Review paper

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Underlying causes of cerebral palsy: public health perspectives

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Abstract

Cerebral palsy (CP) is a neurological pathology that is characterized by a combination of signs and symptoms that occur in neurodegenerative or metabolic disorder during the first few years of life. It is a complex pathology orchestrated by a plethora of different causes. The current diagnostic regimen for CP involves brain magnetic resonance imaging (MRI), and antenatal and perinatal insult. Despite advances in the field of genetics and molecular biology, the evaluating the underlying causes of this severe pathology are still bleak. In this review we have attempted to provide a landscape of the underlying mechanisms of cerebral palsy. We have partitioned this review broadly into genetic and proteomic-based studies, which have enriched our understanding about the pathogenesis of CP.

Key words: *cerebral palsy, neuropathology, disease.*

Introduction

Cerebral palsy (CP) is a major neurodevelopmental disorder that has been reported to affect 1 in 500 children. The causative factors and aetiology of this particular pathology are still obscure [3]. Despite its complex aetiology, magnetic resonance imaging (MRI) has remained an efficient way to diagnose CP. In addition to this hypoxia-ischaemia, placental insufficiency and prenatal infections are well-reported causes to diagnose CP. Despite these advents, the exact cause of this complex disease is still illusive [9,35]. Hypoxic ischaemic injury has been affiliated with the development of CP; it has been estimated that intrapartum hypoxia ischaemia is responsible for nearly 10% cases of CP [43]. Although there have been improvements in obstetric practices, and better antenatal and perinatal care, the incidence rate of CP has increased over the past decades. This has led to the speculation that there are unknown pathophysiological processes that are responsible for the significant elevation of CP cases worldwide. New research has shed light on the involvement of genetic and epigenetic factors in the development of CP. These factors have been estimated to play a significant role in disease aetiology and prevalence. Nearly 30% cases of CP have been reported to involve genetic changes [20]. There has been a growing consensus that dictates the involvement of genetic contribution in the development of CP. Characteristically 4 types of genetic variations play a vital role in the pathogenesis of CP [20]. Understanding these variations can open up new avenues in the detection diagnosis and treatment of CP. Genetic mutations are a continuous threat to the normal cellular function and can trigger aberrant expression of proteins, which ultimately leads to loss of normal cellular functionality. In addition to this genetic predisposition are the main events that determine the genetics

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of CP. Despite their clear involvement in the development of CP, very few studies have been published that address the genetic basis of CP. Advancements in the field of molecular biology, genome-wide association studies (GWAS), RNA-seq, proteomics, and RNAi have brought us a step closer to unravelling the complexities of the human genome and pinpointing genetic variations responsible for the development of various genetic diseases [33]. Despite this understanding, the molecular basis of CP remains unknown. Aberrant neurobiological pathways are the hallmark of CP [20]. Therefore, understanding the genetic aberrations responsible for triggering these neurobiological pathways seems a promising diagnostic/prognostic approach for CP. CP is a complex disease that involves a number of genetic variations and deregulated protein networks, which trigger oxidative stress, inflammation, and ischaemia, leading to neuronal death [8]. Similarly to other neuronal motor diseases such as autism and intellectual disability, understanding the genetics can aid in the development of a framework for the elaboration of the fundamental neurobiological pathways involved in CP [10]. Interestingly, findings to date indicate that a plethora of genes are involved in the development of CP and the majority of these genes are still undiscovered [10]. Genetic mutations in combination with environmental factors determine the outcome of a mutation. Some genetic variations, such as deleterious mutations, are less significant because they do not disrupt protein function and have less profound effects on genes while some mutations are lethal because they profoundly distort the protein and lead to major effects. However, it has been reported that deleterious mutations in combination with environmental factors can transform less damaging mutations into more adverse anomalies. Therefore, some infants with severe variations survive for a relatively long time, while infants having minor variations may not survive for long. This has been well observed in animal models developed for CP.

Epigenetic modifications play a significant role in wide-ranging diseases [12].

Certain exciting studies have provided clues about important genes that may epigenetically contribute to the development and occurrence of cerebral palsy in monozygotic twins [19]. In another study, a team of researchers identified differentially methylated regions in monozygotic twins discordant for CP [31]. However, clinicians still have an incomplete understanding about detailed epigenetic landscape that operates during pathology of cerebral palsy.

Oxidative stress and hypoxia play critical roles in different diseases [29,37]. Likewise, oxidative stress is a causative factor in cerebral palsy. N-acetylcysteine (NAC) was conjugated to PAMAM dendrimers (D-NAC) for the drug delivery across the blood-brain barrier into cells linked with neuro-inflammation [48]. Neuroinflammatory models with newborn motor deficits that mimicked human CP were generated by injection of *Escherichia coli* endotoxin into the uterus of pregnant rabbit dams. Accordingly, within 6 hours of birth, D-NAC was administered intravenously into the kits. Importantly, the kits that received D-NAC demonstrated significantly improved motor control, hypertonia, and coordination [48].

Noteworthy breakthroughs in functional genomics and proteomics have dramatically enhanced our concepts about contributory role of cell signalling pathways in development and diseases [11,13,14,16,17].

Accumulating evidence has shed light on the fact that alteration in the typical molecular signalling pathways specifically involved in the transcription, translation, synaptic function, development of cellular infrastructure, circuitry, neuronal glial signalling, and inflammation can lead to human disease, and their outcomes can be studied in animal models [4]. This can be accurate for CP as well, and devising a genetic model for CP will help to unravel the complexities of this peculiar disease. Advanced genomic studies have helped us in many ways to understand the genetic basis of CP. For instance, genetic association studies have demonstrated that DNA variants (single nucleotide polymorphisms [SNPs]) play a crucial role in determining the susceptibility of an individual towards genetic alteration and their outcomes to an injury or external factors such as thrombosis or haemorrhage. These DNA variants influence the motor outcomes caused by the injury (haemorrhage or thrombosis). Single nucleotide polymorphisms produced through DNA variants are pivotal for the development of CP in a given individual. Copy number variants (CNVs) produced through duplication or deletion account for 20% of CP cases. CNVs studies have been found an interesting approach to delineate the complexities of the CP neurobiology by understanding the deleted/duplicated region of genomic interval. CNVs are crucial diagnostic/prognostic tools for characterizing CP. In addition to CNVs, human-genome sequencing has enabled the

identification of single gene mutations that can lead to the development of CP. These mutations are rare but have adverse outcomes [30].

Genetic causes of cerebral palsy

There are many stumbling blocks that have impeded genetic studies of CP. Insufficient sample size, heterogeneity of samples, and lack of functional validation are the major complications that have slowed the progress in this field. Therefore, only a handful of genes have been discovered so far; however, a number of studies are near to completion, which will broaden our understanding of CP. Gene association studies have been implemented to characterize single nucleotide variants that were found to increase the risk of developing CP. Meta-analysis studies have revealed that polymorphisms present in methylenetetrahydrofolate reductase, apolipoprotein E (ApoE), coagulation factor II-VII, interleukin 6 (IL-6), endothelial nitric oxide synthase, fibrinogen β-polypeptide, plasminogen activator inhibitor 1, tumour necrosis factor α/β, lymphotoxin α precursor, adductin-1, and β-adrenergic receptor were not involved in causing CP. However, IL-6 (rs1800795) was found to be significantly associated [47].

Apolipoprotein E (ApoE) plays a pivotal role in the central nervous system. APOEε2 and APOEε4 genotypes might serve as susceptibility factors in determining neurological outcomes after perinatal brain injury [22]. It has also been previously reported that children with APOEε2/APOEε4 alleles are more likely to die following cerebral injury in the uterus [42].

The presence of the APOEε4 allele was strongly associated with more severe fine motor impairment among children with spastic unilateral cerebral palsy [26].

However, surprisingly, another team of researchers did not find any correlation and reported that APOE had no correlation in a direct way to the developmental sequelae of white or grey matter injuries in extremely preterm infants [5].

Osteopontin is a soluble immune factor involved in axonal regrowth and synaptogenesis after injury. An SNP, namely rs1126616 in the osteopontin gene, has been involved in nearly 700 Chinese patients [39]. These findings suggest that neuronal injuries can be a susceptible cause towards the development of CP, but further evidence is required to validate these results.

Courtesy of next-generation sequencing, a number of genes have been shown to contribute to the pathogenesis of CP. Emerging evidence is providing information about the underlying mechanisms of CP and how cellular pathways crosstalk for the regulation of oxidative stress and inflammation. Surprisingly, linking these genetic mutations to the vital neuronal pathways involved in CP can unravel their important role in neurodevelopmental processes.

Targeted next generation sequencing and whole exome sequencing have aided in the identification of point mutations in the genes *ITPR1*, *KCNC3*, and *SPTBN2* in subjects with ataxic CP [36].

Adaptor protein complex mutations have been linked with CP. AP-4 is a heterotetrameric adaptor protein complex produced by adaptor proteins, which modulates cell trafficking. AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor has been reported to be involved in receptor mediated glutamate excitotoxicity, which in turn promotes hypoxic-ischaemic white matter injury that in turn promotes CP. However AP-4 has been reported to control the cellular trafficking of AMPA and thus prevent excitotoxicity [32]. However, mutations in AP-4 complex can result in AMPA receptor-mediated glutamate excitotoxicity, which leads to hypoxic ischaemia. This mechanism has been shown in a number of CP cases. Patients harbouring AP-4 mutations are prone to develop quadriplegia, microcephaly, intellectual disability, and stunted growth. In addition to this, patients also develop lack of expressive speech [1]. Colpocephaly, decreased white matter, and cerebellar volume loss were also prominent [1].

Preclinical studies

Interestingly, studies have shown that perinatal cerebral hypoxic ischaemic injuries as well as inflammatory injuries are the main causes of cerebral palsy. PLPPR5 is an integral membrane molecule of the plasticity-related family of proteins [44]. It is expressed specifically in spinal cord as well as brain and drives the growth of the neurites. Moreover, it is significantly expressed in the brain, particularly in the regions of higher plasticity, such as the hippocampus. These signals are slightly low in the cerebellum, the cortex, as well as in the striata. Importantly, during the developmental process, expression of PLPPR5 is significant in the spinal cord. Evidently,

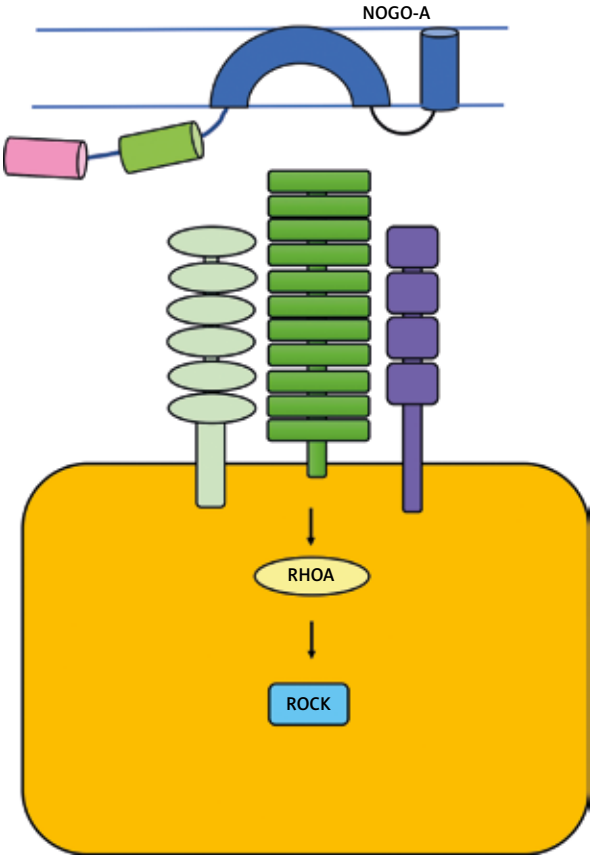

Fig. 1. NOGO-A on cell membranes interacts with multi-subunit receptors comprising ligand binding, signal transduction, and associated proteins.

expression of PLPPR5 mRNA was high in neuron-rich regions, particularly in medial motor nuclei. It has been suggested that PLPPR5 plays a critical part in the modulation of neurons. Experimental analysis indicates that wild-type mice having hypoxic-ischaemic brain injury show better performance as compared to PLPPR5–/– mice, irrespective of melatonin treatment. Moreover, melatonin treatment improves behaviour in the tests for wild-type animal models with hypoxic-ischaemic brain injuries, but not for PLPPR5–/– mice [44].

NOGO-A was characterized initially as a central nervous system-specific inhibitor of axonal regeneration. Scientists have sufficient evidence about regulatory roles of NOGO molecules and their specific receptors in precursor migration, growth of neurites, branching in the developing nervous system as well as a growth-inhibitory role during maturation of the

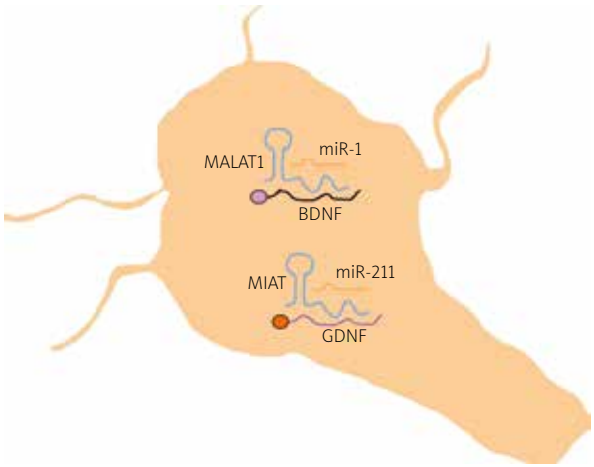

Fig. 2. MALAT1 and MIAT blocked neuronal cell death.

central nervous system. Constraint-induced movement therapy (CIMT) promoted the remodelling of neurons and functional reorganization through inhibition of NOGO-A/NgR/RhoA/ROCK signalling in hemiplegic cerebral palsy mice. CIMT promoted sprouting of the axons and post-stroke motor recovery by blockade of NOGO-A/RhoA/ROCK transduction cascade (Fig. 1) [28].

Non-coding RNAs have been reported to play a fundamental role in different diseases [2].

Vitamin B_1 and B_{12} efficiently inhibited neuronal apoptosis by caucusing blockade of miRNA-mediated targeting of brain-derived neurotrophic factor (BDNF) [24]. miR-1 directly targeted BDNF and enhanced neuronal apoptosis, but MALAT1 interfered with miR-1-mediated targeting of BDNF (Fig. 2). MALAT1 and BDNF levels were found to be reduced in the rodent models of cerebral palsy, but they were restored by treatment with vitamin B_1 and B_{12}. More importantly, vitamin B_1 and B_{12} did not enhance the levels of BDNF and MALAT1 in mice treated with short interfering RNAs for MALAT1 [24]. Moreover, circumstantial evidence indicates that MIAT overexpression reduces apoptotic death of Neuro2A cells [23]. Glial cell line-derived neurotrophic factor (GDNF) was essential for the protection of neurons. MIAT inhibited miR-211-mediated targeting of GDNF (Fig. 2). MIAT overexpression improved motor function of rats with hypoxic-ischaemic (HI) injuries. MIAT was transfected into mice. Long non-coding RNA MIAT was upregulated in striatal tissues of lenti-MIAT-treated groups, while miR-211 was reported

to be reduced considerably. Importantly, expression of GDNF was upregulated in striatal tissues of lenti-MIAT-treated groups. MIAT antagonized miR-211-mediated targeting of GDNF [23].

Natural products can be considered s key to different questions. Natural products have been shown to be highly effective against a broad spectrum of diseases [6,15,27,38].

Gastrodin is a traditional Chinese medicine [18]. Gastrodin is a biologically active product and promotes gross and fine motor performance. Gastrodin prompts the differentiation of macrophage into M2 phenotype by upregulation of BCL6. Gastrodin evidently suppresses H_2O_2-induced apoptotic death in RAW264.7 cells, and these effects are abrogated in BCL6-silenced cells. Subcutaneous injections of Gastrodin at acupuncture points were reported to be an effective, cost-effective, and less-invasive method for the improvement of motor performance in cerebral palsy patients [18].

Intracerebrally transplanted $CD34^+$ haematopoietic stem cells effectively improved sensorimotor performances in hypoxia-ischaemic injury-induced mice. Notably, the treatment also considerably improved hypoxia-ischaemic injury-induced exploratory behaviours and locomotion impairments [7].

Mouse pups were subjected to hypoxia-ischaemia and lipopolysaccharide-induced inflammation (HIL) in an experimental model of cerebral palsy, leading to neuronal injuries in periventricular white matter, neocortex, and hippocampus [41]. Rapamycin (sirolimus), a macrolide compound, has been shown to be an effective inhibitor of mTOR. Rapamycin remarkably blocked laminar disorganization following HIL in the hippocampus of experimental animals. The structure of the hippocampus 1 week and 1 month after treatment with rapamycin was intact in HIL-induced models of CP [41].

Nanotechnological delivery of therapeutic agents has gained interest [25,34,45,46].

CD11b is expressed on the surface of activated microglia that are involved in neurodegeneration and inflammation [21]. It is upregulated by oxidative stress and plays a crucial role in the exacerbation of the neuro-inflammatory processes. Dendrimer-based N-acetyl-l-cysteine (NAC) treatment suppressed neuro-inflammation and markedly improved motor functions in the CP kits. Neuroinflammation is associated with loss of myelination, resulting in the characteristic white matter injuries observed in CP. Dendrimer-based NAC led to a significant increase in myelin in the kits [21].

A wealth of information has shown that activation of microglia can induce neuronal damage through the release of proinflammatory cytokines, ROS, and free radicals. Dendrimer-minocycline conjugates facilitated minocycline to cross the blood-brain barrier and to target activated microglia at the injury sites [40].

Conclusions

Accumulating evidence has begun to shed light on the involvement of genetics in CP. Microarray analysis of CP patients with unknown aetiology can be used as a unifying diagnostic tool for the detection CP. Moreover, progress in whole exome sequencing could be implemented to further delineate the underlying genetic predispositions responsible for CP. The rapidly expanding list of regulators of CP will enable scientists to unravel the complexities of CP and devise new diagnostic strategies that will enable rapid detection. But still many validating studies are needed. Collectively, a large number of genomic discoveries followed by extensive *in vitro* and *in vivo* studies will broaden our understanding of the molecular mechanism involved in CP. This will help in the treatment of fundamental pathophysiology of CP at an early stage.

Disclosure

The authors report no conflict of interest.

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