

## The Role of Inflammatory Cytokines in the Pathogenesis of Cerebral Palsy

Hua Di<sup>1</sup>, Qi He<sup>1</sup>, Yingye Liao<sup>1</sup>, Bill Kalionis<sup>2</sup> and Xiantao Tai<sup>1\*</sup>

<sup>1</sup>School of Acupuncture, Massage and Rehabilitation, Yunnan University of Traditional Chinese Medicine, Kunming 650500, Yunnan, PR China

<sup>2</sup>Department of Perinatal Medicine Pregnancy Research Centre and University of Melbourne Department of Obstetrics and Gynecology, Royal Women's Hospital, Parkville3052, Australia

\*Corresponding author: Xiantao Tai, School of Acupuncture, Massage and Rehabilitation, Yunnan University of Traditional Chinese Medicine, Kunming 650500, Yunnan, PR China, Tel: +86-871-65918024; Fax: +86-871- 65918153; E-mail: [taixiantao@163.com](mailto:taixiantao@163.com)

Rec date: Jan 31, 2016; Acc date: Feb 15, 2016; Pub date: Feb 17, 2016

Copyright: © 2016 Di H, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Cerebral palsy (CP) refers to a group of major neurodevelopmental disorders that affect movement and posture. CP results from damage to the developing brain during pregnancy, or shortly after birth and a growing body of research suggests that inflammation may play a vital role in its development. Here, we review the contribution of inflammatory cytokines (such as NF- $\kappa$  B, IL-6, IL-8, TNF- $\alpha$ ) to the mechanism of CP. Individual cytokines play specific roles in pathogenesis of CP but they also interact with each other and form a complex network of inflammatory reaction-regulating systems. Investigating the mechanisms of action of inflammatory cytokines in the development of CP may contribute not only to our understanding of the pathogenesis of CP but may also lead to more rational and effective intervention strategies.

**Keywords:** Cerebral palsy; Inflammation; Cytokine

### Abbreviations

NF- $\kappa$  B: Nuclear factor kappa B; IL-6: Interleukin-6; IL-17: Interleukin-17; IL-8: Interleukin-8; TNF- $\alpha$ : Tumor Necrosis Factor-alpha; IFN- $\gamma$ : Interferon- $\gamma$ ; MHC-I: Major Histocompatibility complex-I; MHC-II: Major Histocompatibility Complex-II; CD: Cluster of differentiation; MMPs: Matrix Metalloproteinases; VEGF: Vascular Endothelial Growth Factor

### Introduction

Cerebral palsy (CP) was defined at the recent Ninth China Pediatric Cerebral Palsy Conference (2006) as the syndrome caused by non-progressive brain damage and developmental defects from the moment of conception to infancy. The main manifestations of CP are movement disorders and abnormal posture CP may have many complications associated with progressive disease but should be excluded from the central movement disorders and normal children temporary motor retardation [1]. CP is one of the main disabling diseases in children, the clinical manifestations are diverse, and the etiology and pathogenesis is complex and poorly understood. In 1993, Adlinolfi et al. [2] hypothesized that abnormal expression of immune system cytokines may initiate the perinatal brain damage that causes cerebral palsy. Since then, increasing studies have focused on the potential contribution of inflammatory cytokines to the pathophysiology of brain injury [2-4]. The study of its mechanism has important implications for developing rational and effective strategies to prevent CP.

### The Function of Inflammatory Cytokines in Cerebral Palsy

The inflammatory reaction is an important part of the immune response and is closely associated with CP, which is consistent with

prior work from our team [5,6]. The inflammatory reaction involves factors associated with adhesion, metastasis, invasion, and activation of inflammatory cells, as well as the release of inflammatory cytokines. Various inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ), participate in the inflammatory reaction [7-9].

Current studies provide evidence that hypoxic-ischemic brain damage and perinatal intrauterine infection are primary risk factors for CP. Neurologic examinations reveal inflammatory cytokine concentrations in term infants born to mothers with clinical chorioamnionitis are associated with abnormalities. Infants who developed hypoxic-ischemic encephalopathy (HIE) had significantly higher cytokine concentrations. There is speculation that infection and hypoxic-ischemic brain both affect inflammatory cytokines, which may injure cerebral tissue [10,11]. Mounting evidence shows that the higher levels of pro-inflammatory cytokines (e.g. TNF- $\alpha$ , IL-6, IL-8) in the amniotic fluid, plasma, or umbilical cord blood are associated with the occurrence of periventricular leukomalacia (PVL) and CP [12-15]. PVL, is a common brain white matter lesion, and is frequently associated with CP. Some researchers suggest these cytokines could lead to white matter damage in the immature brain by promoting the production of other cytokines, and nitric oxide synthase (NO), which induce leukocyte infiltration as well as the expression of adhesion molecules that result in damage to oligodendrocytes. PVL and white matter damage (WMD) are the main neuronal pathological alterations of CP [16,17].

Animal models provide evidence that in addition to ischemia or reperfusion injury, inflammatory cytokine-induced brain injury may also play an important role in the pathogenesis of CP and PVL. Recently, reverse transcriptase PCR-based methods were used to compare gene expression profiles in brains of mouse pups exposed to lipopolysaccharide (LPS) in utero with those of saline-treated controls. The LPS-treated group showed varied increased levels of pro-inflammatory genes including monocyte chemoattractant protein-1 (MCP-1), IL-6, and interleukin-1 $\beta$  (IL-1 $\beta$ ). Thus a possible mechanism

for adverse neurological outcomes following maternal infection involves elevated cytokine levels [18,19]. Previous studies revealed that following injection of LPS into the uterus of pregnant rats, there was a dose-dependent increase in the expression of tumor necrosis factor- $\alpha$  and IL-1 $\beta$  mRNA in the fetal rat brain. Moreover, there were increased glial fibrillary acidic protein-positive astrocytes, decreased myelin basic protein and altered immunoreactivity of oligodendrocytes (OL) in the hippocampal and the cortex areas of the brain [20,21].

## Nuclear Factor kappa B

Nuclear factor kappa B (NF- $\kappa$ B), one of the multifunctional transcription factors, plays a significant role in the process of immune response, inflammatory reaction, cellular proliferation, survival, transformation and apoptosis. NF- $\kappa$  B is a heterodimer, which comprises two subunit p50 and p65, which efficiently induces diverse cytokines and other substances. These include interleukins (e.g. IL-1, IL-2, IL-6, IL-12), TNF- $\alpha$ , adhesion molecules (e.g. ICAM-1, VCAM-1, ELAM-1) and many enzymes (e.g. COX-2, iNOS) which participate in a cascade effect that culminates in an inflammatory reaction [22-24]. Under physiological conditions, a combination of NF- $\kappa$ B and its inhibitory factor (I- $\kappa$ B) remains in the cytoplasm. After stimulation by various extracellular signals, such as stress, virus infection, reactive oxygen species, free radicals, I- $\kappa$ B is phosphorylated, which releases NF- $\kappa$ B, and allows it to move from cytoplasm into nucleus and bind to promoter regions of its target genes. These target genes include those that initiate the transcriptional programs of immunity and inflammatory response-related genes [25,26].

Numerous studies provided evidence that NF- $\kappa$ B expression in the central nervous system is a potentially major player in brain damage [27-29]. Increasing data supports the notion that NF- $\kappa$ B may play a role in important aspects of human reproduction. In the human decidua, there was a significant increase in the nuclear localization of p65 in decidual tissues at term compared with preterm tissues. However, I- $\kappa$ B significantly increased in the cytoplasm of decidual tissues at term when compared with preterm tissues. These data highlight the potential importance of NF- $\kappa$ B in the control of parturition-related genes [30-32]. Human gestational tissue (placenta, amnion, and choriondecidua) explants treated with LPS, in the presence or absence of the inhibitor of NF- $\kappa$ B activation, sulfasalazine (SASP) showed that SASP treatment significantly inhibited NF- $\kappa$ B activation as well as the release of IL-6, IL-8, and TNF- $\alpha$ . This study demonstrated that NF- $\kappa$ B activation is important in the control of LPS-stimulated proinflammatory cytokine release from the above gestational tissues [33,34].

## Interleukins

Interleukins (IL) are small-molecule markers of inflammation but they are also regulatory proteins with a wide spectrum of activities. At present, more than 20 types of ILs are known. ILs can act by inducing cell differentiation and growth and by inducing functional receptors on the surface of cells that are closely related to those found in inflammatory reaction and the development and progression of cerebral palsy.

IL-6 is a vital inflammatory mediator which is involved in many pathologic and physiological processes of inflammatory disease. IL-6 levels in patient blood plasma acts as a sign of the activation of the cytokine cascade reaction and reflects the relatedness between inflammatory reaction and the severity of disease. There are significant

implications of latest findings in the study of IL-6 [35,36]. Umbilical cord plasma concentration of IL-6 is a significant, independent predictor of PVL-associated lesions. Preterm neonates born to mothers with increased amniotic fluid concentrations of pro-inflammatory cytokines, including IL-6, show increased risk of subsequently developing PVL and CP. Buhimschi et al. [37] provide evidence that amniotic fluid (AF) of women with intra-amniotic inflammation, and umbilical cord blood of neonates, have high levels of IL-6. As well, intra-amniotic inflammation is characterized by significantly elevated cord blood IL-6 levels. The cord blood-to-AF IL-6 ratio could be taken as a determinative indicator that reflects the severity of intra-amniotic inflammation and the inflammatory response in the fetus. In recent experiments, it was found that high IL-6 levels may be associated with an increased risk of neuronal cell necrosis [37,38]. Other researchers provide evidence that IL-6 could induce oligodendrocyte progenitor cells (OPC) to transform into astrocytes, and lead to myelination in the white matter [39,40]. Some researchers have demonstrated that exposure to IL-17A stimulates OPCs to mature and contribute to the inflammatory response [41].

Interleukin-8 (IL-8) is an important inflammatory mediator that is produced primarily by monocyte-macrophage cells, which has significant effects on the chemotaxis and activation of neutrophils, and IL-8 also participates in local inflammation. The mechanism of IL-8 action involves its adherence to the surface of vascular endothelial cells, by activating polymorphonuclear leukocyte (PMN), binding to ligand of chemotactic factors on the vascular endothelial cells. Passing through vascular endothelium along a concentration gradient which is formed by free chemotactic factors, it could enter into the tissue spaces [42,43]. IL-8 is associated with many stages of pregnancy. IL-8 levels in cervical secretions from patients with 37~42 weeks singleton pregnancies were measured by enzyme linked immunosorbent assay (ELISA). The analysis showed that measurement of IL-8 in cervical secretions is an effective method to identify patients at risk of chorioamnionitis [44]. To better understand the inflammatory response in the CNS after chorioamnionitis, mRNA levels of cytokines were determined in different regions of the CNS. Interleukin 1 $\beta$  levels increased in the hippocampus, cortex and cerebellum after LPS exposure, while IL-8 levels increased in the periventricular white matter. These data suggest that intra-amniotic LPS exposure causes acute and region-specific changes in inflammatory markers in the fetal brain [45].

## Tumor Necrosis Factor- $\alpha$

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is an important inflammatory mediator, which is involved in the earliest stages of the inflammatory reaction. TNF- $\alpha$  can activate neutrophils and lymphocytes, increase the permeability of endothelial cells, regulate metabolic activity of other tissues, promote the synthesis and secretion of other cytokines and participate in brain damage.

Hansen et al. studied 74 very preterm infants with a mean gestational age of 27.1 (2.0) weeks who displayed increased levels of proinflammatory cytokines, during the first 72 postnatal hours and then again at 2 years corrected age. Infants born preterm with increased concentrations of TNF- $\alpha$  and IL-6 in cord blood showed an increased risk of impaired developmental outcome and psychomotor developmental index (PDI) <85 at 2 years corrected age [46]. Moreover, increased concentrations of TNF- $\alpha$  in cord blood were associated with cerebral palsy [47,48]. Lin et al. compared 32 preterm children with PVL-induced CP, with the same number of control

preterm children with normal neurodevelopment and matched for gestational age, in order to determine whether preterm children with CP showed altered inflammatory responses at school-age [14]. The data show that TNF- $\alpha$  expression was significantly higher in the plasma ( $53 \pm 16$  pg/ml vs.  $10 \pm 4$  pg/ml,  $p < 0.001$ ) and supernatants of LPS-stimulated PBMCs ( $1736 \pm 252$  pg/ml vs.  $1031 \pm 135$  pg/ml,  $p = 0.003$ ) in the CP group than in the control group. Following LPS stimulation, intracellular levels of TNF- $\alpha$  in PBMCs was significantly higher in the CP group than in the control group. The nonstimulated PBMCs of the CP group also had significantly lower TLR-4 mRNA levels, toll-like receptor 4 (TLR-4), transforming growth factor-beta-activated kinase 1 (TAK1), Jun N-terminal kinase (JNK) and I-kappaB kinase-gamma (I $\kappa$ B kinase- $\gamma$ ) than in the control group. TLR-4 mRNA levels in PBMCs were highly correlated with TNF- $\alpha$  levels in the LPS-stimulated PBMCs. Compared with preterm children with normal neurodevelopment, preterm children with PVL had different inflammatory responses at school age. These changes included not only higher TNF- $\alpha$  level in the plasma, but also changes in the supernatants of LPS-stimulated PBMCs, and in proinflammatory gene expression in PBMCs.

TNF- $\alpha$  can stimulate endothelial cells to express chemokines and adhesion molecules and also change the permeability of blood brain barrier that attract inflammatory cells into the nervous tissue. These processes are associated with cerebral palsy. Vascular endothelial cells are main targets of TNF- $\alpha$  and interleukin-1beta (IL-1 $\beta$ ) and they stimulate endothelial cells to express adhesion molecules (ICAM-1), which attract leucocytes into the peripheral region [49-51]. There is high in situ expression of TNF- $\alpha$  and IL-1 $\beta$ , particularly TNF- $\alpha$ , in the brain tissue of children with PVL. Cell culture experiments show high expression of intercellular adhesion molecule-1 (ICAM-1) by endothelial cells, which is induced by TNF- $\alpha$ , IL-1 $\beta$  [52-54]. TNF- $\alpha$  and IL-6 in neonatal brain damage might link to the reduction of regional cerebral blood flow, which could affect coagulation systems, promote thrombus formation, and thereby induce brain ischemia and hypoxia, as well as generating an abnormal immune response. Furthermore, this could adversely affect OL, astrocytes and medullary sheaths [55,56].

Other researchers have concluded that TNF- $\alpha$  inhibits the differentiation of OPC, and influences the growth and development of myelin [57,58]. In a series of *in vitro* experiments, TNF- $\alpha$  was shown to eradicate OL and trigger apoptosis. The signaling pathway of TNF- $\alpha$  could increase the concentration of ceramide in the cytoplasm which in turn would induce apoptosis through accumulating two types of membrane receptors, caspase-8 and caspase-9, and activating caspase-3 or caspase-7, or activating sphingomyelinase [59-61].

### Other Cytokines

Increasing evidence implicates other cytokines, such as interferon- $\gamma$  (IFN- $\gamma$ ), as well as matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) in the occurrence and progression of CP [62-64].

INF- $\gamma$  is a key factor in central nervous system trauma and human neurodegenerative diseases. Macrophages and astrocytes that is immunoreactive for INF- $\gamma$  antibody, aggregate to the encephalomalacia of PVL children, which implicates INF- $\gamma$  in the pathogenesis of PVL. INF- $\gamma$  plays an important role in the process of PVL by up-regulating the expression of major histocompatibility complex-I (MHC-I), major histocompatibility complex-II (MHC-II),

and cluster of differentiation (CD) cell surface molecules. INF- $\gamma$  can stimulate the production of cytokines and generate a positive feedback effect [65,66]. MMPs are a family of zinc-dependent proteinases involved in the degradation of the extracellular matrix. Many tissue cell types generate and release MMPs, which are dependent on the zinc ion for their catalytic activity [67,68]. In the inflammatory reaction associated with central nervous system disease, MMPs have striking toxic effects on neurons, which could degrade the basal lamina and disrupt the blood-brain barrier, leading to vasogenic brain edema and hemorrhagic transformation [69-71]. Studies confirm the level of MMP-8 can be used to predict the risk of the development of PVL and CP in premature infants [72]. Other studies implicate MMP-9 in the initiation and progression of human labor and delivery, particularly in relation to premature rupture of fetal membranes and other pathological pregnancy conditions [73]. Hypoxic ischemic encephalopathy is a significant factor in the death of term infants and is an important pathogenic factor of cerebral palsy. VEGF promotes vascular endothelial cell proliferation, increases vascular permeability and accelerates neovascularization. Experiments to understand the role of VEGF in hypoxic-ischemic brain damage in animal models are now being reported [74-80]. VEGF may exert a direct neuroprotective effect on endothelial cells and astrocytes in brain by inducing angiogenesis, which directly or indirectly increases cerebral blood flow to ischemic area [81]. The potential model for how the cytokines are involved in CP, in Figure 1.

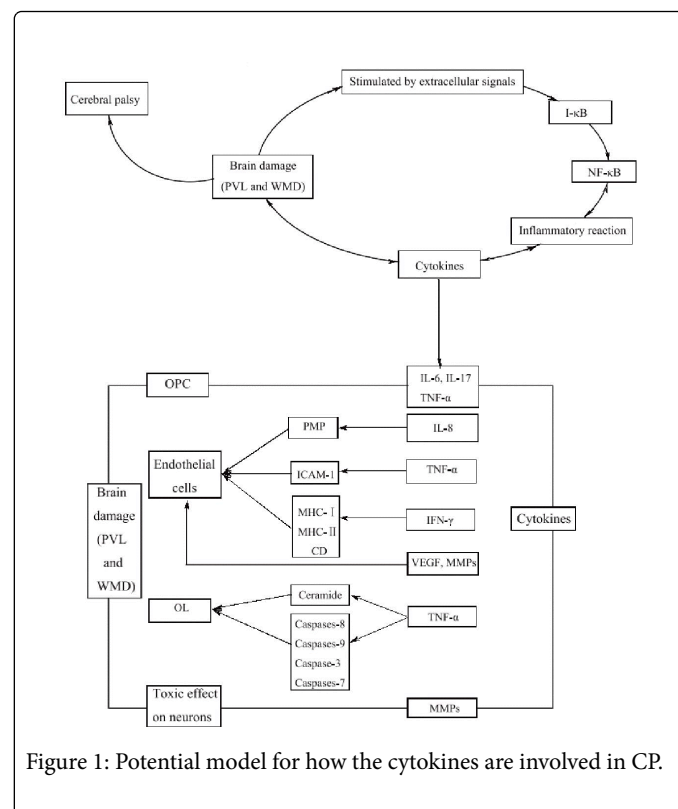


Figure 1: Potential model for how the cytokines are involved in CP.

### Placental Cytokines in the Pathogenesis of CP

CP is a non-progressive motor impairment syndrome and has no effective cure. The etiology of CP and other related perinatal brain injuries remains unknown. However, in the last decade, some evidence suggests that placental infarctions, disproportionate fetal growth, and

inflammatory conditions apparently limited to the placenta, are also associated with an increased risk of CP and other neurologic impairments [82-85]. Additionally, there is a growing body of evidence correlating CP with the production of placental cytokines, which could result in elevated fetal proinflammatory cytokine exposure, and culminate in the development of neonatal neurologic injury [86-88].

Cytokines	Effects	Source
NF-κB	NF-κ B is a heterodimer, which comprises two subunit p50 and p65, which efficiently induces diverse cytokines and other substances. These include interleukins, TNF-α, adhesion molecules and many enzymes which participate in the cascade of the inflammatory reaction.	[22-31]
IL-6	IL-6 is an important inflammatory mediator involved in many pathologic and physiological processes of inflammatory disease. IL-6 levels in the patient blood plasma act as an indicator of the activation of the cytokine cascade reaction.	[32-36]
IL-17	IL-17 exposure stimulates OPCs to mature and participate in the inflammatory response	[37]
IL-8	IL-8 is produced mainly from monocyte-macrophage cells and has significant effects on chemotaxis and activation of neutrophils, and also participates in local inflammation. IL-8 is involved in all stages of pregnancy.	[39-42]
TNF-α	TNF-α is an important inflammatory mediator and involved in the earliest events of the inflammatory reaction. Its actions include activation of neutrophils and lymphocytes, increasing the permeability of endothelial cells, regulating the metabolic activity of nearby tissues, promoting the synthesis and secretion of other cytokines and participation in brain damage.	[43-58]
IFN-γ	INF-γ play an important role in the process of PVL by up-regulating the expression of MHC-I, MHC-II and CD cell surface markers.	[62,63]
MMPs	MMPs are a family of zinc-dependent proteinases involved in the degradation of the extracellular matrix. In the inflammatory reaction of central nervous system disease, MMPs has a striking toxic effect on neurons which can lead to degradation of the basal lamina and disruption of the blood-brain barrier, leading to vasogenic brain edema and hemorrhagic transformation.	[64-73]
VEGF	VEGF promotes vascular endothelial cells to proliferate, increases vascular permeability and accelerates neovascularization.	[74-81]

Table 1: Summary of cytokines and their effects.

Within a prospective cohort study, levels of cytokines IL-1β, IL-6, IL-8, and TNF-α were determined by ELISA by enzyme-linked in maternal blood samples at rupture and delivery, as well as from fetal umbilical cord blood. These data show that inflammation of the fetal side of the placenta was associated with elevated maternal IL-6 and IL-8 at delivery and increased fetal IL-1β, IL-6, IL-8, and TNF-α [89]. The mechanism by which maternal infection can generate a placental inflammatory response was examined in rats exposed to lipopolysaccharide at preterm and near-term gestational ages. Placental cytokine production and activation of the Toll-like receptor 4 (TLR4) pathways were measured by ELISA and Western blot analysis. The finding suggested that preterm placentas may have a greater

placental cytokine response to lipopolysaccharide exposure. Moreover, increased phosphorylated NFκB was detected and this suggests that placental cytokine induction may occur in response to activation of the TLR4 pathway [90,91]. Elovitz et al. [92] found in a rodent model that minor inflammation in the uterus, which was insufficient to induce a maternal systemic response as determined by IL-6 levels, was nevertheless able to elicit a strong inflammatory cytokine response in the placenta, fetus and fetal brain and resulted in permanent changes in gene expression in the offspring [91].

In contrast, studies of inflammatory cytokines including IL-1, IL-6 IL-8 and TNF-α in neonatal blood of very premature infants failed to distinguish those infant with subsequent diagnoses of CP from control children. Other studies show that proinflammatory cytokines, TNF-α, IL-1β, and IL-6, do not cross the term placental barrier, as assessed by ex vivo perfusion experiments [92-94]. Clearly, studies are needed to clarify the contribution of the placenta, if any, to the pathogenesis of CP.

## Conclusion

In conclusion, inflammatory cytokines are likely to play a significant role in the pathogenesis of CP. While each of the inflammatory cytokines has its own characteristic properties and actions, specific combinations of inflammatory cytokines form a complex network that alters the inflammatory reaction and contributes to the pathogenesis of CP. However, the diversity and complexity of inflammatory cytokines limits our understanding of the pathophysiological mechanism underlying CP. Further research into the role of inflammatory cytokines in CP is an essential prerequisite to understanding their mechanism of action, and to developing effective therapies to treat or prevent CP. (The summary of cytokines and their effects were shown in Table 1.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## Acknowledgements

This work was supported by National Natural Science Foundation of China (Grant No. 81460748).

## References

1. Specialty Committee of children rehabilitation in Chinese Association of Rehabilitation Medicine (2007) Specialty Committee of Infantile Cerebral Palsy rehabilitation in China Association of Rehabilitation of Disabled Persons. Definition, diagnostic criteria and clinic classification of cerebral palsy. *Chinese Journal of Physical Medicine and Rehabilitation* 29: 309.
2. Adlinolfi M (1993) Infectious diseases in pregnancy, cytokines and neurological impairment: an hypothesis. *Dev Med Child Neurol* 35: 549-553.
3. Khaksari M, Abbasloo E, Dehghan F, Soltani Z, Asadikaram G (2015) The brain cytokine levels are modulated by estrogen following traumatic brain injury: Which estrogen receptor serves as modulator? *Int Immunopharmacol* 28: 279-287.
4. Camire RB, Beaulac HJ, Willis CL (2015) Transitory loss of glia and the subsequent modulation in inflammatory cytokines/chemokines regulate paracellular claudin-5 expression in endothelial cells. *J Neuroimmunol* 284: 57-66.
5. Ding JW, Tai XT, Xiong L, Yang XJ, Jia J, et al. (2012) Characteristics of inflammatory cytokine gene expression profiles of cerebral cortex and

- white matter of rats with hypoxic-ischemic cerebral palsy. *Journal of Chengdu Medical College* 7: 508-511.
6. Ding JW, Tai XT, Yang XJ, Hua JF, Liao YY, et al. (2012) Regulation of inflammatory cytokine genes in the therapy of massage rehabilitation for cerebral palsy. *Journal of Chengdu Medical College* 7: 527-532.
  7. Barton SK, Melville JM, Tolcos M, Polglase GR, McDougall AR, et al. (2015) Human Amnion Epithelial Cells Modulate Ventilation-Induced White Matter Pathology in Preterm Lambs. *Dev Neurosci* 37: 338-348.
  8. Li X, Shang Q, Zhang L (2014) Comparison of the efficacy of cord blood mononuclear cells (MNCs) and CD34+ cells for the treatment of neonatal mice with cerebral palsy. *Cell Biochem Biophys* 70: 1539-1544.
  9. Wang LF, Zhang J, Chen XC, He L, Zhao XY (2014) [Treatment of cerebral palsy children by integrative medical sequential method: a clinical efficacy observation]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 34: 431-434.
  10. Chau V, McFadden DE, Poskitt KJ, Miller SP (2014) Chorioamnionitis in the pathogenesis of brain injury in preterm infants. *Clin Perinatol* 41: 83-103.
  11. Shalak LF, Laptook AR, Jafri HS, Ramilo O, Perlman JM (2002) Clinical chorioamnionitis, elevated cytokines, and brain injury in term infants. *Pediatrics* 110: 673-680.
  12. Varner MW, Marshall NE, Rouse DJ, Jablonski KA, Leveno KJ, et al. (2015) The association of cord serum cytokines with neurodevelopmental outcomes. *Am J Perinatol* 30: 115-122.
  13. Tsukimori K, Komatsu H, Yoshimura T, Hikino S, Hara T, et al. (2007) Increased inflammatory markers are associated with early periventricular leukomalacia. *Dev Med Child Neurol* 49: 587-590.
  14. Lin CY, Chang YC, Wang ST, Lee TY, Lin CF, et al. (2010) Altered inflammatory responses in preterm children with cerebral palsy. *Ann Neurol* 68: 204-212.
  15. Kaukola T, Satyaraj E, Patel DD, Tchernev VT, Grimwade BG, et al. (2004) Cerebral palsy is characterized by protein mediators in cord serum. *Ann Neurol* 55: 186-194.
  16. Shang Q, Ma CY, Lv N, Lv ZL, Yan YB, et al. (2015) Clinical study of cerebral palsy in 408 children with periventricular leukomalacia. *Exp Ther Med* 9: 1336-1344.
  17. Harvey AR, Randall M, Reid SM, Lee KJ, Imms C, et al. (2013) Children with cerebral palsy and periventricular white matter injury: does gestational age affect functional outcome? *Res Dev Disabil* 34: 2500-2506.
  18. Kumral A, Baskin H, Yesilirmak DC, Ergur BU, Aykan S, et al. (2007) Erythropoietin attenuates lipopolysaccharide-induced white matter injury in the neonatal rat brain. *Neonatology* 92: 269-278.
  19. Liverman CS, Kaftan HA, Cui L, Hersperger SG, Taboada E, et al. (2006) Altered expression of pro-inflammatory and developmental genes in the fetal brain in a mouse model of maternal infection. *Neurosci Lett* 399: 220-225.
  20. Beloosesky R, Weiner Z, Ginsberg Y, Ross MG (2012) Maternal N-acetylcysteine (NAC) protects the rat fetal brain from inflammatory cytokine responses to lipopolysaccharide (LPS). *J Matern Fetal Neonatal Med* 25: 1324-1328.
  21. Cai Z, Pan ZL, Pang Y, Evans OB, Rhodes PG (2000) Cytokine induction in fetal rat brains and brain injury in neonatal rats after maternal lipopolysaccharide administration. *Pediatr Res* 47: 64-72.
  22. Kravtsova-Ivantsiv Y, Shomer I, Cohen-Kaplan V, Snijder B, Superti-Furga G, et al. (2015) KPC1-mediated ubiquitination and proteasomal processing of NF- $\kappa$  B1 p105 to p50 restricts tumor growth. *Cell* 161: 333-347.
  23. Wang L, Zhang J, Wang B, Wang G, Xu J (2015) Blocking HMGB1 signal pathway protects early radiation-induced lung injury. *Int J Clin Exp Pathol* 8: 4815-4822.
  24. Mizutani T, Ishizaka A, Furuichi Y (2015) The Werner Protein Acts as a Coactivator of Nuclear Factor  $\kappa$  B (NF- $\kappa$  B) on HIV-1 and Interleukin-8 (IL-8) Promoters. *J Biol Chem* 290: 18391-18399.
  25. Briscoe T, Duncan J, Cock M, Choo J, Rice G, et al. (2006) Activation of NF- $\kappa$ B transcription factor in the preterm ovine brain and placenta after acute LPS exposure. *J Neurosci Res* 83: 567-574.
  26. Saravanan S, Islam VI, Babu NP, Pandikumar P, Thirugnanasambantham K, et al. (2014) Swertiamarin attenuates inflammation mediators via modulating NF- $\kappa$  B/I  $\kappa$ B and JAK2/STAT3 transcription factors in adjuvant induced arthritis. *Eur J Pharm Sci* 56: 70-86.
  27. Zhao J, Zhang X, Dong L, Wen Y, Zheng X, et al. (2015) Cinnamaldehyde inhibits inflammation and brain damage in a mouse model of permanent cerebral ischaemia. *Br J Pharmacol* 172: 5009-5023.
  28. Ji G, Liu M, Zhao XF, Liu XY, Guo QL, et al. (2015) NF- $\kappa$  B Signaling is Involved in the Effects of Intranasally Engrafted Human Neural Stem Cells on Neurofunctional Improvements in Neonatal Rat Hypoxic-Ischemic Encephalopathy. *CNS Neurosci Ther* 21: 926-935.
  29. Li X, Zhang J, Zhu X, Wang P, Wang X, et al. (2015) Progesterone reduces inflammation and apoptosis in neonatal rats with hypoxic ischemic brain damage through the PI3K/Akt pathway. *Int J Clin Exp Med* 8: 8197-8203.
  30. Evans J, Salamonsen LA (2014) Decidualized human endometrial stromal cells are sensors of hormone withdrawal in the menstrual inflammatory cascade. *Biol Reprod* 90: 14.
  31. Yan X, Sun M, Gibb W (2002) Localization of nuclear factor-kappa B (NF kappa B) and inhibitory factor-kappa B (I kappa B) in human fetal membranes and decidua at term and preterm delivery. *Placenta* 23: 288-293.
  32. Lappas M (2012) Nuclear factor- $\kappa$  B mediates placental growth factor induced pro-labour mediators in human placenta. *Mol Hum Reprod* 18: 354-361.
  33. Lappas M, Permezel M, Georgiou HM, Rice GE (2002) Nuclear factor kappa B regulation of proinflammatory cytokines in human gestational tissues in vitro. *Biol Reprod* 67: 668-673.
  34. Lappas M, Permezel M, Rice GE (2003) N-Acetyl-cysteine inhibits phospholipid metabolism, proinflammatory cytokine release, protease activity, and nuclear factor-kappaB deoxyribonucleic acid-binding activity in human fetal membranes in vitro. *J Clin Endocrinol Metab* 88: 1723-1729.
  35. Nikolov A, Pavlova E, Yarukova N (2011) [Cerebral palsy--perinatal aspects]. *Akush Ginekol (Sofia)* 50: 37-44.
  36. Massaro G, Scaravilli G, Simeone S, Capuano S, Pastore E, et al. (2009) Interleukin-6 and Mycoplasma hominis as markers of preterm birth and related brain damage: our experience. *J Matern Fetal Neonatal Med* 22: 1063-1067.
  37. Buhimschi CS, Dulay AT, Abdel-Razeq S, Zhao G, Lee S, et al. (2009) Fetal inflammatory response in women with proteomic biomarkers characteristic of intra-amniotic inflammation and preterm birth. *BJOG* 116: 257-267.
  38. Kapitanović Vidak H, Catela Ivković T, Jokić M, Spaventi R, Kapitanović S (2012) The association between proinflammatory cytokine polymorphisms and cerebral palsy in very preterm infants. *Cytokine* 58: 57-64.
  39. Falahati S, Breu M, Waickman AT, Phillips AW, Arauz EJ, et al. (2013) Ischemia-induced neuroinflammation is associated with disrupted development of oligodendrocyte progenitors in a model of periventricular leukomalacia. *Dev Neurosci* 35: 182-196.
  40. Viscardi RM, Muhumuza CK, Rodriguez A, Fairchild KD, Sun CC, et al. (2004) Inflammatory markers in intrauterine and fetal blood and cerebrospinal fluid compartments are associated with adverse pulmonary and neurologic outcomes in preterm infants. *Pediatr Res* 55: 1009-1017.
  41. Rodgers JM, Robinson AP, Rosler ES, Lariosa-Willingham K, Persons RE, et al. (2015) IL-17A activates ERK1/2 and enhances differentiation of oligodendrocyte progenitor cells. *Glia* 63: 768-779.
  42. Jundi K, Greene CM (2015) Transcription of Interleukin-8: How Altered Regulation Can Affect Cystic Fibrosis Lung Disease. *Biomolecules* 5: 1386-1398.
  43. Capannolo M, Fasciani I, Romeo S, Aloisi G, Rossi M, et al. (2015) The atypical antipsychotic clozapine selectively inhibits interleukin 8 (IL-8)-induced neutrophil chemotaxis. *Eur Neuropsychopharmacol* 25: 413-424.

44. Yoneda S, Shiozaki A, Ito M, Yoneda N, Inada K, et al. (2015) Accurate Prediction of the Stage of Histological Chorioamnionitis before Delivery by Amniotic Fluid IL-8 Level. *Am J Reprod Immunol* 73: 568-576.
45. Strackx E, Sparnaaij MA, Vlassaks E, Jellema R, Kuypers E, et al. (2015) Lipopolysaccharide-induced chorioamnionitis causes acute inflammatory changes in the ovine central nervous system. *CNS Neurol Disord Drug Targets* 14: 77-84.
46. Hansen-Pupp I, Hallin AL, Hellström-Westas L, Cilio C, Berg AC, et al. (2008) Inflammation at birth is associated with subnormal development in very preterm infants. *Pediatr Res* 64: 183-188.
47. Kaukola T, Kallankari H, Tuimala J, Olsén P, Tammela O, et al. (2013) Perinatal immunoproteins predict the risk of cerebral palsy in preterm children. *Ann Med* 45: 57-65.
48. Wu YW, Croen LA, Vanderwerf A, Gelfand AA, Torres AR (2011) Candidate genes and risk for CP: a population-based study. *Pediatr Res* 70: 642-646.
49. Wei X, Zhang B, Zhang Y, Li H, Cheng L, et al. (2015) Hydrogen Sulfide Inhalation Improves Neurological Outcome via NF- $\kappa$  B-Mediated Inflammatory Pathway in a Rat Model of Cardiac Arrest and Resuscitation. *Cell Physiol Biochem* 36: 1527-1538.
50. Konsman JP, Drukarch B, Van Dam AM (2007) (Peri) vascular production and action of pro-inflammatory cytokines in brain pathology. *Clin Sci (Lond)* 112: 1-25.
51. Cronk JC, Derecki NC, Ji E, Xu Y, Lampano AE, et al. (2015) Methyl-CpG Binding Protein 2 Regulates Microglia and Macrophage Gene Expression in Response to Inflammatory Stimuli. *Immunity* 42: 679-691.
52. Kadhim H, Tabarki B, Verellen G, De Prez C, Rona AM, et al. (2001) Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. *Neurology* 56: 1278-1284.
53. Hofer N, Kothari R, Morris N, Müller W, Resch B (2013) The fetal inflammatory response syndrome is a risk factor for morbidity in preterm neonates. *Am J Obstet Gynecol* 209: 542.
54. Zhao WT, Yu HM (2013) [Research progress on periventricular white matter damage pathogenesis in preterm infants]. *Zhongguo Dang Dai Er Ke Za Zhi* 15: 396-400.
55. Zhao J, Chen Y, Xu Y, Pi G (2013) Effect of intrauterine infection on brain development and injury. *Int J Dev Neurosci* 31: 543-549.
56. Yawno T, Schuilwerve J, Moss TJ, Vosdoganes P, Westover AJ, et al. (2013) Human amnion epithelial cells reduce fetal brain injury in response to intrauterine inflammation. *Dev Neurosci* 35: 272-282.
57. Park H, Solis NV, Louie JS, Spellberg B, Rodriguez N, et al. (2014) Different tumor necrosis factor  $\alpha$  antagonists have different effects on host susceptibility to disseminated and oropharyngeal candidiasis in mice. *Virulence* 5: 625-629.
58. Lin W, Harding HP, Ron D, Popko B (2005) Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-gamma. *J Cell Biol* 169: 603-612.
59. Moylan JS, Smith JD, Wolf Horrell EM, McLean JB, Deevska GM, et al. (2014) Neutral sphingomyelinase-3 mediates TNF-stimulated oxidant activity in skeletal muscle. *Redox Biol* 2: 910-920.
60. Bartha AI, Foster-Barber A, Miller SP, Vigneron DB, Glidden DV, et al. (2004) Neonatal encephalopathy: association of cytokines with MR spectroscopy and outcome. *Pediatr Res* 56: 960-966.
61. Pang L, Zhao X, Liu W, Deng J, Tan X, et al. (2015) Anticancer Effect of Ursodeoxycholic Acid in Human Oral Squamous Carcinoma HSC-3 Cells through the Caspases. *Nutrients* 7: 3200-3218.
62. Hansen-Pupp I, Harling S, Berg AC, Cilio C, Hellström-Westas L, et al. (2005) Circulating interferon-gamma and white matter brain damage in preterm infants. *Pediatr Res* 58: 946-952.
63. Tan J, Zheng X, Zhang S, Yang Y, Wang X, et al. (2014) Response of the sensorimotor cortex of cerebral palsy rats receiving transplantation of vascular endothelial growth factor 165-transfected neural stem cells. *Neural Regen Res* 9: 1763-1769.
64. Gagliano N, Pelillo F, Chiriva-Internati M, Picciolini O, Costa F, et al. (2009) Expression profiling of genes involved in collagen turnover in tendons from cerebral palsy patients. *Connect Tissue Res* 50: 203-208.
65. Yesilirmak DC, Kumral A, Baskin H, Ergur BU, Aykan S, et al. (2007) Activated protein C reduces endotoxin-induced white matter injury in the developing rat brain. *Brain Res* 1164: 14-23.
66. Aarnink A, Dereuddre-Bosquet N, Vaslin B, Le Grand R, Winterton P, et al. (2011) Influence of the MHC genotype on the progression of experimental SIV infection in the Mauritian cynomolgus macaque. *Immunogenetics* 63: 267-274.
67. Silva ML, Ribeiro AP, Silva GA, Sanchez IX, Renzo R, et al. (2015) Expressions of matrix metalloproteinases-1 and -9 and opioid growth factor in rabbit cornea after lamellar keratectomy and treatment with 1% nalbuphine. *Arq Bras Oftalmol* 78: 141-145.
68. Lu S, Xiao X, Cheng M (2015) Matrine inhibits IL-1 $\beta$ -induced expression of matrix metalloproteinases by suppressing the activation of MAPK and NF- $\kappa$ B in human chondrocytes in vitro. *Int J Clin Exp Pathol* 8: 4764-4772.
69. Leonardo CC, Eakin AK, Ajmo JM, Gottschall PE (2008) Versican and brevican are expressed with distinct pathology in neonatal hypoxic-ischemic injury. *J Neurosci Res* 86: 1106-1114.
70. Gao D, Ding F, Lei G, Luan G, Zhang S, et al. (2015) Effects of focal mild hypothermia on thrombin-induced brain edema formation and the expression of protease activated receptor-1, matrix metalloproteinase-9 and aquaporin 4 in rats. *Mol Med Rep* 11: 3009-3014.
71. Petrovska-Cvetkovska D, Dolnec-Baneva N, Nikodijevik D, Chepreganova-Changovska T (2014) Correlative study between serum matrix metalloproteinase 9 values and neurologic deficit in acute, primary, supratentorial, intracerebral haemorrhage. *Prilozi* 35: 39-44.
72. Park CW, Kim SM, Park JS, Jun JK, Yoon BH (2014) Fetal, amniotic and maternal inflammatory responses in early stage of ascending intrauterine infection, inflammation restricted to chorio-decidua, in preterm gestation. *J Matern Fetal Neonatal Med* 27: 98-105.
73. Ozdamar O, Gün I, Müngen E, Atay V (2014) The assessment of the relationship between amniotic fluid matrix metalloproteinase-9 and zinc levels with adverse obstetric outcomes. *Arch Gynecol Obstet* 290: 59-64.
74. Kong L, Bhatt AR, Demny AB, Coats DK, Li A, et al. (2015) Pharmacokinetics of bevacizumab and its effects on serum VEGF and IGF-1 in infants with retinopathy of prematurity. *Invest Ophthalmol Vis Sci* 56: 956-961.
75. Harrigan MR, Ennis SR, Masada T, Keep RF (2002) Intraventricular infusion of vascular endothelial growth factor promotes cerebral angiogenesis with minimal brain edema. *Neurosurgery* 50: 589-598.
76. Zheng XR, Zhang SS, Yin F, Tang JL, Yang YJ, et al. (2012) Neuroprotection of VEGF-expression neural stem cells in neonatal cerebral palsy rats. *Behav Brain Res* 230: 108-115.
77. El Ghazi F, Desfeux A, Brasse-Lagnel C, Roux C, Lesueur C, et al. (2012) NO-dependent protective effect of VEGF against excitotoxicity on layer VI of the developing cerebral cortex. *Neurobiol Dis* 45: 871-886.
78. Vasiljevic B, Maglajlic-Djukic S, Gojnic M, Stankovic S, Ignjatovic S, et al. (2011) New insights into the pathogenesis of perinatal hypoxic-ischemic brain injury. *Pediatr Int* 53: 454-462.
79. Bain JM, Moore L, Ren Z, Simonishvili S, Levison SW (2013) Vascular endothelial growth factors A and C are induced in the SVZ following neonatal hypoxia-ischemia and exert different effects on neonatal glial progenitors. *Transl Stroke Res* 4: 158-170.
80. Wang F, Shen Y, Tsuru E, Yamashita T, Baba N, et al. (2015) Syngeneic transplantation of newborn splenocytes in a murine model of neonatal ischemia-reperfusion brain injury. *J Matern Fetal Neonatal Med* 28: 842-847.
81. Yoshimura S, Morishita R, Hayashi K, Kokuzawa J, Aoki M, et al. (2002) Gene transfer of hepatocyte growth factor to subarachnoid space in cerebral hypoperfusion model. *Hypertension* 39: 1028-1034.
82. Streja E, Miller JE, Wu C, Bech BH, Pedersen LH, et al. (2015) Disproportionate fetal growth and the risk for congenital cerebral palsy in singleton births. *PLoS One* 10: e0126743.

83. Vinnars MT, Vollmer B, Nasiell J, Papadogiannakis N, Westgren M (2015) Association between cerebral palsy and microscopically verified placental infarction in extremely preterm infants. *Acta Obstet Gynecol Scand* 94: 976-982.
84. Burke CJ, Tannenberg AE (1995) Prenatal brain damage and placental infarction—an autopsy study. *Dev Med Child Neurol* 37: 555-562.
85. Strand KM, Andersen GL, Haavaldsen C, Vik T, Eskild A (2015) Association of placental weight with cerebral palsy: population-based cohort study in Norway. *BJOG*.
86. Jacobsson B, Ahlin K, Francis A, Hagberg G, Hagberg H, et al. (2008) Cerebral palsy and restricted growth status at birth: population-based case-control study. *BJOG* 115: 1250-1255.
87. Vedovato S, Zanardo V (2010) [Chorioamnionitis and inflammatory disease in the premature newborn infant]. *Minerva Pediatr* 62: 155-156.
88. Girard S, Tremblay L, Lepage M, Sébire G (2010) IL-1 receptor antagonist protects against placental and neurodevelopmental defects induced by maternal inflammation. *J Immunol* 184: 3997-4005.
89. Redline RW (2007) Infections and other inflammatory conditions. *Semin Diagn Pathol* 24: 5-13.
90. Armstrong-Wells J, Donnelly M, Post MD, Manco-Johnson MJ, Winn VD, et al. (2015) Inflammatory predictors of neurologic disability after preterm premature rupture of membranes. *Am J Obstet Gynecol* 212: e1-e9.
91. Boles JL, Ross MG, Beloosesky R, Desai M, Belkacemi L (2012) Placental-mediated increased cytokine response to lipopolysaccharides: a potential mechanism for enhanced inflammation susceptibility of the preterm fetus. *J Inflamm Res* 5: 67-75.
92. Elovitz MA, Brown AG, Breen K, Anton L, Maubert M, et al. (2011) Intrauterine inflammation, insufficient to induce parturition, still evokes fetal and neonatal brain injury. *Int J Dev Neurosci* 29: 663-671.
93. Nelson KB, Grether JK, Dambrosia JM, Walsh E, Kohler S, et al. (2003) Neonatal cytokines and cerebral palsy in very preterm infants. *Pediatr Res* 53: 600-607.
94. Aaltonen R, Heikkinen T, Hakala K, Laine K, Alanen A (2005) Transfer of proinflammatory cytokines across term placenta. *Obstet Gynecol* 106: 802-807.