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The Role of Inflammatory Cytokines in the Pathogenesis of Cerebral Palsy

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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-κ B, IL-6, IL-8, TNF-α) 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-κ B: Nuclear factor kappa B; IL-6: Interleukin-6; IL-17: Interleukin-17; IL-8: Interleukin-8; TNF-α: Tumor Necrosis Factor-alpha; IFN-γ: Interferon-γ; 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-α), 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-α, 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-1β (IL-1β). 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 uteruses of pregnant rats, there was a dose-dependent increase in the expression of tumor necrosis factor-α and IL 1-β mRNA in the fetal rat brain. Moreover, there were increased glial fibrillary acidic protein–positive astrocytes, decreased myelin basic protein and altered immunoreactivity of o1igodendrocytes (OL) in the hippocampal and the cortex areas of the brain [20,21].

Nuclear Factor kappa B

Nuclear factor kappa B (NF-κB), 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-κ 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-, IL-2, IL-6, IL-12), TNF-α, 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-κB and its inhibitory factor (I-κB) remains in the cytoplasm. After stimulation by various extracellular signals, such as stress, virus infection, reactive oxygen species, free radicals, I-κB is phosphorylated, which releases NF-κB, and allows it to it 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-κB expression in the central nervous system is a potentially major player in brain damage [27-29]. Increasing data supports the notion that NF-κB 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-κB significantly increased in the cytoplasm of decidual tissues at term when compared with preterm tissues. These data highlight the potential importance of NF-κB in the control of parturition-related genes [30-32]. Human gestational tissue (placenta, amnion, and choriodecidua) explants treated with LPS, in the presence or absence of the inhibitor of NF-κB activation, sulfasalazine (SASP) showed that SASP treatment significantly inhibited NF-κB activation as well as the release of IL-6, IL-8, and TNF-α. This study demonstrated that NF-κB 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 1β 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-α

Tumor necrosis factor- α (TNF-α) is an important inflammatory mediator, which is involved in the earliest stages of the inflammatory reaction. TNF-α can activate neutrophils and lymphocytes, increase the permeability of endothelial cells, regulate metabolic activity of other tissues, promote the synthesis and secreti on 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 2years corrected age. Infants born preterm with increased concentrations of TNF-α and IL-6 in cord blood showed an increased risk of impaired developmental outcome and psychomotor developmental index (PDL) <85 at 2 years corrected age [46]. Moreover, increased concentrations of TNF-α 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-α expression was significantly higher in the plasma (53 ± 16 pg/ml vs. 10± 4 pg/ml, p<0.001) and supernatants of LPS-stimulated PBMCs (1736 ± 252 pg/ml vs. 1031 ± 135 pg/ml, p=0.003) in the CP group than in the control group. Following LPS stimulation, intracellular levels of TNF-α 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 (IκB kinase-γ) than in the control group. TLR-4 mRNA levels in PBMCs were highly correlated with TNF-α 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-α level in the plasma, but also changes in the supernatants of LPS-stimulated PBMCs, and in proinflammatory gene expression in PBMCs.

TNF-α 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-α and interleukin-1beta (IL-1β) 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-α and IL-1β, particularly TNF-α, 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-α, IL-1β [52-54]. TNF-α 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-α inhibits the differentiation of OPC, and influences the growth and development of myelin [57,58]. In a series of *in vitro* experiments, TNF-α was shown to eradicate OL and trigger apoptotsis. The signaling pathway of TNF-α 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-γ (IFN-γ), as well as matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) in the occurrence and progression of CP [62-64].

INF-γ is a key factor in central nervous system trauma and human neurodegenerative diseases. Macrophages and astrocytes that is immunoreactive for INF-γ antibody, aggregate to the encephalomalacia of PVL children, which implicates INF-γ in the pathogenesis of PVL. INF-γ 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-γ 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.

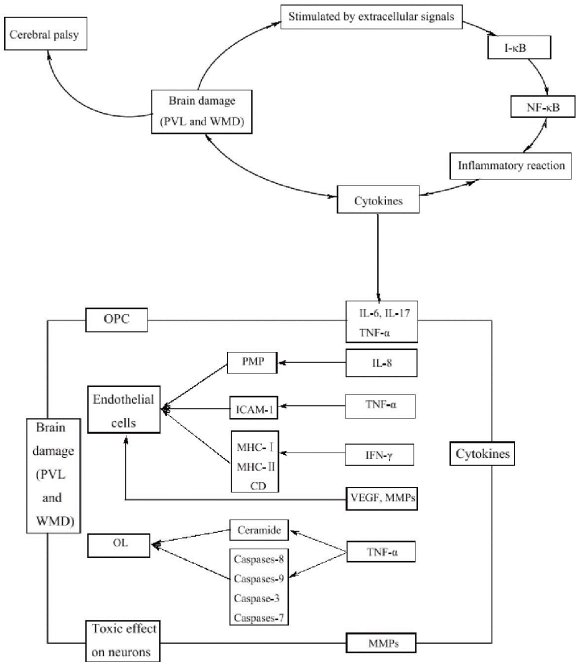

Figure 1: Potential model for how the cytokines are involved in CP.

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.

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