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Impaired oligodendrocyte maturation in preterm infants: Potential therapeutic targets

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ABSTRACT

Preterm birth is an evolving challenge in neonatal health care. Despite declining mortality rates among extremely premature neonates, morbidity rates remain very high. Currently, perinatal diffuse white matter injury (WMI) is the most commonly observed type of brain injury in preterm infants and has become an important research area. Diffuse WMI is associated with impaired cognitive, sensory and psychological functioning and is increasingly being recognized as a risk factor for autism-spectrum disorders, ADHD, and other psychological disturbances. No treatment options are currently available for diffuse WMI and the underlying pathophysiological mechanisms are far from being completely understood. Preterm birth is associated with maternal inflammation, perinatal infections and disrupted oxygen supply which can affect the cerebral microenvironment by causing activation of microglia, astrogliosis, excitotoxicity, and oxidative stress. This intricate interplay of events negatively influences oligodendrocyte development, causing arrested oligodendrocyte maturation or oligodendrocyte cell death, which ultimately results in myelination failure in the developing white matter. This review discusses the current state in perinatal WMI research, ranging from a clinical perspective to basic molecular pathophysiology. The complex regulation of oligodendrocyte development in healthy and pathological conditions is described, with a specific focus on signaling cascades that may play a role in WMI. Furthermore, emerging concepts in the field of WMI and issues regarding currently available animal models are put forward. Novel insights into the molecular mechanisms underlying impeded oligodendrocyte maturation in diffuse WMI may aid the development of novel treatment options which are desperately needed to improve the quality-of-life of preterm neonates.

Contents

Abbreviations: A1R, adenosine 1 receptor; BBB, blood–brain barrier; BMP4, bone morphogenetic protein; CNS, central nervous system; cPVL, cystic periventricular leukomalacia; DAMP, damage-associated molecular pattern; DEHSI, diffuse excessive high signal intensities; DTI, diffusion tensor imaging; EGF, epidermal growth factor; EPO, erythropoietin; ERK, extracellular signal-regulated kinase; FA, fractional anisotropy; GLAST, glutamate aspartate transporter; HDAC, histone deacetylase; ID, inhibitor of differentiation; IGF-1, insulin-like growth factor 1; IL, interleukin; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; miRNA, micro-RNA; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; mTORC, mTOR complex; MYRF, myelin regulatory factor; OL, oligodendrocyte; OPC, oligodendrocyte precursor cell; PAMP, pathogen-associated molecular pattern; PDGF, platelet-derived growth factor; PDGFRα, PDGF receptor alpha; pre-OL, premyelinating oligodendrocyte; PWML, punctate white matter lesions; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; TNF-α, tumor necrosis factor alpha; VWMD, vanishing white matter disease; WMI, white matter injury.

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1. Introduction

Worldwide, over 10% of all babies are born prematurely and their mortality accounts for 35% of all neonatal deaths (Liu et al., 2012a). Over the past years advances in neonatal care have led to decreased neonatal mortality in Western society (EUROCAT, 2013). However, many survivors of preterm birth show considerable morbidity including necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and/or neurological damage (Costeloe et al., 2012; Stoll et al., 2015). Currently, the most common type of brain injury in preterm neonates is diffuse perinatal white matter injury (WMI), in which impaired oligodendrocyte (OL) maturation and myelination result in decreased cognitive, behavioral, and sensory abilities as well as psychological problems later in life (reviewed in Back and Miller, 2014; Volpe et al., 2011). No treatment for diffuse WMI is currently available. This review explores clinical observations regarding diffuse WMI, describes cellular pathophysiological processes underlying arrested OL development in diffuse WMI and highlights several intracellular pathways that may contribute to impeded OL maturation. Furthermore, several suggestions for future research and potential therapeutic strategies are provided.

2. Perinatal white matter injury: Clinical observations and etiology

2.1. Types of WMI

Perinatal WMI occurs in various forms, ranging from severe cystic white matter lesions to subtle changes in the white matter microenvironment (see Table 1). In both clinical and experimental literature, the term WMI is often used regardless of the pattern of injury. The ambiguous term "WMI" can be confusing, considering that this term can pertain to multiple patterns of injury that may

Table 1
Different types of white matter injury and clinical features (for reviews see Benders et al., 2014; de Vries et al., 2013; Rutherford et al., 2010).

Type of WMI	Visible on cranial ultrasound?	Anatomical pathophysiology	Major clinical outcome
Porencephalic cysts	Yes	Severe, often unilateral brain injury in the shape of large porencephalic cysts in the white matter, often resulting from intraventricular hemorrhage	Depending on location of lesion, severe motor disabilities including hemiplegia
Cystic periventricular leukomalacia	Yes	Bilateral cysts in the white matter, often associated with inflammatory and ischemic insults due to hypotension or hypocarbia	Severe motor deficits including cerebral palsy
Punctate white matter lesions	As inhomogeneous echogenicity	Microscopic cysts in the white matter, often localized around the lateral ventricles, that may disappear with age. May originate from hemorrhagic or ischemic origin	Limited data available, but seems to be related to mild cognitive impairment and behavioral problems
Diffuse WMI	Certain aspects: ventriculomegaly, increased size of interhemispheric fissure	White matter atrophy resulting in e.g. ventriculomegaly, thinning of the corpus callosum and accumulated cerebrospinal fluid surrounding the brain. Associated with altered white matter microstructure as indicated by low FA values	Associated with mild cognitive impairment, behavioral problems and psychological problems