


**REVIEW ARTICLE**

# The impact of trophic and immunomodulatory factors on oligodendrocyte maturation: Potential treatments for encephalopathy of prematurity

Josine E. G. Vaes<sup>1,2</sup> | Myrna J. V. Brandt<sup>1</sup> | Nikki Wanders<sup>1</sup> |  
Manon J. N. L. Benders<sup>2</sup> | Caroline G. M. de Theije<sup>1</sup> | Pierre Gressens<sup>3</sup> |  
Cora H. Nijboer<sup>1</sup> 

<sup>1</sup>Department for Developmental Origins of Disease, University Medical Center Utrecht Brain Center and Wilhelmina Children's Hospital, Utrecht University, Utrecht, The Netherlands

<sup>2</sup>Department of Neonatology, University Medical Center Utrecht Brain Center and Wilhelmina Children's Hospital, Utrecht University, Utrecht, The Netherlands

<sup>3</sup>Université de Paris, NeuroDiderot, INSERM, Paris, France

**Correspondence**

Cora H. Nijboer, Department for Developmental Origins of Disease (DDOD), University Medical Center Utrecht Brain Center and Wilhelmina Children's Hospital, Room number KC03.068.0, PO Box 85090, 3508 AB Utrecht, The Netherlands.  
Email: c.nijboer@umcutrecht.nl

**Abstract**

Encephalopathy of prematurity (EoP) is a major cause of morbidity in preterm neonates, causing neurodevelopmental adversities that can lead to lifelong impairments. Preterm birth-related insults, such as cerebral oxygen fluctuations and perinatal inflammation, are believed to negatively impact brain development, leading to a range of brain abnormalities. Diffuse white matter injury is a major hallmark of EoP and characterized by widespread hypomyelination, the result of disturbances in oligodendrocyte lineage development. At present, there are no treatment options available, despite the enormous burden of EoP on patients, their families, and society. Over the years, research in the field of neonatal brain injury and other white matter pathologies has led to the identification of several promising trophic factors and cytokines that contribute to the survival and maturation of oligodendrocytes, and/or dampening neuroinflammation. In this review, we discuss the current literature on selected factors and their therapeutic potential to combat EoP, covering a wide range of in vitro, preclinical and clinical studies. Furthermore, we offer a future perspective on the translatability of these factors into clinical practice.

**KEYWORDS**

cytokines, myelination, neuroinflammation, oligodendrocyte, preterm brain, trophic factors

## 1 | INTRODUCTION

Worldwide, approximately 10% of live-born babies is born preterm, that is, before 37 weeks of gestation. Preterm birth can be subdivided into extremely preterm (<28 weeks), very preterm (28–<32 weeks)

and moderate or late preterm birth (32–<37 weeks; Blencowe et al., 2012) and is associated with multiple neurodevelopmental morbidities, ranging from motor problems and cognitive impairments to an increased risk of psychiatric disorders. The risk of neurological consequences of preterm birth is inversely correlated with gestational age, meaning that extreme preterm infants are most at risk (Deng, 2010; Larroque et al., 2008; Linsell et al., 2018; MacKay, Smith, Dobbie, & Pell, 2010; Moster, Lie, & Markestad, 2008).

Josine E. G. Vaes and Myrna J. V. Brandt contributed equally to this manuscript and share the first authorship.

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Neurodevelopmental morbidities after preterm birth are thought to arise from encephalopathy of prematurity (EoP), an umbrella term used to describe the brain abnormalities that result from impeded brain development due to preterm birth-related complications (Volpe, 2009a). The most prominent hallmark of EoP is white matter injury (WMI); however, neuronal and axonal deficits, such as GABAergic interneuron maldevelopment, have received growing attention over the years (Panda et al., 2018; Stolp et al., 2019; Volpe, 2009b). Preterm WMI is a collective term referring to a spectrum of pathological changes in the developing white matter and is often classified based on neuropathological findings, such as (small) necrotic lesions (Back, 2017; Volpe, 2017). As a result of advances in supportive care, diffuse WMI (dWMI), characterized by global hypomyelination without focal necrosis, is currently the most prevalent form of preterm WMI with reported prevalence rates up to 80% in all affected preterm neonates (Back, 2017; Back & Miller, 2014; Schneider & Miller, 2019). Histopathological findings in dWMI display injured immature oligodendrocytes, along with astrocytosis and microgliosis. Consequently, a deficit of mature myelinating oligodendrocytes is observed, leading to a reduction in axonal myelination (Buser et al., 2012; Lee, 2017; Schneider & Miller, 2019; van Tilborg et al., 2016; Volpe, Kinney, Jensen, & Rosenberg, 2011). Due to the key role of dWMI in EoP, this review will focus primarily on potential treatments aimed at restoration of *white matter* development.

Although treatment options for dWMI in preterm infants are currently limited, research in the last decade has created larger understanding of the pathophysiology underlying myelination failure, pinpointing impaired oligodendrocyte maturation as an critical target for therapeutic intervention. Experimental research has identified several growth factors and cytokines that play essential roles in healthy white matter development or that boost myelination in other (adult) white matter pathologies, such as multiple sclerosis (MS), (neonatal) stroke, and traumatic brain injury. Despite the evident differences in pathophysiology—most of the mentioned diseases are characterized by demyelination of existing white matter tracts while dWMI is associated with impaired myelin formation—, there are some overlapping characteristics, such as insufficient oligodendrocyte maturation and the occurrence of neuroinflammation. Thus, knowledge from previous research in the above-mentioned pathologies could aid in the refinement and identification of potential therapeutic strategies to restore white matter development in (extreme) preterm infants. Using a wide range of *in vivo* and *in vitro* studies, this review aims to integrate the current knowledge on a selection of trophic and immunomodulatory factors that boost oligodendrocyte maturation and white matter development, leading to the identification of potent therapeutic targets to combat preterm dWMI.

## 2 | DEVELOPMENTAL WHITE MATTER (PATHO)PHYSIOLOGY

During normal human brain development, the formation of myelin sheaths by oligodendrocytes starts relatively late, at >32 weeks of

gestation (Back et al., 2001). Before oligodendrocytes are able to produce myelin, the proliferation, migration, and maturation of oligodendrocyte precursors has to be completed. This typically occurs in four stages: (1) oligodendrocyte precursor cells (OPCs) originate from differentiated neural stem cells (NSCs) in the ventral forebrain; (2) OPCs migrate throughout the brain and proliferate to increase their numbers; (3) at the site of destination, OPCs differentiate into premyelinating oligodendrocytes (pre-OLs), which are still non-myelinating cells until (4) differentiation-repressive factors are lifted and pre-OLs differentiate into postmitotic, mature oligodendrocytes that produce myelin to enwrap axons (van Tilborg et al., 2016). Not all OPCs reach this end stage during brain development: a homeostatic pool of OPCs populates the brain to maintain regenerative capacity after oligodendrocyte damage throughout adulthood. Under physiological circumstances, oligodendrocyte maturation is aided by microglia and astrocytes, through the release of essential nutrients, proteins, and cytokines (Hammond, Robinton, & Stevens, 2018; Traffort, Kassoussi, Zahaf, & Laouarem, 2020; Volpe, 2019). Interestingly, interneurons, other cells at risk in EoP pathophysiology, have been reported to regulate oligodendrocyte lineage development, by emitting pro-differentiation cues through transient synaptic input and secreted factors (Benamer, Vidal, & Angulo, 2020; Zonouzi et al., 2015).

The particular vulnerability of white matter in prematurely born infants results from the fact that (extreme) preterm birth coincides with the initiation of oligodendrocyte lineage development. Especially between 24 and 30 weeks of gestation, the brain contains a large population of OPCs and pre-OLs, which are particularly vulnerable to insults associated with preterm birth (van Tilborg et al., 2016; Volpe, 2019). Two major preterm birth-related insults known to affect maturation of pre-OLs to myelinating oligodendrocytes are inflammation and oxygen fluctuations. Moreover, encountering multiple hits is reported to aggravate neonatal brain damage and worsen neurodevelopmental outcome (Brehmer et al., 2012; Volpe, 2019; Volpe et al., 2011).

Inflammation is estimated to occur in 65–79% of very low birth weight or extremely preterm infants, either caused by perinatal immune activation (such as intrauterine infection or maternal fever) or postnatal inflammation/infections (such as neonatal sepsis or necrotizing enterocolitis (NEC) of the immature bowel; Cappelletti, Della Bella, Ferrazzi, Mavilio, & Divanovic, 2016; Volpe et al., 2011). After extremely preterm birth, oxygen fluctuations due to immature lungs and cardiovascular system (hypoxia) and/or the need for ventilation (hyperoxia) are also detrimental to the immature brain (Brehmer et al., 2012).

Inflammation induces the release of pro-inflammatory cytokines into the circulation which subsequently reach the immature brain (Li, Concepcion, Meng, & Zhang, 2017). This process triggers microglia, the resident immune cells of the brain, to shift to a pro-inflammatory (M1) phenotype, stimulating additional release of pro-inflammatory cytokines by these cells in the brain parenchyma (Li et al., 2017). The pro-inflammatory microglial shift may be sustained by multiple hits during pregnancy and following preterm birth (Li et al., 2017; Volpe, 2019).

Pre-OLs possess a high amount of cytokine receptors, and are therefore particularly sensitive to the release of these cytokines in the immature brain, which causes apoptosis (Goldstein, Church, Hesp, Popovich, & McTigue, 2016). Activated microglia cause further harm to immature oligodendrocytes by reducing their trophic factor support, and releasing excessive amounts of glutamate which causes excitotoxicity (Vaes et al., 2019; van Tilborg et al., 2016; Volpe et al., 2011). Similarly, astrocytes respond to inflammation by increased reactivity, during which astrocytes release growth factors that stimulate OPC proliferation but impair oligodendrocyte maturation (Back, 2017; Shioh et al., 2017; van Tilborg et al., 2016). As will become apparent in this review, neuroinflammation and myelination are complexly linked, since cytokines that are secreted during inflammation have a dual role in oligodendrocyte development (Goldstein et al., 2016).

Oxygen fluctuations such as hypoxia and/or hyperoxia can directly and indirectly induce apoptosis and necrosis, and contribute to accumulation of reactive oxygen species (ROS) in the brain (Brill, Scheuer, Bühner, Endesfelder, & Schmitz, 2017; Li et al., 2017; Scheuer et al., 2015). Oligodendrocyte precursors are sensitive to the release of ROS from activated microglia, as they lack enzymes needed to counteract oxidative stress (Back, 2017; van Tilborg et al., 2016). Similarly, oligodendrocyte precursors express a large amount of glutamate receptors, which increases their susceptibility to the release of excess glutamate by microglia and the halted or reversed uptake of glutamate by astrocytes (Back, 2017; van Tilborg et al., 2016). However, astrocytes may also shift to a protective type A2 activation state in response to hypoxic conditions, during which they release neurotrophic factors that stimulate proliferation and survival of multiple cell types, among which oligodendrocytes and their precursors (Liddel & Barres, 2017).

Together, preterm-birth related insults such as inflammation and oxygen fluctuations lead to a reduced number of mature oligodendrocytes and consequent myelin insufficiency in the preterm brain. It is under current debate whether survival of oligodendrocytes precursors is impaired as a result of neuroinflammation and oxygen fluctuations, or whether these hits cause arrested maturation of pre-OLs (Back, 2017; van Tilborg et al., 2016; Volpe, 2019). In fact, both cell death and arrested maturation of oligodendrocyte precursors may contribute to dWMI, as accumulation of ROS and cytokines leads to apoptosis particularly in pre-OLs, and oxygen fluctuations induce the upregulation of trophic factors that sustain OPC proliferation and survival, keeping them in an immature state (Liddel & Barres, 2017; van Tilborg et al., 2016). Thus, reducing the impact of detrimental insults such as inflammation and oxygen fluctuations, plus providing trophic or immunomodulatory factors that stimulate oligodendrocyte maturation and myelination are two important strategies to reduce preterm dWMI.

### 3 | THE ROLE OF GROWTH FACTORS AND CYTOKINES IN OLIGODENDROCYTE MATURATION AND NEUROINFLAMMATION

Although dWMI can lead to life-long neurological impairments, no therapeutic options to promote white matter development in the

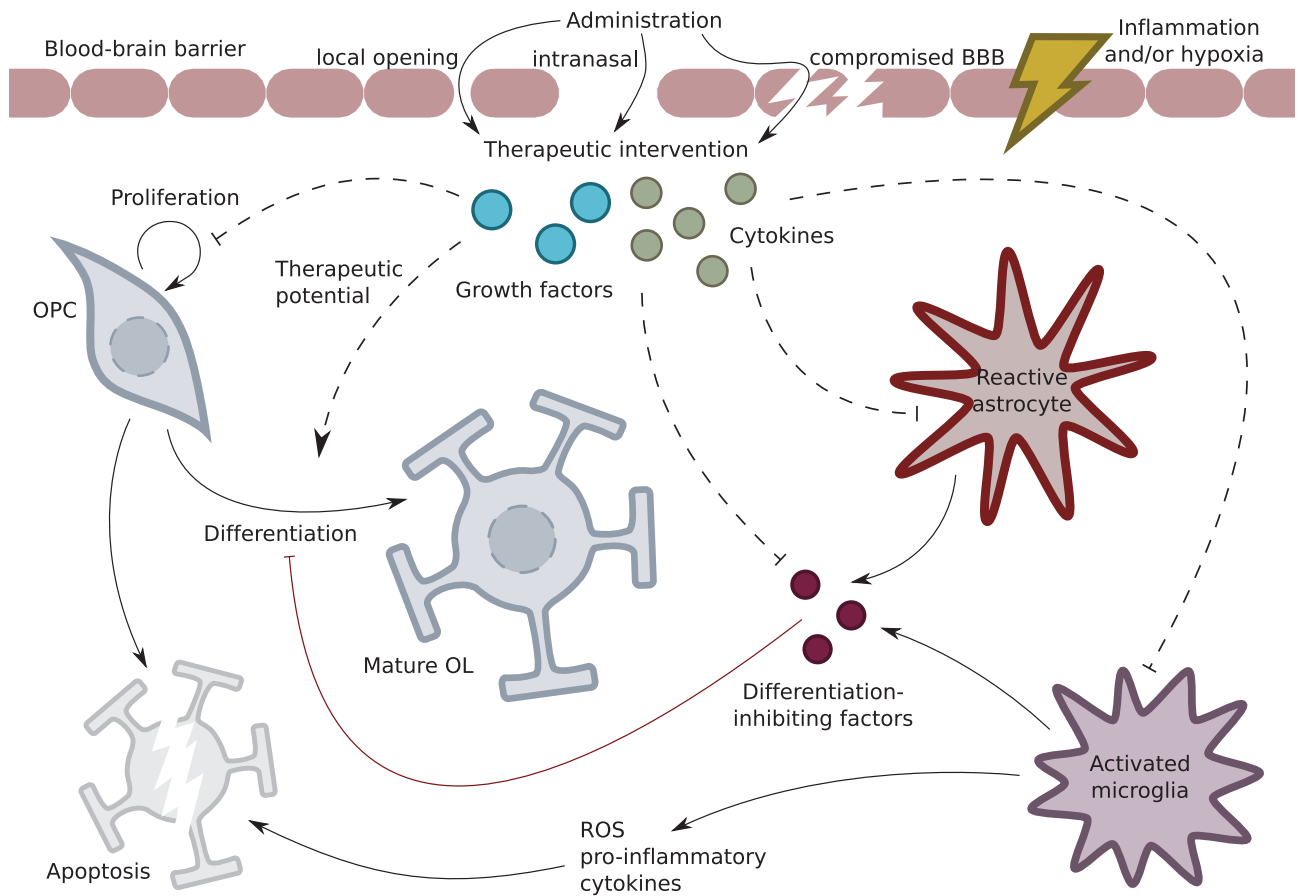
preterm brain are currently available. Future therapies would preferably stimulate oligodendrocyte lineage survival and maturation, increasing the proportion of mature, myelin-producing oligodendrocytes. Stimulation of differentiation could be achieved through growth factors and cytokines that directly affect the oligodendrocyte lineage, boosting maturation and/or survival of oligodendrocyte precursors, or indirectly by modulating neuroinflammation, providing a more favorable intracerebral milieu for myelination (Figure 1). In this review, we integrate the current knowledge on the role of promising growth factors and cytokines in healthy white matter development and oligodendrocyte maturation and neuroinflammation after injury from (a) *in vitro* and (b) *in vivo* animal models and (c) clinical studies, in order to identify potential therapeutic targets for preterm dWMI.

#### 3.1 | Insulin-like growth factor 1

A compelling quantity of experimental studies has provided evidence for the essential role of insulin-like growth factor 1 (IGF-1) in normal fetal white matter development and in regeneration following cerebral injury (D'Ercole & Ye, 2008; Guan, Bennet, Gluckman, & Gunn, 2003; Huang & Dreyfus, 2016). The effects of IGF-1 are mediated by activation of the Type I IGF receptor (IGF1R), broadly expressed on different cell types in the central nervous system (CNS), among which all cells of the oligodendrocyte lineage (D'Ercole & Ye, 2008; Zeger et al., 2007). IGF1R activation is thought to trigger the PI3kinase-Akt (PI3k/Akt) pathway, mitogen-activated protein kinase (MAPK) activation and mammalian target of rapamycin (mTOR) activation, driving mitogenesis, maturation and survival of oligodendrocytes (see Box 2; O'Kusky & Ye, 2012; Palacios, Sanchez-Franco, Fernandez, Sanchez, & Cacicedo, 2005; Wrigley, Arafa, & Tropea, 2017).

Over the years, a wide range of *in vitro* studies have provided evidence of a direct effect of IGF-1 on proliferation and differentiation of healthy oligodendrocyte lineage cells, ultimately resulting in myelination (Barres et al., 1992; Masters, Werner, Roberts, LeRoith, & Raizada, 1991; McMorris, Smith, DeSalvo, & Furlanetto, 1986; Mozell & McMorris, 1991; Roth, Spada, Hamill, & Bornstein, 1995; Wilson, Onischke, & Raine, 2003). However, a study using OPCs derived from *human* fetal tissue did not find a proliferative response following IGF-1 administration, suggesting the mitogenic effect of IGF-1 may be more pronounced in rodents (Wilson et al., 2003). Other than its role in healthy oligodendrocyte development, multiple *in vitro* studies show that IGF-1 promotes differentiation and myelin production, and inhibits oligodendrocyte cell death when exposed to different WMI-associated stimuli (e.g., hypoxia or inflammation; Ness, Scaduto, & Wood, 2004; Pang, Zheng, Fan, Rhodes, & Cai, 2007; Wood et al., 2007; Ye & D'Ercole, 1999).

*In vivo* studies underline the prominent role of IGF-1 in white matter development, as well as in injury repair. Transgenic mice lacking IGF-1 display a dramatic reduction in size of white matter structures, myelination, and oligodendrocyte numbers (Beck, Powell-Braxton, Widmer, Valverde, & Hefti, 1995; Ye, Li, Richards,



**FIGURE 1** The underlying pathophysiology of encephalopathy of prematurity (EoP) and proposed mechanism of therapeutic intervention. Preterm birth-related issues such as inflammation and hypoxia/hyperoxia (yellow flash) are thought to lead to oligodendrocyte (OL) death (apoptosis) and/or a maturational arrest of the oligodendrocyte lineage, through the activation of microglia (purple cell) and astrocyte (red cell) reactivity. Microglia release reactive oxygen species (ROS) and pro-inflammatory cytokines, which leads to the death of vulnerable oligodendrocyte precursors (OPCs). Reactive astrocytes respond to inflammation and/or oxygen fluctuations by reducing their uptake of glutamate and increasing the release of proliferative factors (red dots), that inhibit the differentiation of oligodendrocyte precursor cells (OPCs). The proposed therapeutic effect of growth factor- and cytokine-based treatments is indicated in dotted lines. This review summarizes growth factors (blue dots) and cytokines (green dots) that have the potential to stimulate oligodendrocyte maturation/differentiation and increase survival of these cells directly, while simultaneously inhibiting the harmful neuroimmune response caused by microglia and astrocytes. Several routes of administration are proposed, such as intranasal through a local opening in, or through the compromised blood-brain-barrier (BBB) in the acute phase after brain injury

DiAugustine, & D'Ercole, 2002; Zeger et al., 2007). In line with these findings, mice overexpressing IGF-1 show excessive oligodendrocyte numbers and myelin content (Carson, Behringer, Brinster, & McMorris, 1993; Popken et al., 2004; Ye, Carson, & D'Ercole, 1995). Exogenous IGF-1 treatment in animal models of neonatal brain injury has shown beneficial effects on oligodendrocyte differentiation, survival, and myelination. The effectiveness of IGF-1 therapy in *term* hypoxic/ischemic encephalopathy (HIE) has been studied in both rodent and larger animal models using different routes of administration. Lin, Fan, Rhodes, and Cai (2009) showed a significant improvement in myelination of the subcortical white matter after intranasal IGF-1 treatment in a rat model of *near-term* HIE. Moreover, the authors report a mitogenic effect of IGF-1 administration based on an increase in proliferating NG2+ cells, a marker for OPCs. In a similar rat model, intracerebral IGF-1 treatment induced activation of Akt and

pGSK3 $\beta$ , inhibiting activation of caspases, thereby reducing brain injury (Brywe et al., 2005). These results were confirmed in sheep models of *near-term* HIE, using intracerebral IGF-1 administration (Cao et al., 2003; Guan et al., 2001). In a rodent model of severe preterm WMI, where intracerebral LPS was injected, intranasal IGF-1 therapy was shown to reduce preoligodendrocyte (O4+) and mature oligodendrocyte (CC1+) loss, which resulted in myelin recovery (Cai, Fan, Lin, Pang, & Rhodes, 2011). In these studies, the reported increases in total oligodendrocyte numbers after IGF-1 treatment were attributed to prevention of oligodendrocyte death, with a less prominent role for oligodendrocyte proliferation. Conversely, a previous study from this group showed conflicting outcomes of IGF-1 treatment, detecting both recovery and exacerbation of injury. Coadministration of intracerebral LPS and IGF-1 in a low dose reduced oligodendrocyte loss and myelin deficits, while higher doses

**BOX 1 Jagged-1 and Notch in EoP**

Although the Notch receptor and its ligand Jagged-1 have previously been associated with OPC proliferation thereby regulating the timing of differentiation, Jagged-1 and Notch may be more complexly linked to oligodendrocyte development. Subtle increases in Notch and Sonic hedgehog (Shh) signaling may skew the OPC fate to differentiation instead of recruitment into the homeostatic NG2<sup>+</sup> OPC pool, as was demonstrated in the spinal cord of zebrafish larvae (Ravanelli et al., 2018). In EoP, neuroinflammation and oxygen fluctuations upregulate the expression of Jagged-1 by astrocytes, thereby activating the Notch-pathway which can contribute to the oligodendrocyte maturational arrest (van Tilborg et al., 2016; Yuan & Yu, 2010). This was also shown in a mouse model of neonatal hyperoxia, in which WMI could be rescued by blocking the Notch-signaling pathway using a  $\gamma$ -secretase inhibitor (Du et al., 2017). However, a recent *in vivo* study showed the downregulation of Notch-1 and Hes-1 proteins in the corpus callosum of rat pups subjected to fetal inflammation, which corresponded with reduced maturation of OPCs into mature oligodendrocytes and myelination (Ying et al., 2018). Together, these results indicate that oligodendrocyte development is tightly regulated by the Notch-pathway, and that subtle imbalances in Notch pathway activation caused by EoP lead to failure of myelination.

of IGF-1 led to intracerebral hemorrhage and exacerbation of brain damage (Pang et al., 2010). These damaging effects were not observed following intranasal treatment with IGF-1 nor in any of the other aforementioned studies, implying that caution is only advised when locally injecting (very high) doses of IGF-1 in an acute inflammatory environment. However, intracerebral injection is a clinically unfeasible route of administration in the instable preterm infant. Although these models do not represent the commonly observed pattern of WMI in human preterm infants (i.e., dWMI) and/or use a rather invasive administration method of IGF-1, IGF-1 generally seems to have beneficial effects on the oligodendrocyte lineage.

Results from a handful *in vitro* studies indicate an immunoregulatory effect of IGF-1 directly on astrocytes and microglia, implying an indirect role of IGF-1 on pre-OL differentiation and survival by contributing to a more favorable environment by reducing microglia and astrocyte activation (Dodge et al., 2008; Genis et al., 2014; Grinberg, Dibbern, Levasseur, & Kraig, 2013). Grinberg et al. (2013) demonstrated a reduction in microglial ROS and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) production following IGF-1 supplementation in rat hippocampal slice cultures. Astrocytic ROS and TNF- $\alpha$  production, however, were not reduced by IGF-1. In contrast, Genis et al. (2014) did demonstrate a decrease in ROS levels

following IGF-1 treatment in astrocytic cultures, protecting the brain against oxidative injury.

Evidence for the immunomodulatory properties of IGF-1 obtained from *in vivo* studies seems inconclusive. In a sheep model *near-term* HIE intracerebral IGF-1 administration led to increased proliferation of (reactive) astrocytes and microglia. While reactive (micro)glia are traditionally associated with dWMI pathophysiology, the authors propose that the increased numbers of reactive glial cells after IGF-1 treatment are associated with improvement of white matter repair. It is suggested that the neuroprotective properties of reactive glia might be the result of paracrine signaling (Cao et al., 2003; Guan et al., 2001). Similar observations of potential proregenerative glial subtypes, particularly for astrocytes, have been reported in other studies (Du et al., 2017; Liddel & Barres, 2017; Zhou & Spittau, 2018). The possible role of reactive glia subtypes in perinatal brain injury remains unclear, though in the majority of studies (micro)glia activation is linked to exacerbation of brain injury and a poorer outcome (Baud & Saint-Faust, 2019; Del Bigio & Becker, 1994; Olivier, Baud, Evrard, Gressens, & Verney, 2005; Verney et al., 2012). Intranasal IGF-1 administration in a rodent model of severe LPS-induced preterm WMI reduced microglia activation and peripheral immune cell infiltration, even though pro-inflammatory IL-1 $\beta$  and TNF- $\alpha$  concentrations remained unchanged. The authors hypothesize that the direct anti-inflammatory effect of IGF-1 is likely limited and that the observed attenuation of microglia activation and peripheral immune cell infiltration could be the result of reduced oligodendrocyte apoptosis (Cai et al., 2011). As mentioned previously, another study by this group showed exacerbation of brain injury after local coinjection of a high dose of IGF-1 and LPS. Even though a low dose of IGF-1 did provide protection against oligodendrocyte loss and myelination deficits, it failed to attenuate LPS-induced micro- and astrogliosis and was associated with an increase in peripheral immune cell infiltration. These effects were more pronounced in the higher doses of IGF-1, leading to profuse leukocyte infiltration and subsequent exacerbation of brain injury. The authors suggest that IGF-1 likely negatively affects blood-brain-barrier (BBB) integrity while upregulating chemotactic signaling during episodes of acute inflammation (Pang et al., 2010).

Glial cells are an important source of local IGF-1 production during brain development. Endogenous microglial IGF-1 secretion was shown to be hampered *in vitro* following glutamate treatment in a primary microglial culture obtained from hypoxic rats, mimicking glutamate excitotoxicity in WMI (Sivakumar, Ling, Lu, & Kaur, 2010). These findings are supported by *in vivo* evidence demonstrating a decrease in IGF-1 gene expression in the ipsilateral hemisphere following a hypoxic-ischemic insult in *near-term* rats (Lee, Wang, Seaman, & Vannucci, 1996). Interestingly, this decrease in local IGF-1 secretion seems to be distinctive for the neonatal period, as hypoxia/ischemia in older animals leads to a local upregulation IGF-1 (Gluckman et al., 1992; Lee, Clemens, & Bondy, 1992). These studies emphasize the potential need for IGF-1 supplementation following perinatal hits (Lee et al., 1996; Sivakumar et al., 2010).

Interestingly, evidence from human studies indicated a reduction in circulatory IGF-1 in the first weeks following extreme preterm birth





due to inadequate endogenous IGF-1 production. This relative IGF-1 deficiency during a developmental time-window analogous to the third trimester of pregnancy has been associated with a poorer neurodevelopmental outcome, as well as with retinopathy of prematurity severity and respiratory complications (Hansen-Pupp et al., 2013; Helstrom et al., 2016). These observations, along with the promising pre-clinical data instigated the first feasibility and pharmacokinetics studies using IGF-1 administration in neonates. Even though intravenously administered IGF-1 (including IGF binding protein 3; either from fresh frozen plasma or provided by a pharmaceutical company) was shown to successfully elevate serum IGF1/IGFBP3 concentrations in human extreme preterm infants, IGF-1 half-life was shown to be extremely short (<1 hr; Ley et al., 2013; Lofqvist et al., 2009). Continuous intravenous infusion during a mean of 2 weeks was deemed safe and feasible; however, one-third of all included infants did not reach target serum IGF-1 levels. Additional studies are needed to determine the optimal dosing regimen and to assess treatment efficacy (Hansen-Pupp et al., 2017). Even though IGF-1 has been shown to cross the (intact) BBB by active transport, the proportion of the polypeptide that reaches CNS following intravenous injection is likely limited (Pan & Kastin, 2000; Reinhardt & Bondy, 1994; Thorne, Pronk, Padmanabhan, & Frey II, 2004). An adult rat study comparing intravenous and intranasal administration of IGF-1 showed significantly higher CNS concentrations following intranasal treatment, with similar blood and peripheral tissue levels. Intranasally administered IGF-1 was shown to bypass the BBB, entering the CNS via the olfactory system and trigeminal nerve (Thorne et al., 2004). Thus, while continuous intravenous infusion of IGF-1 would pose a substantial clinical burden with a limited supply to the brain, intranasal IGF-1 administration might offer a less invasive, rapid and direct route to target the CNS (Cai et al., 2011; Lin, Fan, et al., 2009; Liu, Fawcett, Thorne, & Frey II, 2001).

## 3.2 | Epidermal growth factor family

### 3.2.1 | Epidermal growth factor and transforming growth factor alpha

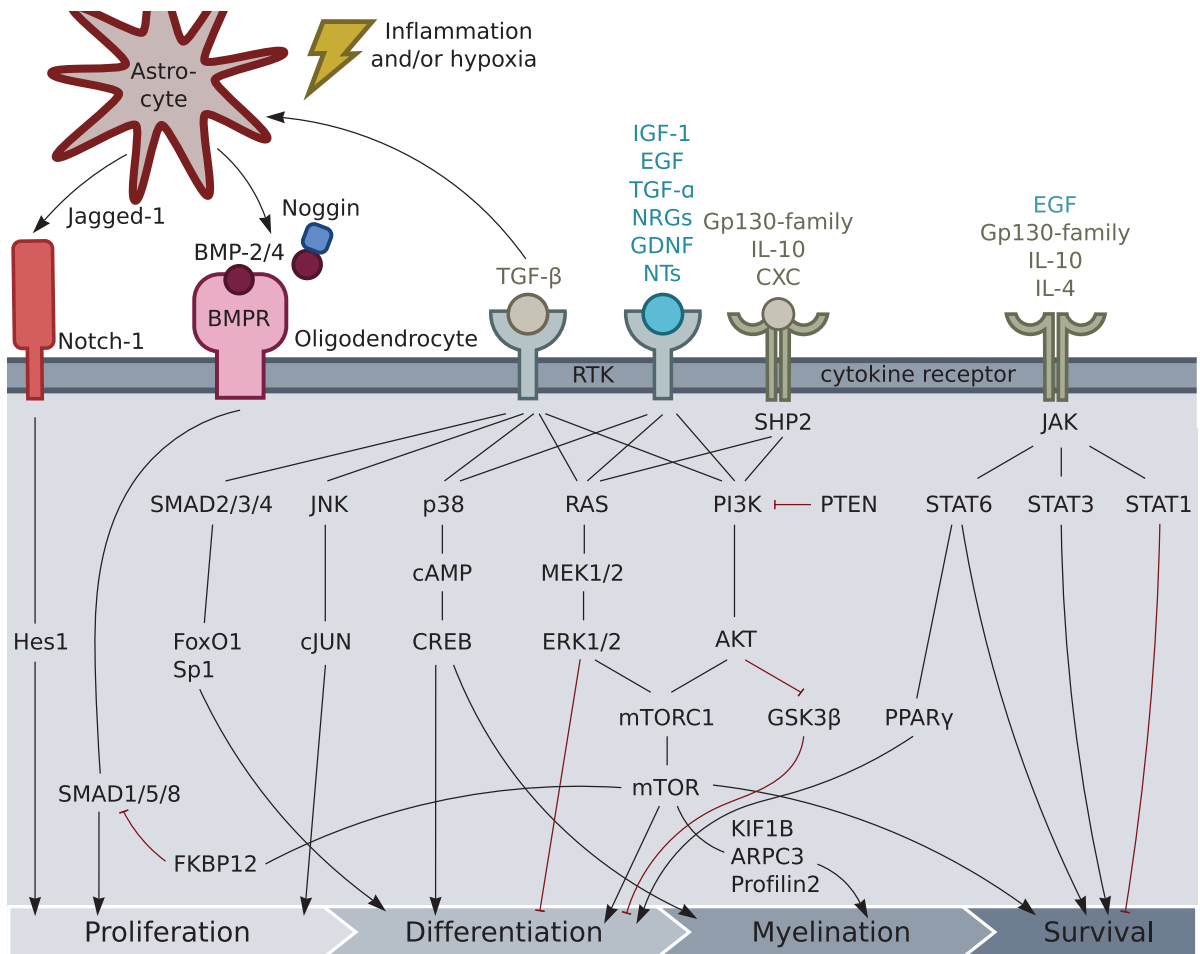
The epidermal growth factor (EGF) family consists of several factors including EGF, heparin-binding EGF (hb-EGF) and transforming growth factor alpha (TGF- $\alpha$ ), that are involved in the proliferation and survival of many cell types, among which cells of the oligodendrocyte lineage (Oyagi & Hara, 2012; Yang et al., 2017). EGF-family members and the EGF receptor (EGFR) are upregulated in the CNS during development and in response to injury, for example, after hypoxia-ischemia (Aguirre, Dupree, Mangin, & Gallo, 2007; Ferrer et al., 1996; Kornblum et al., 1997; Oyagi & Hara, 2012). The EGFR signals through multiple intracellular pathways, such as PI3K/Akt, RAS/ERK, and JAK/STAT (see Box 2; Jorissen et al., 2003).

In vitro studies indicate that during normal white matter development, EGF interacts with the mitogens platelet-derived growth factor AA (PDGF-AA) and basic fibroblast growth factor (bFGF) to skew glial

precursor cells toward OPC cell fate, and to enhance survival and proliferation of OPCs (Yang et al., 2016; Yang et al., 2017). However, when OPCs are cultured with EGF in the absence of PDGF-AA, EGF promotes differentiation into mature (myelin basic protein (MBP)-expressing) oligodendrocytes, indicating a role for EGF in both proliferation and differentiation (Yang et al., 2017). Since cerebral PDGF-levels decrease during third trimester development (Van Heyningen, Calver, & Richardson, 2001), the role of EGF shifts to promote oligodendrocyte differentiation. In contrast, when PDGF is upregulated in response to, for example, pro-inflammatory cytokines (Gard, Burrell, Pfeiffer, Rudge, & Williams, 1995; Silberstein, de Simone, Levi, & Aloisi, 1996), EGF may halt oligodendrocyte differentiation and promote proliferation of the extensive OPC pool that is already present in preterm brain injury, making it a less feasible therapeutic candidate to treat preterm WMI.

In vivo rodent experiments confirm the potential of EGF to stimulate both OPC proliferation and differentiation. In a transgenic mouse model, overexpression of EGFR in CNPase+ cells (i.e., pre-OLs) led to increased proliferation of OPCs, mature oligodendrocyte numbers, MBP expression, and myelinated axons (Aguirre et al., 2007). Conversely, hypoactive EGFR signaling in a mouse mutant reduced the number of OPCs (NG2+) and mature (CC1+) oligodendrocytes and myelination during development, supporting the in vitro evidence that EGF plays a role in both proliferation and maturation. Results from several preclinical studies indicate a protective role of EGF in animal models of white matter pathologies. EGFR-overexpressing neonatal mice were less susceptible to developing dWMI after subjection to chronic hypoxia, while an EGFR-antagonist reduced the number of OPCs, mature oligodendrocytes and production of myelin (Scafidi et al., 2014). This had previously been shown in adult EGFR-overexpressing mice recovering from focal demyelination (Aguirre et al., 2007). Moreover, intranasal treatment with exogenous hb-EGF following neonatal chronic hypoxia reduced apoptosis of mature oligodendrocytes, preserved axonal myelination and improved behavioral outcome, through a reduction of Notch-signaling (see Box 1; Scafidi et al., 2014). Interestingly, in a rabbit model of neonatal intraventricular hemorrhage (IVH), EGF levels were reduced, indicating a deficit in endogenous EGF production after injury (Vinukonda et al., 2016). Intraventricular injection of EGF increased OPC proliferation, oligodendrocyte maturation, and astrogliosis (Vinukonda et al., 2016).

In an in vitro model of HIE, in which OPCs were deprived of oxygen and glucose, treatment with EGF-family member TGF- $\alpha$  significantly reduced apoptosis of OPCs and mature oligodendrocytes through STAT3 signaling (see Box 2), but had no direct effect on oligodendrocyte differentiation or myelination (Dai et al., 2019). This may indicate that TGF- $\alpha$  might preferably be given shortly after WMI is induced to reduce apoptosis of oligodendrocyte precursors. Consistent with in vitro findings, EGF-family member TGF- $\alpha$  also protected OPCs and mature oligodendrocytes against apoptosis in adult ischemic stroke, while TGF- $\alpha$  knockout mice displayed more extensive white matter lesions compared to wild-type mice (Dai et al., 2019). Together, these studies indicate the therapeutic potential of EGF-



**FIGURE 2** Proposed model of intracellular pathways that mediate the different stages of oligodendrocyte development. Astrocytes (red cell), triggered by inflammation and/or hypoxia (yellow flash), produce factors that stimulate oligodendrocyte precursor cell (OPC) proliferation, which contributes to the maturational arrest of oligodendrocytes in preterm WMI. In contrast, several factors discussed in this review either directly or indirectly stimulate oligodendrocyte maturation/differentiation, myelination, and survival, through shared intracellular pathways. IGF-1, insulin-like growth factor 1; EGF, epidermal growth factor; TGF, transforming growth factor ( $\alpha$  and  $\beta$ ); NRGs, neuregulins; GDNF, glial cell-line derived neurotrophic factor; NTs, neurotrophins; Gp130, glycoprotein 130; IL, interleukin (4 and 10); BMP, bone morphogenetic protein; BMPR, BMP receptor; RTK, receptor tyrosine kinase; JAK, janus kinase; STAT, signal transducer and activator of transcription proteins; JNK, c-Jun N-terminal kinase; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; cAMP, cyclic adenosine monophosphate; ERK, extracellular signal-regulated kinase; mTOR, mammalian target of rapamycin; FoxO1, forkhead box protein O1; Sp1, specificity protein 1; CREB, cAMP response element-binding protein, mTORC1, mTOR complex 1; GSK3 $\beta$ , glycogen synthase kinase 3  $\beta$ ; PPAR $\gamma$ , peroxisome proliferator-activated receptor  $\gamma$

family members in protection of oligodendrocyte-lineage cells against apoptosis and stimulating OPC proliferation and differentiation after WMI.

Besides their involvement in oligodendrocyte development and survival, EGF-family members modulate neuroinflammatory processes that contribute to the pathophysiology of EoP. It has been shown in vitro that shedding of hb-EGF by astrocytes can be induced by inflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$ , inducing proliferation of microglia, enhancing their phagocytotic capacity and increasing monocyte migration (Martín, Cordova, & Nieto, 2012; Schenk et al., 2013). TGF- $\alpha$  and EGF are known to promote astrogliosis through the EGFR (Kuhn, Winkler, Kempermann, Thal, & Gage, 1997; Rabchevsky et al., 1998; Weickert & Blum, 1995). Expression of hb-EGF by reactive astrocytes has also been demonstrated in active MS

lesions, which may trigger further inflammatory events in the lesioned area (Schenk et al., 2013). Single treatment with an anti-EGF antibody was therefore beneficial in an experimental autoimmune encephalomyelitis (EAE) mouse model, by shifting NSC differentiation toward neurons and oligodendrocytes instead of astrocytes (Amir-Levy, Mausner-Fainberg, & Karni, 2014). Simultaneous activation of *both* mitogen receptors (bFGF and PDGF) and EGFR further induces neuroinflammation and oligodendrocyte apoptosis in response to pathogens (Parthasarathy & Philipp, 2017), suggesting that supplementation of EGF should not coincide with extensive FGFR and PDGFR activation.

Further research is warranted to design therapies that balance the potential beneficial effect of EGF-family members on oligodendrocyte survival and maturation while avoiding excessive astrogliosis



## BOX 2 Shared intracellular pathways targeting oligodendrocyte survival and maturation

Several trophic and immunomodulatory factors discussed in this review activate shared intracellular pathways downstream of their specific receptors, such as PI3K/Akt, MAPK pathways and JAK/STAT, that are associated with oligodendrocyte survival and maturation (Figure 2). Next to supplementing growth factors and/or cytokines that activate these pathways, a potent treatment strategy for EoP could be to directly target these pathways on a molecular level.

The PI3K/Akt pathway drives oligodendrocyte survival, differentiation and maturation (Ishii, Furusho, Macklin, & Bansal, 2019; Wrigley et al., 2017). Specifically, the downstream activation of mTOR promotes oligodendrocyte survival through inhibition of pro-apoptotic pathways (O'Kusky & Ye, 2012; Wrigley et al., 2017) and stimulates oligodendrocyte differentiation and myelination (Gaesser & Fyffe-Maricich, 2016). Recently, it has been discovered that the pro-differentiating effect of mTOR is elicited by inhibition of BMP signaling, which suppresses the expression of Olig1/2 (see Section 3.3.2; Ornelas et al., 2020; Song et al., 2018). Furthermore, mTOR is involved in oligodendrocyte differentiation by regulating morphological complexity and proper axon ensheathment through downstream targets ARPC3 and profilin2, myelin gene expression, and Mbp RNA transport through mTOR target KIF1B (Musah et al., 2020). Increased expression and signaling of the PI3K/Akt/mTOR pathway was observed for up to two weeks after injury in a mouse model of preterm hypoxia-ischemia Wang et al., 2020. mTOR is likely not the only target of the PI3K/Akt pathway that influences oligodendrocyte development, as OPC-specific inactivation of PTEN, an Akt-inhibitor, led to enhanced differentiation in OPCs independently of mTOR-deletion (González-Fernández et al., 2018). Ablation of GSK3 $\beta$ , a downstream target of Akt that is phosphorylated after PTEN activation, similarly led to increased OPC differentiation, making it a likely mediator of mTOR-independent OPC differentiation (González-Fernández et al., 2018).

The rat sarcoma/extracellular signal-regulated kinases (RAS/ERK) MAP kinase pathway is activated after growth factors (e.g., IGF-1, EGF) bind specific tyrosine kinase receptors, and is involved in all stages of oligodendrocyte lineage progression, but most prominently during myelination (Gaesser & Fyffe-Maricich, 2016; Gonsalvez, Ferner, Peckham, Murray, & Xiao, 2016). Although *in vitro* evidence has revealed a role for RAS/ERK in oligodendrocyte differentiation, this has not been conclusively demonstrated *in vivo* (reviews by Gaesser & Fyffe-Maricich, 2016; Gonsalvez et al., 2016). Moreover, a recent study by Suo,

Guo, He, Gu, and Xie (2019) demonstrated that inhibition of MEK, the direct regulator of ERK1/2, promoted oligodendrocyte differentiation from NPC-derived OPCs *in vitro* and *in vivo* in an EAE model. This has led to the hypothesis that RAS/ERK is not directly involved in OPC differentiation, but does come into play during the process of myelination (Ishii et al., 2019). The RAS/ERK pathway is hypothesized to determine proper myelin thickness relative to axon diameter *in vivo* through ERK1/2 activation (Gaesser & Fyffe-Maricich, 2016; Ishii, Fyffe-Maricich, Furusho, Miller, & Bansal, 2012), and in myelin maintenance throughout adulthood (Ishii et al., 2019). Furthermore, the RAS/ERK pathway has been shown to converge with the PI3K/Akt/mTOR pathway to promote myelination during development and after demyelinating injury at the level of mTORC1, as RAS/ERK by itself could not promote sufficient myelination in mTOR-deficient mice (Ishii et al., 2019). The potential pleiotropic role of the RAS/ERK pathway in both proliferation and myelination could help explain the involvement of some OPC mitogens, such as bFGF (see Section 3.8) during myelination in mature oligodendrocytes.

Another MAP kinase, JNK, has been described to inhibit differentiation of OPCs by promoting proliferation (van Tilborg et al., 2016). The JNK pathway is activated after EoP-associated injury, such as neuroinflammation or oxygen fluctuations, which makes it a salient target for intervention after preterm birth (Bhat, Zhang, & Mohanty, 2007; van Tilborg et al., 2016). Therapeutic inhibition of the JNK pathway rescues myelination after an inflammatory stimulus *in vitro* and in a rat model of preterm dWMI, potentially through inhibiting OPC proliferation which induces differentiation (van Tilborg et al., unpublished results of our group).

Activation of the MAP kinase p38 has also been associated with oligodendrocyte development (Bhat et al., 2007; Chew, Coley, Cheng, & Gallo, 2010). p38 inhibition leads to reduced expression of oligodendrocyte signature genes such as O1 and O4, and reduced myelin production *in vitro* (Bhat et al., 2007). Furthermore, p38MAPK induces phosphorylation of the cyclic adenosine monophosphate response element-binding protein (Bhat et al., 2007), which induces gene transcription that has been proposed to underlie stimulation of oligodendrocyte differentiation and mitogenesis, for example, after innervation of the IGFR (Palacios et al., 2005; Wrigley et al., 2017). Next to its function during normal development, the p38 MAPK pathway has been associated with upregulation after inflammation (Bhat et al., 2007). OPCs from p38a specific knockout mice failed to myelinate after differentiation *in vitro*, and brains of these mouse mutants showed abnormalities in myelin microstructure (Chung et al., 2015). The p38 MAPK has also been shown to interact with other MAP kinases, such as



through inhibition of c-JUN phosphorylation (Chew et al., 2010).

Numerous cytokines, including the interleukin-family of which IL-4, IL-6, IL-10, and IL-11 discussed in this review, activate the JAK/STAT-pathway downstream of their specific receptors (Liu, Gibson, Benveniste, & Qin, 2015). Activation of STAT1 is linked to oligodendrocyte apoptosis (Liu et al., 2015), while STAT3 activation promotes oligodendrocyte survival (Zhang et al., 2011). Furthermore, STAT3 is implicated in myelinogenesis during postnatal brain development, but a mouse model with specific STAT3 ablation in oligodendrocytes showed that it is not essential for developmental myelination (Steelman et al., 2016). However, when STAT3 activation was ablated in oligodendrocytes, maturation and remyelinating capacity after focal demyelination was impaired (Steelman et al., 2016). STAT6 promotes oligodendrocyte differentiation through activation of PPAR $\gamma$  (Zhang et al., 2019).

which may exacerbate neuroinflammation, for example, by targeting the EGFR on oligodendrocytes specifically. Clinical trials involving the exogenous administration of EGF, TGF- $\alpha$  or hb-EGF for the treatment of preterm WMI have not been conducted yet to the best of our current knowledge (clinicaltrials.gov).

### 3.2.2 | Neuregulins

Neuregulins (NRGs) are members of the EGF-family that have been classically linked to myelination through their secretion by neuronal axons (e.g., Taveggia et al., 2008). OPCs and oligodendrocytes also express NRGs, which may give them the capacity to self-regulate their development (Calaora et al., 2001; Raabe, Suy, Welcher, & DeVries, 1997). NRGs signal through different homodimer and heterodimer of the ErbB receptor tyrosine kinases that are related to the EGFR (i.e., ErbB1) and can activate PI3K/Akt and MAPK pathways intracellularly (see Box 2; Canoll, Kraemer, Teng, Marchionni, & Salzer, 1999). NRG1 is the most widely studied NRG, and has been extensively studied in the context of peripheral myelination.

It has been demonstrated *in vitro* that NRG1 possesses isoform-dependent effects on OPCs and oligodendrocytes (Raabe et al., 1997). Specifically, Type II NRG1 glial growth factor 2 (GGF2) promotes proliferation in OPCs through ErbB3, as OPCs differentiate after soluble ErbB3 is administered to neutralize GGF2 (Calaora et al., 2001; Canoll et al., 1999). In contrast, Type I NRG1 isoforms induce differentiation and reduce apoptosis (Raabe et al., 1997). ErbB4, which binds multiple NRGs, was found to be particularly involved in promoting oligodendrocyte maturation and myelination (Lai & Feng, 2004; Sussman, Vartanian, & Miller, 2005). More recently, it has been discovered that Type I isoforms of NRG1 promote a shift in oligodendrocyte

phenotype which increases their responsiveness to glutamate through generation of NMDA receptors (Lundgaard et al., 2013). This enables oligodendrocytes to respond to environmental triggers to enhance their myelin production. NRG1 Type III was also found to be involved specifically in myelination, as oligodendrocytes cocultured with Type III deficient DRGs formed significantly less myelin sheaths (Taveggia et al., 2008).

*In vivo* evidence supports the role of NRGs in myelin formation. Knockout of the nardilysin (Nrd1) gene, an important regulator of NRG1 shedding, resulted in hypomyelination in the CNS and peripheral nervous system, while neuronal Nrd1 overexpression induced NRG1 Types I and III availability and consequent hypermyelination, while the availability of NRG1 Type II was not investigated (Ohno et al., 2009). Similarly, NRG1 Type III knockout mice showed hypomyelination throughout development and adulthood (Ohno et al., 2009; Taveggia et al., 2008). In both studies, numbers of OPCs and mature oligodendrocytes were not altered between mutants and wild types, suggesting that NRG1 Types I and III are specifically involved in myelination and do not play a prominent role in oligodendrocyte lineage progression. In mutant mice with oligodendrocyte-specific impairment in NRG1/ErbB signaling, oligodendrocyte morphology was altered, leading to smaller cells and less myelin production per cell (Roy et al., 2007). NRGs may therefore be a promising therapeutic agent to enhance myelination capacity of mature oligodendrocytes, perhaps in combination with a therapeutic agent that triggers oligodendrocyte survival or maturation. To our knowledge, *in vivo* studies in which NRGs are administered as a therapeutic in models of EoP have not yet been conducted.

Microglia have been shown to release NRG1 Types I and III and NRG3 after stimulation with LPS *in vitro* (Ikawa et al., 2017). *In vivo*, NRG expression was enhanced in microglia and astrocytes after injury (Ikawa et al., 2017; Tokita et al., 2001). This may be a protective response, as exogenous NRG1 $\beta$  treatment partly reduced microglial and astrocytic activation in mice exposed to LPS, leading to reduced inflammatory cytokine production and improved neuronal survival (Xu et al., 2017). However, there have also been some reports indicating antagonism of NRG1 may be beneficial in neuroinflammatory conditions, by reducing the trophic effect of NRG1 on microglia (e.g., Allender et al., 2018). Thus, although NRGs have been reported to be mainly beneficial in the context of neuroinflammation, the effects of NRGs on pro-inflammatory microglia must be examined further to rule out exacerbation of inflammation in EoP. Although not the primary focus of our review, NRGs/ErbBs have also been associated with interneuron migration and development (see Mei & Nave, 2014 for a review), possibly indicating a complex interaction between NRGs, interneurons and oligodendrocytes in EoP.

In humans, genetically caused disturbances in the NRG/ErbB balance have been associated with several neuropsychiatric disorders, such as schizophrenia, depression and bipolar disorder (see review by Mei & Nave, 2014), and have been directly linked to an impaired social performance in children with ASD (Ikawa et al., 2017). Interestingly, NRG1 is endogenously upregulated in human umbilical



endothelial cells after preterm birth, and a SNP increasing its availability is linked to improved neurodevelopmental outcome after preterm WMI (Hoffmann et al., 2010). Considering this and its role in myelination described above, NRG1 has been put forward as a protective agent in preterm WMI (see review by Dammann, Bueter, Leviton, Gressens, & Dammann, 2008). However, more recent evidence points to NRG1 isoform-dependent effects that must be taken into consideration. Further preclinical research regarding the effectiveness of NRGs in EoP is warranted to substantiate the initiation of clinical trials.

### 3.3 | Transforming growth factor beta superfamily

The transforming growth factor beta (TGF- $\beta$ ) superfamily consists of at least 30 cytokines, and can be subdivided into TGF- $\beta$ -type and bone morphogenetic protein (BMP) type-proteins, that play a role in a wide array of physiological processes, among which oligodendrocyte development and gliosis (see Weiss & Attisano, 2013 for a review).

#### 3.3.1 | TGF- $\beta$ -type proteins

There are three isoforms of TGF- $\beta$  that are postulated to play different roles in the CNS during development and disease (Dobolyi, Vincze, Pál, & Lovas, 2012; Stoll et al., 2004). TGF- $\beta$ 1 has been the most studied in the context of oligodendrocyte development. Receptors for TGF- $\beta$  (TGFBR1/activin-like kinase 5 receptor (ALK-5) and TGFBR2) are present on cells of the oligodendrocyte lineage, as well as astrocytes (e.g., Gómez Pinto, Rodríguez, Adamo, & Mathieu, 2018; Hamaguchi et al., 2019), and canonically activates the SMAD pathway, as well as the PI3k/Akt, RAS/ERK, c-JUN N-terminal kinase (JNK) and p38 MAPK pathways discussed in Box 2 (Heldin & Moustakas, 2016).

TGF- $\beta$ 1 has been shown to increase proliferation of OPCs and differentiation to mature oligodendrocytes in vitro (Gómez Pinto et al., 2018; McKinnon, Piras, Ida, & Dubois-Dalcq, 1993). The mitogenic effect of TGF- $\beta$ 1 on OPCs is likely to be indirect and mediated through astrocytes, which secrete Jagged-1 upon stimulation with TGF- $\beta$ 1 (Gómez Pinto et al., 2018; Zhang et al., 2010). Through activation of the Notch-1 receptor on OPCs, Notch ligands such as Jagged-1 stimulate OPC proliferation to prevent early differentiation, thereby regulating the timing of oligodendrocyte lineage progression (van Tilborg et al., 2016; Wang et al., 1998). Jagged-1 is also secreted by adult oligodendrocytes, possibly to signal to OPCs that the region is sufficiently myelinated (Wang et al., 1998). However, the relationship between the Notch pathway and oligodendrocyte development is likely more complex, which is highlighted in Box 1. OPCs also express TGF- $\beta$  receptors, and direct TGF- $\beta$ 1 stimulation is believed to exert a maturational effect (Gómez Pinto et al., 2018; Hamaguchi et al., 2019), likely after Jagged-1 expression by astrocytes is downregulated during normal development (e.g., Wang et al., 1998).

In a series of loss- and gain-of-function experiments, Palazuelos, Klingener, and Aguirre (2014) demonstrated that TGF- $\beta$  signaling is critical for OPC differentiation in vivo, by mediating cell cycle

withdrawal through SMAD2/3/4 and downstream FoxO1 and Sp1 activation. It is therefore perhaps surprising that the TGF- $\beta$  pathway was found to be upregulated in a rat model of neonatal HI brain injury at preterm-equivalent age in humans (Sun, Zhou, Sha, & Yang, 2010). Although TGF- $\beta$  is able to stimulate differentiation of oligodendrocytes, the upregulation of TGF- $\beta$  after HI injury may have adverse effects on EoP pathology through Jagged-1 expression by astrocytes. Therefore, studies in HI-injured neonatal rats have aimed to target the TGF- $\beta$  pathway by antagonizing the ALK-5 (or TGFBR1), that mediates the effect of TGF- $\beta$  on astrocytes. In a model of preterm injury, the ALK-5 antagonist SB505124 decreased microgliosis and astrogliosis, improved oligodendrogenesis and myelination, and promoted autophagy of potentially toxic debris (Guardia Clausi & Levison, 2017; Kim et al., 2017). However, when hypoxic-ischemic injury was induced at a later postnatal age in mice (p9 instead of p6), administration of the ALK-5 antagonist exacerbated hippocampal injury and functional outcome (Kim et al., 2017). It can be speculated that astrogliosis caused by TGF- $\beta$ /ALK-5 signaling after preterm birth negatively impacts oligodendrocyte maturation through Jagged-1 expression, while astrogliosis is necessary for demarcating lesions in hypoxic-ischemic injury at term (Kim et al., 2017) or in adult stroke (Cekanaviciute et al., 2014). Thus, in vitro and in vivo evidence suggests that TGF- $\beta$  can have a dual role in the developing brain by inducing oligodendrocyte maturation directly through TGF- $\beta$  receptors on OPCs on the one hand, but on the other hand triggering astrocytes to produce Jagged-1 that preserves OPC immaturity by inducing proliferation (e.g., Wang et al., 1998). TGF- $\beta$ -based therapies to combat EoP should therefore be aimed at oligodendrocyte-lineage cells specifically, for example, by using NG2+-targeted nanoparticles (Rittchen et al., 2015), or TGF- $\beta$  should be given in combination with a Jagged-1 antagonist.

Besides its effect on oligodendrocytes and astrocytic scar formation, TGF- $\beta$  is also involved in microglia homeostasis and activation (Bohlen, Friedman, Dejanovic, & Sheng, 2019). TGF- $\beta$  is often mentioned as an anti-inflammatory cytokine, either dampening the pro-inflammatory response, or skewing microglial activation to the neuroprotective M2-phenotype (Dobolyi et al., 2012). Administration of TGF- $\beta$ 1 has been shown to specifically induce microglial apoptosis in vitro (Xiao, Bai, Zhang, & Link, 1997). In addition, TGF- $\beta$ 2 administration reduced spontaneous myelin phagocytosis by microglia in vitro, while it had no effect on the amount of microglia that were recruited (Stoll et al., 2004). Substantive evidence demonstrating the protective potential of TGF- $\beta$  isoforms against excitotoxicity is also available (Dobolyi et al., 2012).

Together, these results underline a potential protective effect for TGF- $\beta$  in EoP. As of yet, no clinical trials using TGF- $\beta$  or ALK-5 antagonists have been registered in the clinical trials database (clinicaltrials.gov).

#### 3.3.2 | Bone morphogenetic proteins and Noggin

BMPs form the second major protein class of the TGF- $\beta$  superfamily, and BMP receptors are present on oligodendrocytes during all

developmental stages (See et al., 2004). Intracellularly, BMPs activate the SMAD pathway as well as the MAPK p38 pathway (see Box 2; Eixarch, Calvo-Barreiro, Montalban, & Espejo, 2018; Shijo et al., 2018). Through SMAD1/5, BMPs downregulate the expression of Olig1/2 (Song et al., 2018).

In vitro studies illustrate the inhibitory role of BMPs on oligodendrocyte maturation. It has been shown that BMP-4 applied to primary oligodendrocytes or brain slices irreversibly inhibits OPC differentiation into myelinating cells (Morell, Tsan, & O'Shea, 2015; Reid et al., 2012; See et al., 2004). Similarly, BMP-2 cooperates with mitogen PDGF to restrict oligodendrocyte differentiation (Adachi, Takanaga, Kunimoto, & Asou, 2005). Oxidative stress has been reported to cause BMP-4 expression leading to oligodendrocyte maturational arrest (Reid et al., 2012). Since the BMP-family negatively impacts oligodendrocyte maturation, it was hypothesized that the BMP-2/4-antagonist Noggin could protect against white matter damage. Indeed, Noggin overexpression led to increased oligodendrocyte differentiation in an in vitro model using neurospheres (Morell et al., 2015).

In a mouse model of late preterm hypoxic-ischemic injury, transgenic mice that overexpressed Noggin were protected against WMI, as shown by preservation of cells across the oligodendrocyte-lineage, and subsequent increased myelination (Dizon, Maa, & Kessler, 2011). In a rabbit model of IVH, treatment with Noggin similarly rescued oligodendrocyte maturational arrest, preserved myelination, and decreased astrogliosis (Dummula et al., 2011).

Besides their role halting oligodendrocyte maturation, BMPs have been implicated in neuroinflammation in MS and amyotrophic lateral sclerosis (ALS) pathophysiology (Eixarch et al., 2018; Shijo et al., 2018). BMP-4 expression by astrocytes was found to be increased in a mutant rat model for ALS, and Noggin was effective at dampening the neuroimmune response, reducing astrogliosis and microglial activation (Shijo et al., 2018). In an in vitro model of oxygen/glucose deprivation and reperfusion, Noggin induced release of iron from microglia, aiding the process of remyelination after injury (Shin et al., 2018). BMP signaling affects differentiation of interneuron subpopulations differently, stimulating differentiation of parvalbumin interneuron differentiation, but halting somatostatin interneuron development (Mukhopadhyay, McGuire, Peng, & Kessler, 2009). This suggests upregulation of BMPs in EoP may alter interneuron development as well as oligodendrocyte maturation.

In humans, elevation of BMP-4 in the brain has been associated with IVH in preterm infants (Dummula et al., 2011). Although results from preclinical studies show that BMP-antagonist Noggin is a promising option for the treatment of EoP, more research in preclinical models is warranted before clinical trials can be initiated (clinicaltrials.gov).

### 3.3.3 | Glial cell line-derived neurotrophic factor family

The glial cell line-derived neurotrophic factor (GDNF) family has also recently emerged as a potential candidate for treatment of white

matter pathologies. GDNF-family members have ranging affinities to the GDNF family receptor  $\alpha$  (GFR $\alpha$ ) subtypes, and these receptors are differentially expressed on cells of the oligodendrocyte lineage, suggesting that each GDNF-family member may play a unique role during oligodendrocyte development (Razavi et al., 2015; Strelau & Unsicker, 1999). When bound by a GDNF-family member, the designated GFR $\alpha$  receptor couples with a tyrosine kinase Ret-receptor to activate the MAPK and PI3K/Akt signaling pathways (see Box 2; Duarte, Curcio, Canzoniero, & Duarte, 2012).

Not much is known about the direct effects of the GDNF-family on OPCs or mature oligodendrocytes. In an in vitro model of stroke using oxygen and glucose deprivation, immediate treatment with GDNF increased OPC proliferation and differentiation into myelinating oligodendrocytes which persisted for several days after the insult, while reducing oligodendrocyte apoptosis (Li, Mao, Chen, Qian, & Buzby, 2015).

In line with the in vitro evidence, stereotactic intracerebral injection with GDNF in a rat model of periventricular leukomalacia showed similar beneficial effects on oligodendrocyte maturation and myelination (Li, Mao, et al., 2015). Transplantation of GDNF-overexpressing NSCs showed promising effects in a mouse model of EAE by increasing numbers of OPCs, mature oligodendrocytes and myelin content (Gao et al., 2016). However, overexpression of the GDNF-family member persephin in mesenchymal stem cells (MSCs) did not show an additive beneficial effect compared to wild-type MSCs in a mouse model of neonatal HI injury (van Velthoven, Braccioli, Willems, Kavelaars, & Heijnen, 2014). More research is needed to assess the therapeutic potential of GDNF-family members in preterm dWMI.

GDNF is produced by astrocytes and microglia in response to injury (Duarte Azevedo, Sander, & Tenenbaum, 2020) and has been found to be protective after brain ischemia through promotion of neuronal survival (see review by Duarte et al., 2012). However, sustained GDNF activation may prolong neuroinflammation (Duarte Azevedo et al., 2020).

GDNF and its family members have not yet been tested in clinical trials in preterm infants (clinicaltrials.gov), but have been clinically tested and found safe for the treatment of Parkinson's disease and neuropathic pain (e.g., Marks, Baumann, & Bartus, 2016; Rolan et al., 2015; Whone et al., 2019).

## 3.4 | Neurotrophins

The neurotrophin (NT) family consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, NT-4/5, and NT-6. Each NT acts with high affinity on a preferred receptor of the tropomyosin-related kinase (Trk) family and with low affinity to the p75 NT receptor present on oligodendrocytes (Acosta, Cortes, MacPhee, & Namaka, 2013; Huang & Reichardt, 2001; Wong, Willingham, Xiao, Kilpatrick, & Murray, 2008). Through activation of the Trk/p75 receptors, NTs have been linked to activation of the PI3K/Akt, MAPK, and signaling pathways (see Box 2; Cohen, Marmur, Norton, Mehler, & Kessler, 1996; Huang & Reichardt, 2001; Ness, Mitchell, &



Wood, 2002). NTs and their receptors are upregulated starting from early embryonic neurodevelopment (Bernd, 2008) and likely provide trophic support to neurons and oligodendrocytes throughout life. After CNS injury, expression of NTs and their receptors has been shown to be increased (Acosta et al., 2013; Huang & Reichardt, 2001; Ness et al., 2002).

In vitro results indicate that NTs, through their preferred receptors, may have different effects on cells of the oligodendrocyte lineage. BDNF, well-known for its trophic effect on the brain, has been shown to enhance myelination in a model where DRG neurons are cocultured with oligodendrocytes (Xiao et al., 2010). Furthermore, it was found that the effect of BDNF on myelination was mediated by TrkB expression on oligodendrocytes, as myelination of both DRG subtypes expressing either TrkA or TrkB occurred after BDNF supplementation, and this effect was only suppressed by a TrkB-inhibitor. In an in vitro model of chemically induced hypoxic injury, astrocyte-conditioned medium containing BDNF promoted OPC differentiation (Miyamoto et al., 2015). This study also showed that the beneficial effect of BDNF was halted by use of the PI3K-inhibitor LY294002 or when astrocyte-conditioned medium was depleted of BDNF with a TrkB-Fc decoy receptor (Miyamoto et al., 2015). Not much is known about the effect of NT-4/5 on oligodendrocyte maturation, but this NT shares about 95% sequence homology with BDNF and also binds to TrkB, suggesting it may have a similar beneficial effect (Dhobale, 2014). Similar to BDNF, NT-3 induced substantial axonal myelination when oligodendrocytes were cocultured with DRG neurons, as well as survival and proliferation of OPCs and mature oligodendrocytes (Barres et al., 1994; Saini et al., 2005; Yan & Wood, 2000). In an isolated OPC culture, biofabricated sponges emitting NT-3 subtly increased differentiation of primary OPCs toward the pre-OL stage, but the population of MBP+ mature oligodendrocytes was similar to the untreated condition, indicating NT-3 only affected oligodendrocyte differentiation but not final maturation (Mekhail, Almazan, & Tabrizian, 2015). In another experiment where DRG neurons were cocultured with oligodendrocytes, administration of NGF indirectly reduced spontaneous myelination through TrkA present on DRG neurons, whereas NGF had no effect on myelin expression of purified OPCs, or when oligodendrocytes were cocultured with DRG neurons lacking TrkA (Chan et al., 2004). This is in contrast to BDNF, which directly affects myelination of oligodendrocytes (Xiao et al., 2010). NGF has also been reported to cause apoptosis of mature oligodendrocytes cultured from neonatal rat brains through p75/JNK (see Box 2; Casaccia-Bonnel, Carter, Dobrowsky, & Chao, 1996), but apoptosis was not seen after NGF administration to postmitotic oligodendrocytes isolated from human tissue (Ladiwala et al., 1998).

Trophic effects of NTs on myelination were largely confirmed in animal models. In BDNF+/- mice, oligodendrocyte numbers are reduced and myelination is impaired in the forebrain during the postnatal period (Nicholson et al., 2018; Vondran, Clinton-Luke, Honeywell, & Dreyfus, 2010; Xiao et al., 2010). TrkB is likely a mediator of myelination through BDNF, as conditional knockout of TrkB in oligodendrocytes restricted formation of thick myelin sheaths during

development (Wong, Xiao, Kemper, Kilpatrick, & Murray, 2013). In models of neonatal WMI, knockdown of BDNF expression in astrocytes reduces oligodendrogenesis and exacerbates WMI (Miyamoto et al., 2015), whereas upregulation of BDNF and TrkB through induced histone acetylation increases OPC proliferation, oligodendrocyte maturation and myelination, and improved behavioral outcome (Huang et al., 2018). In a model of neonatal hypoxic-ischemic injury, genetically modified MSCs that overexpressed BDNF did not have a superior effect on reducing white matter damage compared to empty-vector MSCs, but did decrease lesion size and motor outcome compared to empty vector-MSCs (Van Velthoven et al., 2013; van Velthoven et al., 2014). NT-3 has been proven effective in rescuing myelination and enhancing remyelination in mouse models of MS (Fressinaud, 2005; Jean, Lavialle, Barthelaix-Pouplard, & Fressinaud, 2003; Zhang et al., 2012) and spinal cord injury (Thomas et al., 2014). Finally, TrkA-agonist BNN27, which mimics the effects of NGF but with improved pharmacokinetics, protects the brain from demyelination and stimulates oligodendrocyte maturation in a cuprizone-induced mouse model of MS (Bonetto, Charalampopoulos, Gravanis, & Karagogeos, 2017).

A vast amount of literature is available about the role of NTs, particularly BDNF, in neuroinflammation. It is generally accepted that NT release functions as a protective mechanism following neuroinflammation, as NT insufficiency is linked to a wide array of neuropsychiatric conditions with a neuroinflammatory component (Lima Giacobbo et al., 2019). While neuroinflammation can induce NT release in astrocytes, an excess of pro-inflammatory cytokines, particularly IL-1 $\beta$ , can also halt neurotrophic support (Ohja et al., 2018; Tong et al., 2012). Nonetheless, NGF and BDNF have been shown to promote a neuroprotective phenotype in microglia (Lai et al., 2018; Neumann, Misgeld, Matsumuro, & Wekerle, 1998; Rizzi et al., 2018) and reduce astrogliosis in in vitro studies (Cragolini, Huang, Gokina, & Friedman, 2009). These results support the notion that NTs contribute to dampening the immune response in the injured brain.

In human studies, lowered maternal and cord blood BDNF, NGF, and NT-3 levels have been reported in preterm compared to term born infants (Dhobale, 2014). However, postnatal inflammation in extremely preterm neonates has been associated with an upregulation of NTs in blood (Leviton et al., 2017), which likely serves as an endogenous protective response, as increased systemic NT levels have been linked to improved cognitive outcomes at 10 years of age (Kuban et al., 2018). In sum, endogenous production of NTs, particularly BDNF, has been associated with improvement of neurodevelopmental outcome following preterm birth, and exogenous NT supplementation could provide a valuable treatment option to enhance oligodendrocyte maturation and reduce neuroinflammation. Systemic administration of NTs is likely complicated by restricted passage of these large molecules over the (intact) BBB (Kastin, Akerstrom, & Pan, 2003; Pardridge, 2003). Alternative strategies to ensure optimal delivery of NTs are discussed in Section 4. Currently, no clinical trials have been initiated in preterm infants, but several have been planned and/or conducted for the treatment of traumatic and degenerative brain diseases (clinicaltrials.gov).

### 3.5 | Glycoprotein 130 receptor cytokine family

Glycoprotein 130 (gp130) is a cytokine receptor subunit that interacts with several cytokine receptors like the soluble receptors for IL-6, IL-11, LIF, and CNTF, and is localized throughout the brain on both neurons and glial cells (Watanabe et al., 1996). For IL-6, the IL-6R is minimally present on human oligodendrocytes (Cannella & Raine, 2004), therefore it mainly communicates through gp130 using a process called trans-signaling, during which a cytokine binds its soluble receptor that in turn engages the transmembrane gp130 receptor (Rothaug, Becker-Pauly, & Rose-John, 2016). Gp130 intracellularly activates the JAK/STAT and SHP2 pathways, the latter triggering the downstream RAS/ERK and PI3K/Akt pathways (see Box 2; e.g., Zhang et al., 2011).

In vitro, gp130 ligands have been shown to promote maturation of primary OPCs, and subsequently stimulate myelination in vitro through activation of the STAT3 pathway (CNTF and LIF: Fischer, Wajant, Kontermann, Pfizenmaier, & Maier, 2014; Rittchen et al., 2015; Steelman et al., 2016; IL-6/IL-6R: Valerio et al., 2002; Zhang et al., 2011; Zhang, Chebath, Lonai, & Revel, 2004; IL-11: Zhang et al., 2006). IL-11, CNTF, and LIF have also been shown to increase survival of oligodendrocyte lineage cells (Stelman et al., 2016; Zhang et al., 2006; Zhang et al., 2011). Interestingly, it was shown for IL-11 that its antiapoptotic effect is predominantly mediated by STAT3 in cells of the neural lineage such as OPCs, but can be pro-apoptotic through STAT1 signaling in CD11c+ dendritic cells (Zhang et al., 2011), indicating a differential effect of IL-11 on downstream STAT subtype involved based on cell lineage. Whether this pro-apoptotic effect of IL-11 extends to (Cd11c+) microglia has not been examined yet. In an in vitro model where OPCs were exposed to TNF- $\alpha$ , IL-11 reduced caspase cleavage, suggesting that IL-11 is protective against apoptosis even in the presence of an inflammatory stimulus (Zhang et al., 2011). Additionally, in a BV-2 microglial cell line culture, IL-11 dose-dependently inhibited myelin phagocytosis (Maheshwari et al., 2013). In a glial coculture, activation of the TNF- $\alpha$  receptor TNFR2 on astrocytes led to enhanced LIF production, which consequently stimulated oligodendrocyte maturation, suggesting TNFR2 mediates a protective effect of LIF in response to TNF- $\alpha$  (Fischer et al., 2014).

In vivo evidence implicating gp130 ligands in oligodendrocyte maturation and myelination comes largely from animal models of MS. Knockout of IL-11R $\alpha$ , LIF, or CNTF in MS models exacerbated demyelination and oligodendrocyte loss compared to wild-type mice, while increasing glial reactivity (Butzkueven, Emery, Cipriani, Marriott, & Kilpatrick, 2006; Linker et al., 2002; Zhang et al., 2011). In line with the knockout studies, local overexpression of IL-11 increased mature oligodendrocytes and remyelination, and decreased microglial activation in a cuprizone-induced mouse model of MS (Maheshwari et al., 2013). LIF has also been shown to be a beneficial trophic factor for myelination during postnatal development, as LIF knockout mice showed reduced optic nerve myelination (Ishibashi, Lee, Baba, & Fields, 2009). Therapeutic targeting of NG2+ OPCs/pre-OLs with nanoparticles containing LIF has proven to be effective in promoting remyelination after focal demyelinating injury (Rittchen et al., 2015).

In contrast, LIF activation has also been shown to adversely influence oligodendrocyte maturation after perinatal hypoxic-ischemic injury through the induction of Notch signaling, which promotes NSC/OPC proliferation rather than maturation (Covey & Levison, 2007).

Although the effect of gp130-ligands has been well established in relation to oligodendrocyte survival and maturation (e.g., D'Souza, Alinauskas, & Antel, 1996; Mayer, Bhakoo, & Noble, 1994), they are upregulated during neuroinflammation and have contrasting effects (Davis & Pennypacker, 2018; Rothaug et al., 2016; Winship & Dimitriadis, 2017). IL-11 treatment decreases TNF- $\alpha$  expression and skews microglia toward a protective M2 phenotype in the adult rodent brain (Pusic, Pusic, Kemme, & Kraig, 2014). Through gp130, LIF has also been shown to increase expression of antioxidant genes in oligodendrocytes, which may decrease damage caused by oxidative stress from excessive ROS production by reactive microglia (Rowe et al., 2014). In contrast, IL-6 and CNTF/soluble CNTFR $\alpha$  have been shown to induce pro-inflammatory microglial activation (Lin, Jain, Li, & Levison, 2009; Rothaug et al., 2016), which may exacerbate neuroinflammation during EoP.

In humans, elevated levels of IL-11 in decidua have been found after preterm compared to term birth (Cakmak et al., 2005). These increased IL-11 levels have been linked to induction of parturition in preterm neonates, as a protective response to circumvent excessive maternal inflammation (Winship & Dimitriadis, 2017). Elevated IL-11 in plasma of preterm infants is also associated with sepsis and NEC during the postnatal period, whereas it is not detectable in term-born infants (McCloy, Roberts, Howarth, Watts, & Murray, 2002). Although gp130 ligands seem promising for oligodendrocyte differentiation and maturation, gp130-based therapies must be tailored to maximize their anti-inflammatory potential if they are used for the treatment of EoP. Clinical trials with CNTF, LIF, IL-6, and IL-11 in preterm infants have not yet been initiated (clinicaltrials.gov). CNTF is being tested in implants for the treatment of adult retinopathies (e.g., Chew et al., 2019).

### 3.6 | Interleukin-4 and interleukin-10

Due to their canonical status as anti-inflammatory cytokines, much research has been conducted on IL-10 and IL-4 in neuroinflammatory pathologies (e.g., Kwilasz, Grace, Serbedzija, Maier, & Watkins, 2015). Production of IL-10 and IL-4 by immune cells shifts the microglial phenotype to enhance recovery (Kwilasz et al., 2015), thereby counteracting the effects of pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and granulocyte-macrophage colony stimulating factor (GM-CSF; Butovsky et al., 2006; Hashimoto, Komuro, Yamada, & Akagawa, 2001). All in all these anti-inflammatory cytokines contribute to a more favorable environment for neuronal and oligodendrocyte survival (Yang et al., 2009). Although protection by IL-4 and IL-10 is believed to be largely mediated through their role in dampening adverse inflammatory events, IL-4 and IL-10 can also directly target their respective receptors present on cells of the oligodendrocyte-lineage (Molina-Holgado, Vela, Arevalo-Martin, & Guaza, 2001; Zanno





et al., 2019). Intracellularly, IL-10 activates the JAK/STAT and PI3K/Akt pathways (see Box 2; Zhou, Peng, Insolera, Fink, & Mata, 2009) while it is known IL-4 targets PPAR $\gamma$  in OPCs, potentially through STAT6 (Zanno et al., 2019; Zhang et al., 2019).

In primary OPCs and oligodendrocytes, IL-4 and IL-10 are able to increase survival under pro-inflammatory conditions, by decreasing the expression of iNOS and production of NO by oligodendrocyte and cocultured glial cells (Molina-Holgado et al., 2001; Paintlia, Paintlia, Singh, & Singh, 2006). IL-10R activation in neurons enhances survival under excitotoxic conditions through PI3K/Akt and JAK/STAT3 pathway activation (Zhou et al., 2009), which might also hold true for oligodendrocytes. Aside from their antiapoptotic effects, IL-10 and IL-4 promote neurogenesis and oligodendrogenesis (Butovsky et al., 2006; Yang et al., 2009). Specifically, oligodendrogenesis is instigated via IGF-1 production by IL-4-conditioned microglia (Butovsky et al., 2006). The studies on direct effects of IL-4 on OLs are conflicting as some studies find no direct effects of IL-4 on cells of the oligodendrocyte-lineage in vitro (Butovsky et al., 2006; Psachoulia et al., 2016), others report inhibition of differentiation of these cells (Zanno et al., 2019) or stimulation of OPC differentiation through transcription factor PPAR $\gamma$  (Zhang et al., 2019).

Treatment with IL-10 in vivo has shown promise in several models of neonatal brain injury. For instance, IL-10 decreased white matter lesion size after neonatal excitotoxic brain injury in mice (Mesples, Plaisant, & Gressens, 2003). A study by Pang, Rodts-Palenik, Cai, Bennett, and Rhodes (2005) showed that IL-10 decreased apoptosis and enhanced presence of pre-OLs, mature oligodendrocytes, and MBP density in a rat model of intrauterine infection. Microglial activation and astrogliosis were also reduced after IL-10 treatment (Pang et al., 2005). NSCs modified to overexpress IL-10 rescued demyelination in a model for MS, by suppressing the infiltration and stimulating the apoptosis of peripheral immune cells and causing a more favorable intracerebral milieu (Yang et al., 2009). IL-10 overexpression also favored differentiation of NSCs into neurons or oligodendrocytes instead of astrocytes in vitro and in vivo, thereby reducing astrogliosis and stimulating remyelination.

It has been shown that IL-4 may elicit a different response in neonates versus adults in in vivo experimental models. In a rat model of intrauterine growth restriction, IL-4 was significantly increased in the brain of growth-restricted pups, and treatment with a neutralizing IL-4 antibody directly after birth improved oligodendrocyte maturation and white matter development, by decreasing the Th2 neuro-inflammatory response (Zanno et al., 2019). In contrast, IL-4-based therapies show great promise in regenerating white matter in models of adult inflammatory brain injury (Zhang et al., 2019).

Preterm infants that homozygously carry the IL-10 "high producer" allele were less vulnerable to development of periventricular WMI as assessed by ultrasound echodensities, and showed a better neurodevelopmental outcome at 2 years of age (Dördelmann et al., 2006). In conclusion, IL-10 and IL-4 protect oligodendrocytes against inflammatory conditions, either by increasing survival or by halting neuroinflammatory processes. Although both IL-10 and IL-4 seem to positively affect remyelination in adults, only IL-10 is deemed

safe in neonatal models. To our knowledge, IL-4 and IL-10 have not been explored in clinical trials of preterm brain injury (clinicaltrials.gov).

### 3.7 | CXC chemokine family

The CXC-family is a subclass of chemotactic cytokines (i.e., chemokines) that are expressed in the CNS, and their receptors have been found on cells of the oligodendrocyte lineage, as well as other CNS cell types (Bajetto, Bonavia, Barbero, & Schettini, 2002; Banisadr, Rostène, Kitabgi, & Parsadaniantz, 2005). CXCRs have been reported to activate the RAS/ERK and PI3K/Akt pathways in oligodendrocytes (Tian et al., 2018).

CXCL1 was found to promote OPC proliferation in rat isolated OPC cultures (Robinson, Tani, Strieter, Ransohoff, & Miller, 1998) and human preterm fetal brain slices (Filipovic & Zecevic, 2008), but only in conjunction with astrocytes and/or PDGF, suggesting that CXCL1 acts together with other factors to mediate the proliferative effect on oligodendrocytes (Bradl & Lassmann, 2010). The direct effect of CXCL1 on oligodendrocytes was studied in transgenic mice, in which knocking out its receptor CXCR2 led to a reduced number of mature oligodendrocytes and consequent hypomyelination, but an increased population of OPCs (Padovani-Claudio, Liu, Ransohoff, & Miller, 2006). In a study by Wang et al. (2020), it was shown that a CXCR2 antagonist was effective in stimulating OPC proliferation and differentiation in a cuprizone-induced mouse model of MS. Only a small subpopulation of oligodendrocytes expresses CXCR2 in human fetal and adult MS tissue (Filipovic, Jakovcevski, & Zecevic, 2003; Filipovic & Zecevic, 2008), therefore CXCL1 acts mainly on human oligodendrocytes through other cell types such as astrocytes (Bradl & Lassmann, 2010).

CXCL12, another member of the CXC-family, exerts different effects on OPCs and oligodendrocytes through its two receptors CXCR4 and CXCR7 (Kremer et al., 2016; Maysami et al., 2006). Initially, CXCL12 stimulates migration of OPCs through CXCR4 that activates downstream MEK/ERK and PI3K/Akt pathways (Tian et al., 2018). During normal development, CXCR4 is downregulated and CXCR7 is upregulated (Dziembowska et al., 2005; Göttle et al., 2010), thereby switching the role of CXCL12 to promote differentiation and maturation through CXCR7 in later stages of development (Göttle et al., 2010; Kremer et al., 2016). Although downregulated during development, CXCR4 was also found to be crucial for oligodendrocyte maturation in a mouse model of cuprizone-induced demyelination, where blockade of the CXCR4 receptor using either a pharmacological or genetic (lentiviral) approach, decreased the number of mature oligodendrocytes, while increasing the preoligodendrocyte population (Patel, McCandless, Dorsey, & Klein, 2010).

Next to direct effects of CXC-chemokines on cells of the oligodendrocyte-lineage, they could indirectly affect EoP through their role in inflammatory processes. For example, CXCL1 and CXCL5 can contribute to neuroinflammation through their mutual receptor

CXCR2. In a rat model of hypoxic-ischemic injury, antagonizing CXCR2 attenuated microglial activation which rescued myelination and BBB integrity, whereas supplementing CXCL5 caused the opposite effect (Wang, Tu, Lin, & Huang, 2016). Antagonizing CXCR2 similarly reduced neuroinflammation and preserved white matter microstructure in a mouse model of chorioamnionitis (Yellowhair et al., 2019). CXCL12 secretion by microglia is increased in response to hypoxia *in vitro* and in neonatal and adult rodents after hypoxic-ischemic injury (Kaur, Sivakumar, Yip, & Ling, 2009; Li et al., 2015), but CXCL12 expression is downregulated in brain endothelial cells *in vitro* after stimulation with LPS or TNF- $\alpha$  (Silwedel et al., 2018). In contrast to CXCL1 and CXCL5, decreased CXCL12 levels caused by neuroinflammation may cause additional harm, as was shown in an EAE model where antagonism of CXCL12 exacerbated WMI (Miljkovic et al., 2011).

In humans, upregulation of certain CXCs have been implicated in several CNS diseases with an inflammatory hallmark, such as MS, Alzheimer's disease, and ischemic stroke (Mirabelli-Badenier et al., 2011), and are also associated with preterm birth (Aminzadeh et al., 2012; Keelan et al., 2004; Malamitsi-Puchner et al., 2006). CXC-family members have not yet been used in clinical trials for the prevention of EoP (clinicaltrials.gov).

### 3.8 | Other factors

Several other (growth) factors have been implicated in oligodendrocyte lineage development and survival, but evidence underlining their potential efficacy and working mechanisms to combat EoP are still limited. Factors such as bFGF, PDGF, granulocyte-CSF (G-CSF), and hepatocyte growth factor (HGF) are primarily known as (OPC) mitogens (Armstrong, Le, Frost, Borke, & Vana, 2002; PDGF: Baron, Metz, Bansal, Hoekstra, & de Vries, 2000; Frost, Nielsen, Le, & Armstrong, 2003; bFGF: Goddard, Berry, Kirvell, & Butt, 2001; Hill, Patel, Medved, Reiss, & Nishiyama, 2013; Hu et al., 2008; Mela & Goldman, 2013; Mitew et al., 2014; Ohya, Funakoshi, Kurosawa, & Nakamura, 2007; Sil, Periyasamy, Thangaraj, Chivero, & Buch, 2018; Wilson et al., 2003; HGF: Yan & Rivkees, 2002), which keep OPCs in the cell cycle and restrict their differentiation. Concomitant upregulation of several of these factors after brain injury may help sustain the immature OPC population (Armstrong et al., 2002; Furusho, Roulois, Franklin, & Bansal, 2015) and thus inhibit myelination. However, some of these factors could contribute to oligodendrocyte maturation and subsequent myelination, either through a direct effect on oligodendrocytes or through facilitating a better intracerebral milieu.

bFGF and PDGF are significantly reduced in preterm compared to term umbilical cord blood (Gródecka-Szwajkiewicz et al., 2020). Both bFGF and PDGF are known to stimulate OPC proliferation, but bFGF may exert this effect through inhibition of maturation, keeping OPCs in the cell cycle, while PDGF induces both proliferation and maturation (Murtie, Zhou, Le, Vana, & Armstrong, 2005). However, more recent studies with selective knockout mice have implicated FGFR1/2

in proper myelin formation, axonal ensheathment, and in remyelinating capacity after injury (Furusho et al., 2015; Furusho, Dupree, Nave, & Bansal, 2012). FGFR3 is present on OPCs and is downregulated after hypoxic-ischemic injury (Furusho et al., 2012; Qu et al., 2015). Prolonged *i.p.* treatment with bFGF ameliorated WMI in a HI rat model, through increasing the number of myelinated axons and thickness of the myelin sheath, while upregulating FGFR3 expression in pre-OLs (Qu et al., 2015). bFGF therapy has also shown some efficacy in restoring myelination in mouse models of MS (Dehghan, Javan, Pourabdolhossein, Mirnajafi-Zadeh, & Baharvand, 2012; Furusho et al., 2012). Consistent with *in vitro* evidence, PDGF-A was found to be important for oligodendrocyte maturation as endogenous production was reduced after hyperoxia in neonatal rats, corresponding to a reduction in mature oligodendrocytes and hypomyelination (Scheuer et al., 2015). Similarly, PDGF- $\alpha$ +/- mice had a reduced number of mature oligodendrocytes in the corpus callosum after 6-weeks recovery from cuprizone treatment to mimic MS (Murtie et al., 2005). Although primarily known as OPC mitogens, novel roles for bFGF and PDGF in oligodendrocyte maturation and myelination that have been discovered more recently may warrant further investigation into these factors for the treatment of EoP.

An upregulation in G-CSF levels in umbilical cord blood and amniotic fluid has been associated with preterm brain injury (Lu et al., 2018; Lu, Zhang, Wang, & Lu, 2016). Increased levels of G-CSF may be a protective response, as some results have indicated efficacy of G-CSF against hallmarks of EoP, such as neuroinflammation (Jellema et al., 2013; Kadota et al., 2012; Peng, 2017; Song et al., 2016), excitotoxicity (Neubauer et al., 2016) and apoptosis through activation of the JAK/STAT, PI3K/Akt, and ERK pathways (see Box 2; Kim et al., 2008; Yata et al., 2007). Consequently, improved oligodendrocyte maturation and myelination after G-CSF treatment was observed in an ovine model of preterm brain injury (Jellema et al., 2013) and in traumatic nerve injuries (Kadota et al., 2012; Song et al., 2016). Conflicting results have been obtained in rodent models of preterm brain injury, ranging from adverse effects of G-CSF on brain injury and apoptosis, to positive or absent effects after delayed administration (Keller et al., 2006; Neubauer et al., 2016; Schlager et al., 2011). Together, these results indicate some positive effects of G-CSF on apoptosis and inflammation exist, but timing seems crucial to its efficacy in EoP. Enteral administration of G-CSF has already been utilized in preterm infants to induce feeding tolerance and reduce the risk of NEC (El-Ganzoury et al., 2014), but studies on the effect of G-CSF on the preterm brain have not been conducted yet (clinicaltrials.gov). However, G-CSF has been tested for the treatment of several other neurological diseases, such as Parkinson's disease and cerebral palsy (Koh et al., 2018; Tsai et al., 2017).

c-Met receptor ligands HGF and CD82 are also involved in oligodendrocyte lineage progression. HGF mostly contributes to OPC proliferation and migration, keeping OPCs in an immature state and decreasing after birth (Mela & Goldman, 2013; Ohya et al., 2007; Yan & Rivkees, 2002). In contrast, expression of the c-Met antagonist



CD82 emerges later in postnatal brain development and is involved in oligodendrocyte maturation and myelination (Mela & Goldman, 2009, 2013). However, no in vivo evidence is available on efficacy of CD82 administration in models of white matter pathologies.

#### 4 | FUTURE PERSPECTIVES

In this review, we have illustrated that a wide range of growth factors and cytokines can impact oligodendrocyte lineage maturation and microglia/astrocyte activation during healthy brain development and after injurious conditions like dWMI (Table 1). For some factors, such as IGF-1, a large body of evidence supporting its beneficial potential in dWMI is available from both in vitro and in vivo models of (neonatal) WMI. Other factors like GDNF and CNTF have been implicated in healthy oligodendrocyte development, or increased expression of factors like IL-11 and EGF, has been shown as an (inadequate) endogenous protective response following (diffuse) WMI but currently lack vigorous evidence in models of preterm dWMI. Moreover, for some of these factors, like LIF, NGF, TGF- $\alpha$ , and GDNF, evidence seems inconclusive as some studies describe beneficial properties where others describe detrimental effects of the factor on oligodendrocyte lineage development or neuroinflammation. With the current knowledge, many challenges still lie ahead when translating these experimental in vitro and in vivo studies on trophic and immunomodulatory factors to the field of EoP and clinical application further down the line.

One of these challenges is the interpretation of data obtained in experimental rodent models of oligodendrocyte development to the human developing brain and to interpret data of other (adult) white matter pathologies to preterm dWMI. Even though rodent and human white matter development share similarities, such as the origin and migratory pattern of OPCs and the caudal-to-rostral pattern of myelin formation, there are also some apparent dissimilarities (van Tilborg et al., 2018). For example, while rodent oligodendrocytes widely express CXCR2, the receptor that mediates the pro-differentiation effect of CXCL1, CXCR2 expression in human oligodendrocytes is scarce (Filipovic & Zecevic, 2008). Similarly, the pro-differentiating effect of bFGF was shown to be limited in human OPCs (Wilson et al., 2003), making these factors less attractive for clinical application. Thus, potential differences between species should be considered carefully when translating a promising factor from experimental studies to the clinic. To facilitate translationability from rodent studies to humans, van Tilborg et al. (2018) proposed the use of human iPSC-derived OPCs to complement the limited supply of fetal human tissue, as an alternative to study the efficacy of these factors on human oligodendrocyte lineage development. iPSCs could also be used to generate cerebral organoids, providing a more complex structure to study the therapeutic potential of trophic factors, including the interaction with other glial cell types (Kim et al., 2019; Madhavan et al., 2018; Ormel et al., 2018). Moreover, when interpreting data from other (adult) animal models, differences in the pathophysiology of preterm dWMI compared to other (adult) white matter diseases should be

considered. In preterm dWMI, myelin formation is hampered due to a developmental oligodendrocyte *maturation arrest*, while in neonatal stroke or HIE, loss of white matter volume is accompanied by pronounced oligodendrocyte apoptosis. In addition, preterm dWMI is caused by impaired a priori myelination, whereas in adult models of stroke or other neurodegenerative diseases preexisting myelin sheaths are damaged and need to be remyelinated by the trophic therapies. Furthermore, other white matter disease models like MS have a considerable different pathophysiology in which immune system dysfunction causes demyelination (Compston & Coles, 2002; Gutierrez-Fernandez et al., 2013; Mifsud, Zammit, Muscat, Di Giovanni, & Valentino, 2014). Thus, to make the next step toward clinical application, additional research on the efficacy of promising factors in clinically relevant models of preterm dWMI, in combination with in vitro experiments using human glial cells is strongly advised.

Another challenge in clinical translationability is determination of the most optimal treatment strategy for preterm dWMI. One option would be to select the most promising candidate factor for monotherapy, preferably an all-round factor that boosts oligodendrocyte maturation while simultaneously dampening neuroinflammation. As summarized in this review, BDNF, NRG1, IL-11, LIF, IL-10, and CXCL12 seem to possess these all-round properties, and are therefore, in our opinion, the most promising candidates for monotherapy. Even though IGF-1 possibly does not tick both these boxes, we believe it should be considered as a monotherapeutic option, due to the extensive amount of evidence on its role in healthy white matter development and potential to boost myelination after neonatal brain injury, gathered from multiple in vitro and in vivo models. Moreover, recent clinical research has deemed IGF-1 administration to extreme preterm infants to be safe (Ley et al., 2013; Lofqvist et al., 2009). Another option is administration of a cocktail of multiple promising factors, aimed at oligodendrocyte survival, differentiation, and reduction of neuroinflammation. The contents and timing of such a trophic/immunomodulatory factor-cocktail could be given in a tailor-made way, following the patient's disease course, for example, by administration of factors with anti-inflammatory properties during episodes of inflammation. Tailor-made treatment could also reduce safety-related issues, by preventing adverse effects that could result from an interaction with the environment, such as a high dose of IGF-1 during an episode of acute inflammation. Another strategy to prevent side effects due to undesirable interactions could be targeted delivery of factors to specific cell types in the brain, using nanoparticles (McMillan, Batrakova, & Gendelman, 2011; Rittchen et al., 2015). In recent years, natural or synthetic nanoparticles, binding or encapsulating a multitude of therapeutic agents, have been proposed as carriers for targeted delivery of drugs to the CNS surpassing the BBB (see below; Barbu, Molnár, Tsibouklis, & Górecki, 2009; Nag & Delehanty, 2019; Patra et al., 2018). Additionally, nanoparticles were shown to release the drug of interest in a controlled manner, preventing high, potentially toxic drug concentrations and prolonging the therapeutic effect (Nag & Delehanty, 2019; Teleanu, Negut, Grumezescu, Grumezescu, & Teleanu, 2019). Interestingly, pioneer studies have shown the potential of engineered nanoparticles

expressing cell-specific ligands on their outer surface, allowing cell-specific targeting, limiting undesirable interactions with other cell types (Rittchen et al., 2015). Although promising, some hurdles for clinical application of nanoparticles remain. Ligand-specificity might prove to be challenging, especially considering potential changes in receptor expression on the surface of target cells, either in development or in response to environmental cues (i.e., inflammation; Luo, Yang, Zhou, & Hu, 2020; Mi, Cabral, & Kataoka, 2020). Moreover, additional challenges include reliable reproducibility in nanoparticle syntheses, the avoidance of nanoparticle clearance by macrophages using nanoparticle coatings, and the optimization of biodegradability and subsequent clearance of nanoparticles after administration (Nag & Delehanty, 2019). The proposed route of personalized medicine to ensure optimal treatment efficacy and safety for each individual patient could be supported by identification of biomarkers, for instance the low serum IGF-1 observed in (extreme) preterm infants.

Aside from serum concentrations in preterm patients, analysis of genetic profiles could contribute to development of personalized medicine, for example, by selecting children that lack the protective NRG1 SNP discussed earlier, or children with genetic variants that are associated with exacerbation of neuroinflammation (van Tilborg et al., 2016). Apart from factor-based therapy, other therapies that affect cerebral growth factor and cytokine concentrations during brain development have been identified, such as nutritional interventions (Hortensius, van Elburg, Nijboer, Benders, & de Theije, 2019; Keunen, Van Elburg, Van Bel, & Benders, 2015) and MSC therapy (Vaes et al., 2019). These treatments could be used in conjunction with additional trophic factor or cytokine supplementation or possibly serve as an overarching alternative. Even though stem cell therapy and/or nutritional interventions could be considered as a more desirable option, due to a more continuous secretion of trophic and/or immunomodulatory factors, these therapies limit manipulation of the exact

**TABLE 1** Factors promoting each stage of oligodendrocyte lineage progression and survival, and their effects on neuroinflammation

	Proliferation	Differentiation	Myelin sheath formation	OL survival	Inflammation
IGF-1	●	●●		●●	○
EGF-family					
EGF	(●)	●●		○	Pro
TGF- $\alpha$				●●	○
NRGs	● (GGF2)	●	●●	●	○
TGF- $\beta$ family					
TGF- $\beta$	(●)	●●			Anti
Noggin		●●			
GDNF	●●	●●	●●	●●	○
Neurotrophins		●●	●●		Anti
Gp130 family					
IL-6		●			Pro
IL-11		●●		●	Anti
CNTF		●		●	Pro
LIF	○	●	●●	●	Anti
IL-4		○		●	Anti
IL-10		●●		●●	Anti
CXCL1/5	(●)	●			Pro
CXCL12	●	●			Anti
Other factors					
bFGF	●●		●●		
PDGF	●●	●●			
G-CSF		○	○	○	Anti
HGF	●●				
CD82		●	●		

Note: ● = only in vitro evidence available; ●● = in vitro and in vivo evidence available; ○ = inconclusive; (●) = indirect effect (i.e., through interaction with other factors or cell types such as astrocytes).

Abbreviations: bFGF, basic fibroblast growth factor; CD82, cluster of differentiation 82; CNTF, ciliary neurotrophic factor; CXCL, CXC ligand; EGF, epidermal growth factor; G-CSF, granulocyte colony-stimulating factor; GGF2, glial growth factor-2; GDNF, glial cell-line derived neurotrophic factor; Gp130, glycoprotein 130; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor 1; IL, interleukin (6, 4, 10, and 11); LIF, leukemia inhibitory factor; NRGs, neuregulins; OL, oligodendrocyte; PDGF, platelet-derived growth factor; TGF, transforming growth factor ( $\alpha$  and  $\beta$ ).



protein cocktail composition (Hortensius et al., 2019; Keunen et al., 2015; Vaes et al., 2019). For this reason, some studies propose genetic modification of MSCs, inducing (transient) overexpression of specific beneficial factors in a controlled manner (Vaes et al., 2019). Additional preclinical studies with back-to-back comparison of the efficacy of monotherapy, cocktails of factors or overarching therapies like stem cell therapy in models of preterm dWMI are needed to substantiate these statements.

Treatments with a small number of trophic factors described in this review have made the first steps toward clinical application in Phase I/II studies. Among things to consider in the process of clinical translation of these promising factors are the timing and mode of administration. Even though the optimal timing of treatment is still unclear, one could speculate that treatment with beneficial factors during a time window analogous to healthy white matter development, and thus prevention of myelination failure, could prove to be most effective. This strategy would entail long-term treatment during the first, vulnerable weeks of life after (extreme) preterm birth to aid white matter development. Additionally, the route of administration should be considered carefully. In animal studies, factors are often administered using intracerebral injections, intraperitoneal injection, or intravenous infusion. Despite being relatively noninvasive and easy to implement, systemic administration of most of these factors is likely complicated due to loss of protein in the periphery, a relatively short half-life, and restricted passage over BBB, leading to limited supply to the CNS (Lochhead & Thorne, 2012; Thorne et al., 2004). These issues could be less pronounced following intravenous treatment in the early stages of injury, as BBB integrity has been reported to be compromised following inflammation in preterm infants (Douglas-Escobar & Weiss, 2012; Moretti et al., 2015; Yap & Perlman, 2020; Zhao, Chen, Xu, & Pi, 2013). Moreover, CNS delivery of (larger) molecules following systemic administration could be improved via focused ultrasound or use of nanoparticles. Focused ultrasound has been applied to transiently open the BBB in targeted areas, promoting entry of drugs from the circulation into the brain (Burgess, Shah, Hough, & Hynynen, 2015; Konofagou et al., 2012). Similarly, nanoparticles were shown to induce local toxic effects, leading to BBB permeabilization, or support BBB passage through facilitation of endothelial trans- or endocytosis (Saraiva et al., 2016; Zhou, Peng, Seven, & Leblanc, 2018). Aside from these options, one could speculate that loss of trophic or immunomodulatory factors in the periphery following intravenous administration could still benefit the preterm patient with multiorgan failure, by dampening systemic inflammation and aiding in development of other organs. Optimal CNS delivery could be attained by local intracerebral injection, preferably using viral vector-mediated gene transfer, inducing long-lasting expression of the transgene, avoiding repeated invasive injections (Bemelmans et al., 2006; Brizard et al., 2006; Lim, Airavaara, & Harvey, 2010). Intranasal administration provides a noninvasive method of local delivery of therapeutic agents to the brain, bypassing the BBB, and therefore might prove to be the most favorable route to directly target the CNS (Hanson & Frey, 2008; Lochhead & Thorne, 2012; Thorne et al., 2004; Vaes et al., 2019).

Although not our primary focus, preterm birth-related events, that is, hypoxia and inflammation, have been shown to disrupt the development of other immature cell types, such as cortical interneurons (Ardalan et al., 2019; Duchatel et al., 2019; Lacaille et al., 2019; Stolp et al., 2019). Interestingly, interneurons have been shown to play a role in oligodendrocyte development (Benamer et al., 2020; Zonouzi et al., 2015) and could therefore be essential for healthy white matter development. Thus, interventions aimed to target the common pathophysiological pathways are likely to positively impact multiple aspects of EoP, potentially restoring both myelination failure and interneuron deficits.

Despite the challenges yet to overcome for clinical translation, this review proposes a broad range of potential therapeutic trophic/immunomodulatory targets, known to aid myelination by directly boosting oligodendrocyte lineage development and/or by modulation of neuroinflammation. Future studies are urgently needed to refine these treatment strategies for preterm dWMI, in order to improve the neurodevelopmental prospects for these vulnerable patients.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ORCID

Cora H. Nijboer  <https://orcid.org/0000-0003-1223-1861>

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