study, white matter injury was demonstrated in an animal model of neonatal Escherichia coli sepsis in 5-day-old rat pups [27]. Experimental studies show that early-life Escherichia coli exposure can also have long-term effects, influencing the vulnerability to other factors in adulthood, for example, age-related cognitive decline [28] as well as attenuated glial and cytokine responses to amphetamine challenge [29].

In recent years, coagulase-negative staphylococci (CONS) have emerged as the most prevalent and important neonatal pathogens, responsible for approximately 50% of all episodes of late-onset neonatal sepsis in neonatal intensive care units around the world [30–33]. CONS cause significant morbidity, mortality, and healthcare costs worldwide in preterm newborns, especially in very low birth weight infants [34–38]. The vulnerability of preterm infants to CONS infection has been suggested to be due to the special characteristics of the premature infant’s innate immunity [39]. Although there is no direct evidence of CONS causing perinatal brain injury, the presence of CONS in the chorioamnion space at delivery is associated with increased risk for the development of cerebral palsy in preterm infants [40, 41]. Further, in children with an established diagnosis of cerebral palsy, who are admitted to pediatric intensive care, there is a high rate of carriage of abnormal bacteria, including CONS [42].

In very low birth weight preterm infants with early onset neonatal sepsis, the rate of group B streptococcal (GBS) infections is relatively low in comparison with E. coli infections [17]. There is no direct evidence of GBS sepsis playing a role in cerebral palsy; however, nearly half of all infants who survive an episode of GBS meningitis suffer from long-term neurodevelopmental sequelae [43]. Further, extensive cortical neuronal injury was found in GBS-infected neonatal rats, which was mediated through reactive oxygen intermediates [44, 45].

3. Toll-Like Receptor-Mediated Vulnerability of the Immature Brain

3.1. Toll-Like Receptors. Toll-like receptors (TLRs) play a central role in primary recognition of infectious and viral pathogens. The presence of all 13 known TLRs has been demonstrated in the brain [46–48]. TLR4 mediates cellular activation in response to LPS derived from Escherichia coli [49], while CONS [39] and GBS infections [50] are, at least partly, believed to be mediated by TLR2. Interestingly, the role of TLRs in nonbacterial-induced brain injury has also recently been highlighted [51]. TLRs signal through the recruitment of intracellular adaptor proteins, followed by activation of protein kinases and transcription factors that induce the production of inflammatory mediators (Figure 1). The adaptor protein MyD88 is used by most TLRs, except TLR3, while the TRIF adaptor protein is used only by TLR3 and TLR4. LPS-induced activation of TLR4 elicits, via both MyD88 and TRIF, a broad inflammatory response in tissues, including the immature brain [52].

3.2. TLR Expression during Brain Development. There is relatively little information regarding the expression of TLRs in the developing brain. During embryonic life, protein expression of both TLR-3 and -8 has been identified [53, 54], while TLR-2 expression is relatively low before birth and increases during the first two weeks of life [55]. We have shown that mRNA for TLR1-9 is expressed in the neonatal mouse brain [56]. It appears that some of the TLRs may play important roles during normal brain development, as TLR2 inhibits neural progenitor cell proliferation during the embryonic period, and TLR3 deficiency increases proliferation of neural progenitor cells, while TLR8 stimulation inhibits neurite outgrowth [53–55]. In support, TLR2 and TLR4 have been shown to regulate hippocampal neurogenesis in the adult brain [57].

3.3. LPS-Induced Brain Injury. We, and others, have shown that systemic administration of LPS results in brain injury in both fetal and newborn animals [58–60]. These injuries appear, both histologically and by MRI analysis, to be very similar to those found in preterm infants [61]. Furthermore, it is now well established that pre-exposure to LPS can increase the vulnerability of the immature brain to hypoxia-ischemia (HI), in both rats [62, 63] and mice [64]. These effects are TLR4 [65] and MyD88 dependent [64, 66]. In a recent study, it was also shown that a very low dose of LPS, specifically increased the vulnerability of the immature white matter [67]. Low-dose LPS (0.05 mg/kg) sensitized HI injury in P2 rat pups by selectively reducing myelin basic protein expression and the number of oligodendrocytes while increasing neuroinflammation and blood-brain barrier damage in the white matter. The neuroinflammatory responses to LPS/HI appears to be age dependent [68]. Rat pups subjected to LPS/HI at P1 responded with weak cytokine response, while there was a prominent upregulation of cytokines in P12 pups subjected to the same insult. Interestingly, IL-1β was upregulated at both ages; IL-1β injections sensitize the newborn brain to excitotoxicity [69] and repeated IL-1β exposure during the neonatal period induces preterm like brain injury in mice [70].

Although it has clearly been demonstrated that LPS can increase the vulnerability to HI, under certain circumstances LPS can also induce tolerance to brain injury. We have
shown that the time interval between LPS exposure and the subsequent HI is imperative to the outcome [71, 72], where a 24 h interval seems to induce a tolerant state that makes the brain less vulnerable. This has been confirmed by others who have implicated several possible mechanisms, including upregulation of corticosterone [73], which is further supported by the fact that administration of dexamethasone prevents learning impairment following LPS/HI in neonatal rats [74]. Furthermore, Akt-mediated eNOS upregulation in neurons and vascular endothelial cells have been implicated in LPS-induced preconditioning [75].

The importance of the time interval between LPS and other insults seems to be a generalized phenomenon. We have recently demonstrated in an in vitro model that conditioned medium from LPS-activated microglia affects the antioxidant Nrf2 system and cell survival in astrocytes in a time-dependent manner. LPS-induced inflammation had dual, time-dependent, effects on the Nrf2 system in that sustained activation (72 h) of GSK3beta and p38 downregulated the Nrf2 system, changes that were not observed with a 24 h (tolerance) interval [76, 77]. These studies support our previous report demonstrating that reductions in antioxidants were more pronounced when HI was preceded by LPS injection in 8-day rats 3 days prior to the HI insult [78].

3.4. Other TLRs in Perinatal Brain Injury. Compared to TLR4, much less is known about other TLRs in perinatal brain injury. As mentioned above, TLR2, TLR3, and TLR8 can affect normal brain development [53–55]. Activation of TLR2 in neonatal mice decreases volume of cerebral gray matter, white matter in the forebrain, and cerebellar molecular layer [79]. Furthermore, Akt-mediated eNOS upregulation in neurons and vascular endothelial cells have been implicated in LPS-induced preconditioning [75].

Maternal viral immune activation is believed to increase the risk of psychiatric disorders such as schizophrenia in offspring, and in order to examine this relationship, several authors have investigated the vulnerability of the fetal brain to synthetic double-stranded RNA, polyriboinosinic-polycytidilic acid (poly I:C), a TLR3 agonist. Maternal injection with poly I:C towards the end of gestation (≥G15) causes sensorimotor gating deficits in the adult offspring in mice [80] and increased sensitivity to the locomotor-stimulating effects of MK-801 [81]. The effects of Poly I:C appear to be gestational age dependent [82]. Maternal Poly I:C injection on GD9, but not GD17, significantly impaired sensorimotor gating and reduced prefrontal dopamine D1 receptors in adulthood, whereas prenatal immune activation
in late gestation impaired working memory, potentiated the locomotor reaction to a NMDA-receptor antagonist, and reduced hippocampal NMDA-receptor subunit 1 expression. In particular, Poly I:C injections early during rodent pregnancy affect structural brain development, such as a transient decrease of myelin basic protein in the neonatal offspring [83] and cerebellar pathology [84].

4. Conclusion

*E. coli* infections are common in preterm neonates, and considerable evidence suggests that *E. coli*-induced inflammation play a role in the development of white matter damage in preterm infants. There is much less data available concerning the importance of two other common neonatal pathogens, CONS and GBS, in perinatal brain injury. Furthermore, it is becoming clear that TLRs have important roles during development and may be involved in both pathogen-induced damage as well as so-called “sterile” HI-induced inflammation. In order to better understand the underlying causes of perinatal brain injury, the interaction between common neonatal pathogens and TLRs in the newborn brain deserves further investigation.

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References

[1] N. Marlow, D. Wolke, M. A. Bracewell, and M. Samara, “Neurologic and developmental disability at six years of age after extremely preterm birth,” *The New England Journal of Medicine*, vol. 352, no. 1, pp. 9–19, 2005.

[2] O. Dammann and A. Leviton, “Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn,” *Pediatric Research*, vol. 42, no. 1, pp. 1–8, 1997.

[3] H. Hagberg and C. Mallard, “Effect of inflammation on central nervous system development and vulnerability,” *Current Opinion in Neurology*, vol. 18, no. 2, pp. 117–123, 2005.

[4] A. Leviton and F. H. Gilles, “An epidemiologic study of perinatal telencephalic leukoencephalopathy in an autopsy population,” *Journal of the Neurological Sciences*, vol. 18, no. 1, pp. 53–66, 1973.

[5] R. G. Faix and S. M. Donn, “Association of septic shock caused by early-onset group B streptococcal sepsis and periventricular leukomalacia in the preterm infant,” *Pediatrics*, vol. 76, no. 3, pp. 415–419, 1985.

[6] D. J. Murphy, P. L. Hope, and A. Johnson, “Neonatal risk factors for cerebral palsy in very preterm babies: case-control study,” *British Medical Journal*, vol. 314, no. 7078, pp. 404–408, 1997.

[7] M. E. Msall, G. M. Buck, B. T. Rogers et al., “Multivariate risks among extremely premature infants,” *Journal of Perinatology*, vol. 14, no. 1, pp. 41–47, 1994.

[8] M. Wheater and J. M. Rennie, “Perinatal infection is an important risk factor for cerebral palsy in very-low-birthweight infants,” *Developmental Medicine and Child Neurology*, vol. 42, no. 6, pp. 364–367, 2000.

[9] D. K. Shah, L. W. Doyle, P. J. Anderson et al., “Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term,” *Journal of Pediatrics*, vol. 153, no. 2, pp. 170–175, 2008.

[10] J. J. Volpe, “Postnatal sepsis, necrotizing enterocolitis, and the critical role of systemic inflammation in white matter injury in premature infants,” *Journal of Pediatrics*, vol. 153, no. 2, pp. 160–163, 2008.

[11] T. Schmitz, A. Heep, F. Groenendaal et al., “Interleukin-1β, interleukin-18, and interferon-γ expression in the cerebrospinal fluid of premature infants with posthemorrhagic hydrocephalus-markers of white matter damage?” *Pediatric Research*, vol. 61, no. 6, pp. 722–726, 2007.

[12] B. J. Stoll, N. I. Hansen, I. Adams- Chapman et al., “Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection,” *JAMA*, vol. 292, no. 19, pp. 2357–2365, 2004.

[13] C. R. Martin, O. Dammann, E. N. Allred et al., “Neurodevelopment of extremely preterm infants who had necrotizing enterocolitis with or without late bacteraemia,” *Journal of Pediatrics*, vol. 157, no. 5, pp. 751–756, 2010.

[14] E. M. Graham, C. J. Holcroft, K. K. Rai, P. K. Donohue, and M. C. Allen, “Neonatal cerebral white matter injury in preterm infants is associated with culture positive infections and only rarely with metabolic acidosis,” *American Journal of Obstetrics and Gynecology*, vol. 191, no. 4, pp. 1305–1310, 2004.

[15] T. Michael O’Shea, K. L. Klinepeter, P. J. Meis, and R. G. Dillard, “Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants,” *Paediatric and Perinatal Epidemiology*, vol. 12, no. 1, pp. 72–83, 1998.

[16] D. K. Benjamin, B. J. Stoll, A. A. Fanaro et al., “Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months,” *Pediatrics*, vol. 117, no. 1, pp. 84–92, 2006.

[17] B. J. Stoll, N. I. Hansen, R. D. Higgins et al., “Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of Gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002–2003,” *Pediatric Infectious Disease Journal*, vol. 24, no. 7, pp. 633–639, 2005.

[18] D. K. Shah, A. J. Daley, R. W. Hunt, J. J. Volpe, and T. E. Inder, “Cerebral white matter injury in the newborn following *Escherichia coli* meningitis,” *European Journal of Paediatric Neurology*, vol. 9, no. 1, pp. 13–17, 2005.

[19] S. Kannan, F. Saadani-Makki, O. Muzik et al., “Microglial activation in perinatal rabbit brain induced by intrauterine inflammation: detection with 11C-(R)-PK11195 and small-animal PET,” *Journal of Nuclear Medicine*, vol. 48, no. 6, pp. 946–954, 2007.

[20] T. M. Yuan, H. M. Yu, W. Z. Gu, and J. P. Li, “White matter damage and chemokine induction in developing rat brain after intrauterine infection,” *Journal of Perinatal Medicine*, vol. 33, no. 5, pp. 415–422, 2005.

[21] T. Debillon, C. Gras-Leguen, S. Leroy, J. Caillon, J. C. Rozé, and P. Gressens, “Patterns of cerebral inflammatory response in a rabbit model of intrauterine infection-mediated brain
lesion," *Developmental Brain Research*, vol. 145, no. 1, pp. 39–48, 2003.

[22] J. K. Davies, R. H. Shikes, C. I. Sze et al., “Histologic inflammation in the maternal and fetal compartments in a rabbit model of acute intra-amniotic infection,” *American Journal of Obstetrics and Gynecology*, vol. 183, no. 5, pp. 1088–1093, 2000.

[23] Bo Hyun Yoon, Chong Jai Kim, R. Romero et al., “Experimentsally induced intrauterine infection causes fetal brain white matter lesions in rabbits,” *American Journal of Obstetrics and Gynecology*, vol. 177, no. 4, pp. 797–802, 1997.

[24] Y. Pang, S. Rodts-Palenik, Z. Cai, W. A. Bennett, and P. G. Rhodes, “Suppression of glial activation is involved in the protection of IL-10 on maternal *E. coli* induced neonatal white matter injury,” *Developmental Brain Research*, vol. 157, no. 2, pp. 141–149, 2005.

[25] S. Rodts-Palenik, J. Wyatt-Ashmead, Y. Pang et al., “Maternal infection-induced white matter injury is reduced by treatment with interleukin-10,” *American Journal of Obstetrics and Gynecology*, vol. 191, no. 4, pp. 1387–1392, 2004.

[26] K. L. Wallace, J. Lopez, J. P. Shafter, A. Wells, I. A. Paul, and W. A. Bennett, “Interleukin-10/Ceftiraxone prevents *E. coli*-induced delays in sensorimotor task learning and spatial memory in neonatal and adult Sprague-Dawley rats,” *Brain Research Bulletin*, vol. 81, no. 1, pp. 141–148, 2010.

[27] G. Loron, P. Olivier, H. See et al., “Ciprofloxacin prevents myelination delay in neonatal rats subjected to *E. coli* sepsis,” *Annals of Neurology*, vol. 69, no. 2, pp. 341–351, 2011.

[28] S. D. Bilbo, “Early-life infection is a vulnerability factor for aging-related glial alterations and cognitive decline,” *Neurobiology of Learning and Memory*, vol. 94, no. 1, pp. 57–64, 2010.

[29] S. T. Bland, J. T. Beckley, L. R. Watkins, S. F. Maier, and S. D. Bilbo, “Neonatal *Escherichia coli* infection alters glial, cytokine, and neuronal gene expression in response to acute amphetamines in adolescent rats,” *Neuroscience Letters*, vol. 474, no. 1, pp. 52–57, 2010.

[30] B. J. Stoll, N. Hansen, A. A. Fanaroff et al., “Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants,” *The New England Journal of Medicine*, vol. 347, no. 4, pp. 240–247, 2002.

[31] B. J. Stoll, N. Hansen, A. A. Fanaroff et al., “Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network,” *Pediatrics*, vol. 110, no. 2, pp. 285–291, 2002.

[32] M. J. Bizzarro, C. Raskind, R. S. Baltimore, and P. G. Gallagher, “Seventy-five years of neonatal sepsis at Yale: 1928–2003,” *Pediatrics*, vol. 116, no. 3, pp. 595–602, 2005.

[33] I. R. Makhoul, P. Sujov, T. Smolkin, A. Lusky, and B. Reichman, “Pathogen-specific early mortality in very low birth weight infants with late-onset sepsis: a national survey,” *Clinical Infectious Diseases*, vol. 40, no. 2, pp. 218–224, 2005.

[34] B. J. Stoll and N. Hansen, “Infections in VLBW infants: studies from the NICHD Neonatal Research Network,” *Seminars in Perinatology*, vol. 27, no. 4, pp. 293–301, 2003.

[35] C. Vuong and M. Otto, “Staphylococcus epidermidis infections,” *Microbes and Infection*, vol. 4, no. 4, pp. 481–489, 2002.

[36] D. Isaacs, “A ten year, multicentre study of coagulase negative staphylococcal infections in Australasian neonatal units,” *Archives of Disease in Childhood*, vol. 88, no. 2, pp. F89–F93, 2003.

[37] C. M. Healy, K. G. Hulten, D. L. Palazzi, J. R. Campbell, and C. J. Baker, “Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit,” *Clinical Infectious Diseases*, vol. 39, no. 10, pp. 1460–1466, 2004.

[38] J. B. López Sastre, D. Coto Caloto, B. Fernández Colomer et al., “Neonatal sepsis of nosocomial origin: an epidemiological study from the ‘Grupo de Hospitales Castrillo’,” *Journal of Perinatal Medicine*, vol. 30, no. 2, pp. 149–157, 2002.

[39] T. Strunk, P. Richmond, K. Simmer, A. Currie, O. Levy, and D. Burgner, “Neonatal immune responses to coagulase-negative staphylococci,” *Current Opinion in Infectious Diseases*, vol. 20, no. 4, pp. 370–375, 2007.

[40] R. Mittendorf, R. Covert, J. Kohn, N. Roizen, B. Khoshnood, and K. S. Lee, “The association of coagulase-negative staphylococci isolated from the choioamnion at delivery and subsequent development of cerebral palsy,” *Journal of Perinatology*, vol. 21, no. 1, pp. 3–8, 2001.

[41] R. Mittendorf, N. Roizen, A. Moawad, B. Khoshnood, and K. S. Lee, “Association between cerebral palsy and coagulase-negative staphylococci,” *The Lancet*, vol. 354, no. 9193, pp. 1875–1876, 1999.

[42] K. Thorburn, M. Jardine, N. Taylor, N. Reilly, R. E. Sargison, and H. K. F. Van Saene, “Antibiotic-resistant bacteria and infection in children with cerebral palsy requiring mechanical ventilation,” *Pediatric Critical Care Medicine*, vol. 10, no. 2, pp. 222–226, 2009.

[43] M. S. Edwards, M. A. Renc, and A. A. M. Haffar, “Long-term sequelae of group B streptococcal meningitis in infants,” *Journal of Pediatrics*, vol. 106, no. 5, pp. 717–722, 1985.

[44] Y. S. Kim, R. A. Sheldon, B. R. Elliott, Q. Liu, D. M. Ferriero, and M. G. Tauber, “Brain injury in experimental neonatal meningitis due to group B streptococci,” *Journal of Neurology and Experimental Neurology*, vol. 54, no. 4, pp. 531–539, 1995.

[45] S. L. Leib, Y. S. Kim, L. L. Chow, R. A. Sheldon, and M. G. Tauber, “Reactive oxygen intermediates contribute to necrotic and apoptotic neuronal injury in an infant rat model of bacterial meningitis due to group B streptococci,” *The Journal of Clinical Investigation*, vol. 98, no. 11, pp. 2632–2639, 1996.

[46] M. Bsibsi, R. Ravid, D. Gervic, and J. M. Van Noort, “Broad expression of Toll-like receptors in the human central nervous system,” *Journal of Neurology and Experimental Neurology*, vol. 61, no. 11, pp. 1013–1021, 2002.

[47] B. B. Mishra, U. M. Gundra, and J. M. Teale, “Expression and distribution of Toll-like receptors 11-13 in the brain during murine neurocysticercosis,” *Journal of Neuroinflammation*, vol. 5, article 53, 2008.

[48] B. B. Mishra, P. K. Mishra, and J. M. Teale, “Expression and distribution of Toll-like receptors in the brain during murine neurocysticercosis,” *Journal of Neuroimmunology*, vol. 181, no. 1-2, pp. 46–56, 2006.

[49] R. I. Tapping, S. Akashi, K. Miyake, P. J. Godowski, and P. S. Tobias, “Toll-like receptor 4, but not Toll-like receptor 2, is a signaling receptor for *Escherichia* and *Salmonella* lipopolysaccharides,” *Journal of Immunology*, vol. 165, no. 10, pp. 5780–5787, 2000.

[50] P. Henneke and R. Berner, “Interaction of neonatal phagocytes with interleukin-10,” *Infection and Immunity*, vol. 74, no. 6, pp. 3085–3095, 2006.

[51] E. Henglein and R. Berner, “Interaction of neonatal phagocytes with group B streptococcus: recognition and Response,” *Infection and Immunity*, vol. 74, no. 6, pp. 3085–3095, 2006.

[52] U. K. Hanisch, T. V. Johnson, and J. Kipnis, “Toll-like receptors: roles in neuroprotection?” *Trends in Neuroscience*, vol. 31, no. 4, pp. 176–182, 2008.

[53] R. Mittendorf, R. Covert, J. Kohn, N. Roizen, B. Khoshnood, and K. S. Lee, “Association between cerebral palsy and coagulase-negative staphylococci,” *The Lancet*, vol. 354, no. 9193, pp. 1875–1876, 1999.
proliferation,” *Journal of Neuroscience*, vol. 28, no. 51, pp. 13978–13984, 2008.

[54] Y. Ma, J. Li, I. Chiu et al., “Toll-like receptor 8 functions as a negative regulator of neurite outgrowth and inducer of neuronal apoptosis,” *Journal of Cell Biology*, vol. 175, no. 2, pp. 209–215, 2006.

[55] E. Okun, K. J. Griffioen, T. Gen Son et al., “TLR2 activation inhibits embryonic neural progenitor cell proliferation,” *Journal of Neurochemistry*, vol. 114, no. 2, pp. 462–474, 2010.

[56] L. Stridh, P. L.P. Smith, A. S. Naylor, X. Wang, and C. Mallard, “Regulation of Toll-like receptor 1 and -2 in neonatal mice brains after hypoxia-ischemia,” *Journal of Neuroinflammation*, vol. 8, article 85, 2011.

[57] A. Rolls, R. Shechter, A. London et al., “Toll-like receptors modulate adult hippocampal neurogenesis,” *Nature Cell Biology*, vol. 9, no. 9, pp. 1081–1088, 2007.

[58] J. R. Duncan, M. L. Cock, J. P. Y. Scheerlinck et al., “White matter injury after repeated endotoxin exposure in the preterm ovine fetus,” *Pediatric Research*, vol. 52, no. 6, pp. 941–949, 2002.

[59] C. Mallard, J. Patkai, J. C. Renauld, P. Evrard, and P. Gressens, “Proinflammatory cytokines and interleukin-9 exacerbate excitotoxic lesions of the newborn murine neopallium,” *Annals of Neurology*, vol. 47, no. 1, pp. 54–63, 2000.

[60] L. Yang, H. Sameshima, T. Ikeda, and T. Ikenoue, “Lipopolysaccharide induces both a primary and a secondary phase of sensitization in the developing rat brain,” *Pediatric Research*, vol. 58, no. 1, pp. 112–116, 2005.

[61] X. Wang, H. Hagberg, C. Nie, C. Zhu, T. Ikeda, and C. Mallard, “Dual role of intrauterine immune challenge on neonatal and adult brain vulnerability to hypoxia-ischemia,” *Journal of Neuropathology and Experimental Neurology*, vol. 66, no. 6, pp. 552–561, 2007.

[62] T. Ikeda, L. Yang, T. Ikenoue, C. Mallard, and H. Hagberg, “Endotoxin-induced hypoxic-ischemic tolerance is mediated by up-regulation of corticosterone in neonatal rat,” *Pediatric Research*, vol. 59, no. 1, pp. 56–60, 2006.

[63] J. Dean, Y. van de Looij, S. V. Sizonenko et al., “Delayed cortical signaling regulates acute neuronal toxicity of LPS-stimulated microglia:Involvement of p38 MAPK,” *Glia*, vol. 59, no. 5, pp. 785–799, 2011.

[64] F. Correa, E. Ljunggren, C. Mallard, M. Nilsson, S. G. Weber, and M. Sandberg, “The Nr2r-inducible antioxidant defense in astrocytes can be both up- and down-regulated by activated microglia:Involvement of p38 MAPK,” *Glia*, vol. 60, no. 7, pp. 743–755, 2011.

[65] L. Shi, S. E. P. Smith, N. Malkova, D. Tse, Y. Su, and P. H. Patterson, “Activation of the maternal immune system alters cerebellar development in the offspring,” *Brain, Behavior, and Immunity*, vol. 23, no. 1, pp. 116–123, 2009.

[66] A. Zuckerman and I. Weiner, “Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring,” *Journal of Psychiatric Research*, vol. 39, no. 3, pp. 311–323, 2005.

[67] U. Meyer, M. Nyffeler, B. K. Yee, I. Knuesel, and J. Feldon, “Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice,” *Brain, Behavior, and Immunity*, vol. 22, no. 4, pp. 469–486, 2008.

[68] M. Makinodan, K. Tatsumi, T. Manabe et al., “Maternal immune activation in mice delays myelination and axonal development in the hippocampus of the offspring,” *Journal of Neuroscience Research*, vol. 86, no. 10, pp. 2190–2200, 2008.

[69] L. Shi, S. E. P. Smith, N. Malkova, D. Tse, Y. Su, and P. H. Patterson, “Activation of the maternal immune system alters cerebellar development in the offspring,” *Brain, Behavior, and Immunity*, vol. 23, no. 1, pp. 116–123, 2009.