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Review

Maturation-dependent sensitivity of oligodendrocyte lineage cells to apoptosis: implications for normal development and disease

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Apoptosis plays a crucial role in brain development by ensuring that only appropriately growing, migrating, and synapse-forming neurons and their associated glial cells survive. This process involves an intimate relationship between cell–cell interactions and developmental cues and is further impacted by environmental stress during neurogenesis and disease. Oligodendrocytes (OLs), the major myelin-forming cells in the central nervous system, largely form after this wave of neurogenesis but also show a selective vulnerability to cell death stimuli depending on their stage of development. This can affect not only embryonic and early postnatal brain formation but also the response to demyelinating pathologies. In the present review, we discuss the stage-specific sensitivity of OL lineage cells to damage-induced death and how this might impact myelin survival and regeneration during injury or disease.
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Apoptosis is a major form of programmed cell death required for the normal development of metazoan tissues, including the brain.[1] During embryonic development of the brain, many more cells than ultimately needed are generated and then selection occurs, resulting in the apoptotic depletion of the surplus cells. The importance of the apoptotic pathway in early brain development has been demonstrated by the targeted deletion in mice of the death-specific cysteine proteases caspase-3 or caspase-9, or of the co-activator Apaf-1, all of which cause severe brain overgrowth and perinatal death.[2,3]

In the adult brain, 90% of the cells belong to the glial lineage, which includes oligodendrocytes (OLs), astrocytes and microglia. The glia ensures proper development, function and repair of the neuronal network. This is possible through continuous cross-talk between the glia and neurons mediated by neurotransmitters, cytokines, growth and trophic factor secretion and signaling in a reciprocal manner.[4–7] In the central nervous system (CNS), OLs are responsible for axon myelination, which insulates the electrical signals transmitted between neurons. OL and neuron development is tightly regulated and the myelin sheath is constructed only when OLs reach maturity and neurons have grown appropriately. In response to injury or during the course of neurological diseases, the neuron–glia network can be replenished to some extent but the degree of repair is dependent on the developmental stage of the OL. This complexity is compounded by the differential sensitivity of OL lineage cells to apoptotic stimuli. In the present review, we will first briefly examine the stages of differentiation of OL cells and then discuss several diseases that are impacted by OL apoptosis, noting how the stage of cell differentiation governs the sensitivity to apoptosis.

Defined Stages of OL Development

Oligodendrocyte development can be divided into four distinct stages according to the temporal expression of cell surface markers and morphology (Table 1).[8] In the first stage, OL progenitor cells (OPCs) originate from the neuroepithelium of the ventricular region during the early embryonic life and from the subventricular region of the brain in late embryonic development and in early postnatal life. OPCs are highly proliferative and motile bipolar cells. They are recognized by the A2B5 antibody, which detects the GT3 ganglioside and its derivatives (Figure 1). They also express the GD3 ganglioside, platelet-derived growth factor receptor (PDGFαR) and the proteoglycan NG2.[9] PDGFαR is probably the best-characterized OPC marker. Its expression is regulated by

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Abbreviations: Aβ, amyloid beta peptide; CNS, central nervous system; EAAT, excitatory amino-acid transporter; FGF-2, fibroblast growth factor 2; GalC, galactocerebroside; GluR, glutamate receptor; GluT, glutamate transporter; GSH, glutathione; GSHPx1, glutathione peroxidase 1; HI, hypoxia-ischemia; HII, hypoxia-ischemia insult; HSP, heat shock protein; IGF-1, insulin-like growth factor 1; JNK, Jun N-terminal kinase; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; OL, oligodendrocyte; OPC, oligodendrocyte precursor cell; PARP, poly ADP ribose polymerase; PDGFR, platelet derived growth factor receptor; PLP, proteolipid protein; PMD, Perlizaeus–Merzbacher disease; PVL, periventricular leukomalacia; PWMI, periventricular white matter injury; ROS, reactive oxygen species; Sema4D, Semaphorin 4D; SOD, superoxide dismutase; THR, thyroid hormone receptor
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Table 1 Characteristics of the four stages of OL differentiation

	Undifferentiated		Differentiated	
	Stage 1 OPC	**Stage 2 Pro-OL**	**Stage 3 Immature OL**	**Stage 4 Mature OL**
Morphology	Bi-polar	Branching processes	Mature arborization	Myelin sheaths around axons
Motility	Yes	No	No	No
Cell division	Yes	Yes	No	No
A2B5, PDGFαR	+	+	–	–
O4	–	+	+	+
GalC, CNPase	–	–	+	+
MBP, PLP, MAG, MOG	–	–	–	+

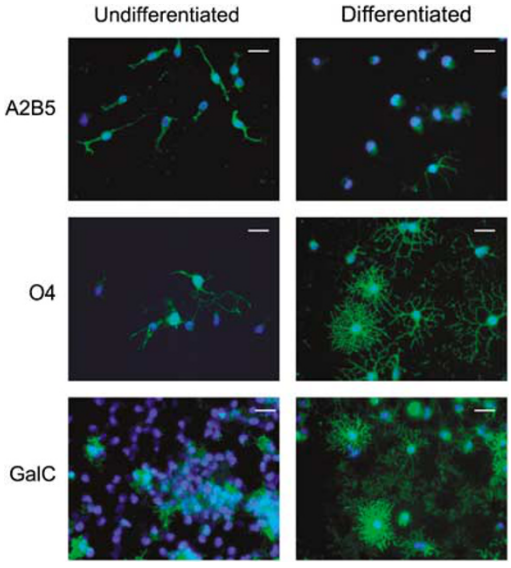

Figure 1 Changes in the morphology and antigenic profile of OPCs during differentiation. Primary cultures of OPC isolated from newborn rat brains cultured in a medium containing PDGF, FGF and insulin remain undifferentiated and continue to proliferate while expressing the marker A2B5 (undifferentiated). Removal of PDGF and FGF for 4 days results in the differentiation/maturation of these OPCs into postmitotic OLs that begin to express the markers O4 and, subsequently, GalC (differentiated). Bar = 10 μm

the Olig1 and Olig2 transcription factors, which are themselves regulated by the gradient expression of the Sonic Hedgehog morphogen. Mash1 has also been shown to specify OPCs and regulate PDGFαR expression in the ventral forebrain.[10] PDGFα is a powerful mitogen, stimulating proliferation, motility and survival of OPCs.

Most of the early OPC markers are maintained in the pro-OLs (stage 2), but this transition is accompanied by the additional expression of the O4 marker (Figure 1). O4 is again the name of an antibody that detects sulfatides and an unidentified sulfated glycoconjugate POA.[11] Pro-OL cells still divide but are no longer motile and begin to extend multiple processes. At the end of the pro-OL stage, differentiation into more mature OLs is accompanied by a complete cell cycle arrest. This terminal differentiation is prevented by the Notch1/Jagged interaction on OLs and neurons respectively, showing one example of how neurons control OL development.[12] Neuronal input is not necessary for the cell cycle exit, but rather an intrinsic OL process is employed. Dugas *et al.*[13] have recently shown that expression level of $p57^{Kip2}$, a cell cycle inhibitor, is increased with OPC division number, which correlates with slower proliferation and higher sensitivity to T3, an OL maturation hormone.

Differentiated OLs are further divided into two stages, the immature (stage 3) and the mature (stage 4) OLs. At the OL differentiation step, expression of A2B5, PDGFαR and NRG2 (neuregulin-2) is repressed, whereas the O4 marker is maintained (Table 1). Immature OLs do not form myelin yet but show maturation of their arborization and start expressing galactocerebroside (GalC) and 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) (Figure 1). In addition, mature OLs will express the myelin proteins myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated glycoprotein (MAG) and myelin OL glycoprotein (MOG) and begin to form the myelin sheath around axons.[8] Myelination involves the extension of processes in flat lipid-rich sheets of membranes that will wrap axons in many spiral layers. One mature OL can form multiple myelin sheaths around several different neurons.

Environmental factors in OL development. It is well documented that neural stem cells develop within a specific environmental niche and, following migration, often reside in an entirely different region of the nervous system to their precursors.[14] OL lineage cells are no exception to this rule[15] and so are also vulnerable to changes in their immediate environment. It has been shown that OPCs are more sensitive to environmental stress signals than more mature OLs.[16,17] For example, we have previously reported that treatment of OPCs with selected stress signals, such as ultraviolet radiation, dramatically decreases their survival in a time- and dose-dependent manner, while postmitotic OLs are resistant.[18] This selective vulnerability is, in part, due to the downregulation of Jun N-terminal kinase (JNK) 3 expression and activity during OL differentiation. However, this reduction in JNK3 does not confer resistance of the cells to ceramide, which is a potent inducer of OL apoptosis at any stage of maturation.[19]

OPC differentiation into mature OLs necessitates proper signaling from extracellular factors expressed within the developmental niche. Along the various developmental stages, OL sensitivity to these factors varies considerably. As mitogen and growth factors ensure proliferation and

growth, responsiveness to such agents also affects sensitivity to cell death. Artificially controlling the levels of these factors thus offers promising therapeutic potential. The following are a few examples.

FGF-2 (fibroblast growth factor 2) is a mitogen that upregulates PDGFαR, blocks differentiation of pro-OLs into immature OLs and blocks myelin protein production.[20] FGF-2 has multiple receptors that are not expressed to the same extent in all OL stages. This allows for pro-OL cultures to revert to OPCs in the presence of PDGFα and FGF-2.[9] Mature OLs, however, stop myelin production when treated with FGF-2 but do not revert to expression of OPC markers.[21] IGF-1 (insulin-like growth factor 1) is a well-established OPC proliferation and OL myelination factor. Deleting the IGF-1 receptor in cells at the Olig1- or PLP-expressing stages *in vivo* reduces OL cell number in the brain. This is a result of both slower proliferation and increased apoptosis.[22] IGF-1 is a factor studied for its regeneration potential as a therapeutic agent after brain injury. Conversely, CNTF (ciliary neurotrophic factor) is an example of an OL differentiation factor that fails on its own to stimulate re-myelination *in vivo* after injury.[23] The T3 thyroid hormone is a good example of a factor whose developmental effects depend on the expression pattern of its receptors. It promotes OPC specification and proliferation when interacting only with the thyroid hormone receptor (THR) α receptor,[24] but it also plays a role in myelin protein production in mature OLs when both THRα and β are expressed.

Whether through secreted factors or direct contact, OLs need the presence of other cell types in the brain. Although it was originally shown that *in vitro* OLs can differentiate and produce myelin proteins without the presence of axons, it was later shown that axon contact is necessary for proper OL development *in vivo*.[25] This is at least in part due to integrin-mediated contact survival.[26,27] OLs that fail to make contact with target axons die. In turn, OL production of neurotrophins (NTs) such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and NT3 not only supports OLs but also neuronal survival. Similarly, GalC, sulfatide and myelin proteins are essential for axon function[28] and microglia are also involved in OL support; for example, the cytokine transforming growth factor β (TGFβ) induces OPC chemotaxis indirectly by stimulating microglia to produce hepatocyte growth factor (HGF) which then triggers OPCs migration.[29,30]

Adult OPCs. Although OL progenitors are most active during embryonic development and perinatal life, 5–8% of glial cells in the adult brain are OPCs,[31] giving potential for OL regeneration after injury. However, the adult OPCs show slower motility and a longer cell cycle and developmental time course than perinatal OPCs.[32,33] Nevertheless, it has been demonstrated that some adult cells expressing NG2 and PDGFαR are proliferative and can differentiate into mature OLs after injury.[34,35] Also promising for adult brain injury recovery are the discoveries of the putative reversion of rodent OPCs into multipotent CNS stem cells[36] as well as the generation of neurons from OPCs.[4]

OLs and Disease

Oligodendrocyte precursor cells are especially sensitive to oxidative stress and to glutamate-related excitotoxicity. Their vulnerability to these two insults (which are often intertwined) contributes to the underlying pathology of several diseases and brain injuries (Table 2).

Glutamate excitotoxicity. The excitatory neurotransmitter glutamate is primarily synthesized in the brain by astrocytes[37] and can stimulate both neurons and glia through interactions with specific receptors and transporters. Excessive glutamate excitation causes excitotoxicity and can trigger apoptosis. In a manner similar to growth factors, sensitivity to excitotoxicity depends on the OL developmental stage. For example, AMPA and kainate receptors to glutamate (GluRs) are expressed in developing OLs, but not in human adult OLs[38] and the NMDA receptor (another GluR) is expressed only on OL processes throughout myelination.[39,40] The seven-membrane-spanning G-coupled metabotropic glutamate receptors (mGluRs) of groups I, II and III are expressed in OPCs but only low levels are present on mature OLs.[41] Finally, glutamate transporters (GluTs), which can uptake glutamate into cells and regulate its extracellular levels are also developmentally regulated: excitatory amino-acid transporter (EAAT) 1 and EAAT2 are expressed in oligodendrocytes while EAAT3 is expressed in a subpopulation of adult OPCs.[42] Interestingly, OL vulnerability to glutamate was first shown in culture by Oka *et al*.[43] as mediated by GluTs, but it was later shown that GluRs also mediate OL excitotoxicity.[44,45]

Excitotoxic cell death in OLs can be mediated in different ways (reviewed in Matute *et al*.[46]). In many cases, a calcium influx is generated by AMPA/kainate receptor activity. Mitochondria accumulate the overloaded calcium, which leads to their depolarization, subsequent cytochrome *c*

Table 2 Factors increasing vulnerability to cell death during OL differentiation

OPCs	Postmitotic OL
Higher AMPA/kainate receptor expression	Necessity for axon contact
Higher mGluR expression	Higher NMDA receptor expression
Expression of calcium-sensitive GluR subunits	Sema4D sensitivity
Lower MnSOD expression	PLP mutations (in PMD patients)
Lower glutathione peroxidase expression	
Higher Bax expression	
Higher caspase-3 expression	
Lower Bcl-x_L expression	

release into the cytosol and production of reactive oxygen species (ROS, discussed below). Cytochrome *c* release into the cytosol triggers the intrinsic caspase activation pathway and thus causes apoptosis. Some models have also shown that maximal AMPA receptor stimulation can trigger necrosis. The role of mitochondria in this process is also exemplified in mild cases of excitotoxic insult, where apoptosis can be prevented by overexpression of Bcl-2 and Bcl-x_L, two antiapoptotic family members.[47,48] Also, in pro-OLs, pro-apoptotic Bax translocation into mitochondria is a glutamate-mediated event that can be prevented by IGF-1.[49] Additionally, OPC vulnerability to excitotoxicity mediated by calcium influx is also influenced by the fact that (1) the particular GluR subunits expressed in OPCs are those that confer high calcium permeability[50,51] and (2) OPCs (unlike neurons) do not express calcium-binding proteins for maintenance of intracellular calcium homeostasis.[52]

ROS and cellular defenses. Reactive oxygen species are a necessary evil for cells that carry out oxidative phosphorylation for energy generation. In the production of ATP the mitochondrial respiratory chain also produces superoxide (O_2^-), a highly reactive species that can cause protein oxidation, DNA mutations or lipid peroxidation. In addition to this direct damage, superoxide can inactivate proteins that contain iron, and the liberation of iron can further increase production of ROS[53] (see below). Cells have evolved defenses to counteract the potential dangers of excessive ROS production, including enzymes such as SODs (superoxide dismutase), peroxidases and catalase, as well as direct antioxidants such as glutathione (GSH) (Figure 2).

There are three forms of SOD within humans: SOD1 and 3 contain copper and zinc in their reactive center while SOD2 contains manganese. Manganese SOD (MnSOD) is mitochondrial while Cu/ZnSOD is cytoplasmic or extracellular. Examination of rat OLs in culture revealed that Cu/ZnSOD levels were similar in both OPCs and mature OLs, while increased MnSOD expression and activity (four times greater) was observed in OLs.[54] When OPCs were engineered to overexpress MnSOD, the mitochondrial membrane potential was maintained and less cell death was observed in the face of an oxidative insult. The dismutation of superoxide leads to the production of hydrogen peroxide, a relatively stable species that can travel further distances than superoxide and has the potential to create a very reactive hydroxyl radical ($OH\cdot$) through interactions with iron or copper in cells by means of the Fenton reaction. Hydroxyl radicals can also attack proteins, lipids and DNA. Therefore, it is important that hydrogen peroxide be removed so as to reduce the chance of hydroxyl formation at cellular locations like the nucleus, plasma membrane or ER where many targets of oxidative damage exist.

Pertinent to this review are two types of enzymes that can act on hydrogen peroxide: catalase and glutathione peroxidase (GSHPx). Catalase is primarily a peroxisomal enzyme that converts hydrogen peroxide into water and oxygen. In hydrogen peroxide clearance assays, mature rat OLs in culture had an eight fold greater antioxidant capacity compared to pro-OLs.[55] GSH is a cellular antioxidant formed

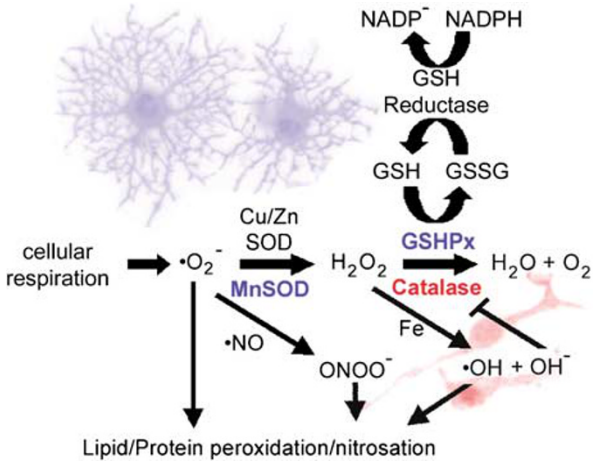

Figure 2 Reactive oxygen species (ROS) and the antioxidant defenses of oligodendrocytes. Enzymes in blue show elevated activity in mature OLs compared to OPCs, while the activity of catalase (in red) is reduced in OPCs. Superoxide is produced as a by-product of mitochondrial respiration and is converted to hydrogen peroxide by superoxide dismutases. Non-dismutated superoxide can either directly cause lipid peroxidation or participate in the formation of peroxynitrate, a more damaging species. Hydrogen peroxide can react with iron in cells to form hydroxyl radicals, leading to other negative oxidation events. Glutathione peroxidase (GSHPx) and catalase remove hydrogen peroxide, yet in OPCs catalase has been shown to be inactivated by ROS, while GSHPx prevented this inactivation in OLs

from cysteine, glutamate and glycine. GSH peroxidase 1 (GSHPx1) is both a cytosolic and a mitochondrial enzyme that utilizes GSH to detoxify peroxides. The free sulfur within cysteine reacts with peroxides to become oxidized, while the peroxide is converted to water or less reactive alcohols. A cycle exists within the cell to regenerate reduced GSH through the enzyme GSH reductase and NADPH. One of the rate-limiting steps of GSH synthesis is the availability of cyst(e)ine.[56] A sodium-independent transport system known as x_c^- has been described (Sato *et al*.[57] and references therein, Periera *et al*.[58]) where extracellular cystine is transported into cells with a concomitant export of glutamate from the cell, in accordance with the normal concentration gradient of high intracellular glutamate and low extracellular cystine. However, this transporter may be reversed, where glutamate can be imported and cystine exported. Since OPCs are sensitive to glutamate-induced excitotoxicity, it is important to bear in mind this interplay between GSH production (antioxidant defense) and extracellular glutamate.

In rat OL cultures, catalase, GSH reductase and steady-state GSH levels[55] were found to be similar between OPCs and mature OLs. However, GSH peroxidase levels were higher in OLs than OPCs. This elevation of GSHPx was 'doubly protective' in that catalase activity was maintained in the face of oxidative stress in OLs, while OPCs (with less GSHPx) were found to have inactivated catalase in the same condition.[54,55] The authors found that chemically inhibiting GSHPx in mature OLs led to an increased vulnerability to hydrogen peroxide and a reduction of catalase activity, indicating that GSHPx help maintain antioxidant defenses as a primary peroxidase in addition to protecting catalase activity. Independent studies have also confirmed that OPCs have less GSHPx activity than OLs.[59] Finally, mature OLs

also have more GSH available after peroxide incubation than OPCs, and consequently less caspase-3 activation and poly ADP ribose polymerase (PARP) cleavage were observed in peroxide-treated OL cells.[60] In a separate model of oxidative-stress induced apoptosis, Khorchid *et al*.[61] similarly revealed that OPCs have less GSH available after oxidative injury and that they show preferential activation of caspases-9 and -3 followed by PARP cleavage compared to mature OLs. Bax levels are also reportedly higher in OPCs compared to 6- and 12-day OL cultures, while procaspase-3 levels decrease during the same timeframe. Finally, 6- and 12-day cultures of OLs had significantly greater levels of the antiapoptotic Bcl-x_L compared to OPCs. Collectively, these observations support a hypothesis that OPCs are more vulnerable to oxidative stress than their more mature counterparts.

Oligodendrocytes contain high amounts of iron. While iron is necessary for the production of myelin[62] it has been shown that even immature OLs express transferrin and ferritin.[63] Iron can cause increases in ROS, and such deleterious effects of high intracellular concentrations of iron have been reported in the OL lineage (reviewed in Bartzokis[64]). Thus, while OLs at all stages of differentiation may contain high amounts of iron, in light of the findings above (that OPCs have lower levels of GSHPx) OPCs may be more sensitive to iron-mediated ROS generation and subsequent apoptosis. Thus, overall OPCs are differentially sensitive to oxidative stress,[65,66] in large part due to lower levels of antioxidant defense enzymes and antiapoptotic proteins in combination with higher levels of pro-apoptotic Bcl-2 family members (Table 2).

ROS and excitotoxicity in periventricular white matter injury. Periventricular white matter injury (PWMI) can range from focal cystic necrotic lesions of cerebral white matter (periventricular leukomalacia, PVL) to diffuse damage of myelin. Because of advances in neonatal care, cystic necrotic lesions of PVL are declining,[67] and focal or diffuse WMI is now the predominant lesion clinically observed. Both cystic PVL and diffuse white matter disease are characterized by reduced white matter volume, reduced brain growth and features, suggesting abnormal myelination by magnetic resonance imaging.[68–70] Up to 25% of patients suffering from PWMI develop cerebral palsy,[71,72] while as many as 50% may display cognitive and learning disabilities by the time they reach school age.[73] Since a prominent feature of white matter injury is a chronic disturbance in myelination, it was hypothesized that OLs are the major target cells in PWMI.[74] Indeed, it has been demonstrated that OPCs are the predominant cell type in human cerebral white matter during the 23–32 week (gestational) time of peak incidence of PWMI.[75] The selective death of these progenitors could severely disrupt myelination in newborn infants since the pool of dividing cells with OL potential would be significantly depleted.

Cerebral hypoxia-ischemia (HI) is thought to be a prominent insult in PWMI. As reviewed in Back *et al*.,[76] basal cerebral blood flow is lower in pre-term neonates than in full-term infants. The reduced blood flow to white matter can lead to HI. Since the predominant cell type in the white matter, OPCs, are less well equipped to handle oxidative stress they are vulnerable to apoptosis. Data comparing the sensitivity of 2- and 7-day rat pups to a hypoxic-ischemic insult (HII) lend credence to this hypothesis. It is known that in 2-day rat pups, the white matter is predominantly made up of OPCs, while in 7-day pups it consists of more differentiated OLs.[77] In this regard, the brains of 2-day pups closely resemble the white matter milieu of 23- to 32-week-old humans. Overall, the white matter of 7-day pups is more resistant to HI; examination of the 2-day pups 24 h after the HII showed elevated apoptosis of pro-OLs.[78] Similarly, in a study examining autopsied brain tissue from human PVL cases,[79] elevated nitrosative and oxidative damages were seen in pro-OLs.

Another factor contributing to PWMI is glutamate excitotoxicity, to which OPCs are also selectively vulnerable. Elevated glutamate levels can be detected in white matter after HI,[46,80,81] and as discussed previously, OPCs are sensitive to glutamate release and will die by apoptosis. The importance of glutamate toxicity in HI was demonstrated using a rat pup model of carotid ligation with hypoxia.[82] As seen in other studies, OPCs were more sensitive to HI. However, pretreatment of the pups with the AMPA receptor agonist NBQX immediately after hypoxia reduced the severity of injury. Finally, glutamate can also affect OPC survival in PWMI through non-receptor means by the aforementioned x_c^- cystine/GluT. Elevated external glutamate can cause this transporter to 'reverse' and internalize glutamate while releasing intracellular cystine.[83,84] The decreased levels of cystine result in a reduced availability of GSH for scavenging ROS produced during HI, further sensitizing OPCs. Thus, the death of immature OLs via excitotoxic and oxidative stress mechanisms greatly contributes to the pathology of PWMI.

An increasing number of studies indicate that antenatal infection is a common antecedent of PWMI.[85–87] Furthermore, in full-term newborn infants[88] and in animal models,[89] the combined exposure of infection and HI dramatically increases the risk of cerebral palsy and brain injury,[88] suggesting an interaction between systemic infections and HI. Increased concentrations of inflammatory cytokines in umbilical cord blood are associated with cerebral lesions in pre-term infants.[85] Moreover, such pro-inflammatory cytokines released during bacterial infection may mediate the damage leading to white matter lesions.[90] While more recent studies tracking inflammatory cytokines[91] or intrauterine infection[92] in pre-term birth suggest a more complex relationship between infection and cerebral palsy,[93] it is clear that there is a correlation between neuroinflammation and PWMI.[94–96] We have identified one potential mechanism for the induction of apoptosis by HI, which suggests at least one common pathway with inflammatory injury, involving changes in the expression of TNF family proteins such as Fas/CD95.[97] Recent data showing expression of Toll-like receptors on microglia have added further complexity to this field, as these receptors transduce signals triggered by infection via pathways that involve pro-inflammatory signaling mechanisms.[98] During combined infection (of mother or fetus) and HI, pro-inflammatory cytokines crossing the damaged fetal blood–brain barrier can act directly on OPCs to induce apoptosis or perhaps activate resident microglia (e.g. through Toll-like receptors), which then secrete oligotoxic molecules such as glutamate (Figure 3). Taken together, these data suggest a combined role for infection and HI converging

on the expression and activity of the pro-inflammatory cytokines proteins to cause demyelination leading to brain damage.[99–101]

OPC vulnerability in multiple sclerosis: an update. While the involvement of neuroinflammation and OPCs in PWMI may not be direct, the role of OL death in the neuroinflammatory demyelinating disease multiple sclerosis (MS) is well established. Some of the earliest pathological changes in MS lesions are increases in OL apoptosis associated with microglial activation.[102,103] Cytokines released by activated microglia have been shown to trigger OL apoptosis (reviewed in Aktas *et al*.[104]) and microglia can also trigger excitotoxicity-induced apoptosis in OPCs by releasing glutamate.[46,105,106]

Autoantibodies against epitopes within myelin and related proteins have been commonly observed in MS.[107] However, some autoantibodies seem to recognize epitopes, such as NG2, that are expressed only in OPCs.[108] Similarly, a heat shock protein (HSP) expressed selectively in OPCs is another autoantibody target in MS.[109] *In vitro* studies with this anti-HSP autoantibody determined that complement-mediated death occurred in OPCs, but not in pro-OLs.

Besides complement, autoantibodies and pro-inflammatory cytokines, recent findings with another class of molecules emphasizes the vulnerability of immature OLs in MS. Semaphorins were first identified as axonal guidance molecules, and now represent a family of over 30 members. In addition to axonal guidance, several members have been shown to have immune functions.[110] Using a co-culture system of immune cells and OLs, Semaphorin 4D (Sema4D/CD100) has been reported to induce OL apoptosis in a caspase-3-dependent manner.[111] Importantly, Sema4D is found in the CSF of patients suffering from demyelinating disease with T-lymphocytes expressing Sema4D present in demyelinated lesions of the spinal cord.[112] Further experiments in the same study revealed a specific window of vulnerability; Sema4D seems to induce apoptosis in immature OLs, while OPCs are protected in the *in vitro* co-culture system. Earlier studies describe the paucity of pro-OLs in chronically demyelinated lesions in MS patients while larger numbers of OPCs are seen.[113,114] Thus, while speculative, it is tempting to conclude that molecules such as Sema4D may selectively reduce the OL population at a stage of differentiation where the precursors have stopped dividing but are yet to initiate myelination.

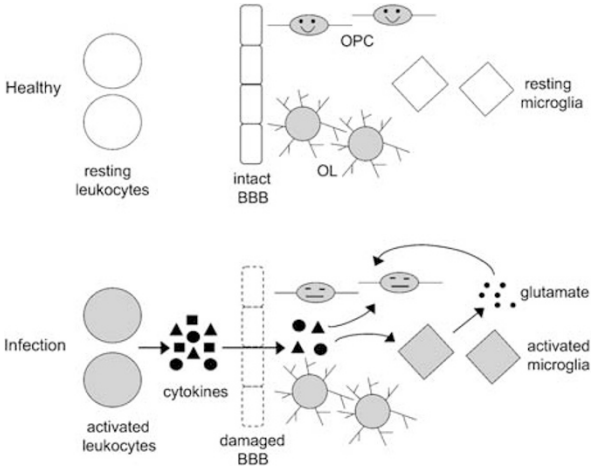

Figure 3 Hypothetical model of oligodendrocyte loss in the damaged neonatal brain. In the healthy fetus in the absence of infection (top panel), fetal and maternal leukocytes are resting and the circulating levels of pro-inflammatory cytokines are low. Following bacterial infection (bottom panel), proinflammatory cytokines enter the fetal circulation from the mother (having been generated in response to infection). Alternatively, they may arise in the fetal blood as part of the fetal immune response. Cytokines can cross the damaged fetal blood–brain barrier (BBB) into the fetal brain. Here, they either act as direct toxins to OPCs or activate resident microglia (e.g. through Toll-like receptors), which then secrete oligotoxic molecules such as other cytokines or glutamate. These can affect both the development of oligodendrocytes from precursor cells and can damage newly formed postmitotic oligodendrocytes

Active myelination increases OL susceptibility to apoptosis. The unique function of the mature OL – to ensheath axons with myelin – places distinctive vulnerabilities on the mature(ing) OLs that are not seen at earlier stages of development. The staggeringly high metabolic demands during myelination are extraordinary: in a single OL myelinating multiple axonal segments, it has been calculated that the amount of protein synthesized daily during the peak of myelination can be up to three times the weight of the perikaryon of the OL.[115] Thus, in such an environment, it may be anticipated that tolerance for error in protein production or transport is low. The etiology of Perlizaeus–Merzbacher disease (PMD) demonstrates the dire consequences of such an occurrence.

A key component of myelin is the PLP. The *PLP* gene encodes two membrane proteins, PLP and the smaller DM-20, via alternative splicing in exon 3. Gene duplication events of *PLP* are the most common cause of PMD[116] but many point mutations are also observed, all along the protein. Different PLP mutations can result in either severe or mild forms of PMD.[117] Severe PMD is characterized by extensive apoptosis of mature OLs and very little compacted myelin. In contrast, there is less OL apoptosis in mild PMD although the cells are inefficient at properly synthesizing normal myelin sheaths.

Important early work with the *jimpy* mouse model of PMD (a frameshift mutation in *PLP*) helped establish that the disease was in fact due to a toxic gain of function of PLP mutants, rather than being a disease of deficiency of normal PLP.[118] It is now accepted that the toxic gain of function is the ability of mutant PLP to cause the unfolded protein response in the ER and potentially signal apoptosis. Mutations that misfold one PLP splice variant could be mild, while those mutations that affect both splice variants would be more severe.

Data from both *jimpy* and MD (a rat model of PMD) indicate that some PLP point mutations cause OLs to fail to fully differentiate and die by caspase-3-mediated apoptosis. With the MD point mutant, stage-specific staining revealed that OPCs do not differentiate beyond the immature OL stage and die by apoptosis. Consequently, very few MBP^+ and no MOG^+ cells were observed.[119] It is interesting that in addition

to point mutations and duplication events, deletion or truncation mutations are present in the *plp* gene but seem to cause only mild forms of PMD. Thus, mice lacking the gene show normal OL development, although in late adulthood progressive neurological deterioration occurs. Surprisingly, the deficits are not seen in myelin itself, but rather in axonal damage; this is also observed in some PMD patients.

Myelinating OL death and contribution to diseases of disconnection: Alzheimer's and Schizophrenia. One hypothesis arising from examination of axonal damage in PLP mutants and various other protein components of myelin (Garbern[115] and references therein) is that 'complete' myelin with wild-type PLP has a neuroprotective effect on axons. If indeed complete myelin is neuroprotective, it is possible that death (and subsequent loss of myelin) of mature OLs may contribute to neuronal pathologies through the loss of neuroprotection of the axons. While the actual act of a single OL ensheathing an axon may be completed within days, myelination of axons within the brain occurs all the way through the fifth decade of life. Interestingly, those OLs that differentiate and myelinate later in life do not produce the same thickness of myelin around axons. Hence, the neurons myelinated by these later OLs may be more susceptible to damage,[64] perhaps including amyloid beta peptide (Aβ)-mediated neurotoxicity (see below).

Once myelination is complete, mature OLs still have higher energy requirements for the maintenance of their lipid-rich myelin membrane. As discussed previously, a by-product of metabolism is the increased production of ROS. While mature OLs do have increased antioxidant defenses compared to OPCs, the combination of increased metabolism, elevated iron and lipid content may be such that their survival is in the balance and any additional insult could be fatal. In this regard, it is interesting to note that Aβ-induced apoptosis in mature OLs *in vitro* is attenuated in the presence of an antioxidant.[120] Aβ also indirectly contributes to oxidative stress by upregulating inducible nitric oxide synthase (iNOS) in mature OLs through a TNF-α-mediated ceramide pathway.[121] Finally, injection of Aβ into the corpus callosum of rats induced myelin damage and OL apoptosis. In this experiment, activated microglia were also seen,[122] further implicating pro-inflammatory molecules such as TNF-α. These observations raise the intriguing possibility that, in addition to neurons, mature OLs are also susceptible to the toxicity of Aβ, further contributing to the progressive neurological decline in Alzheimer's.

At the cutting edge of OL research, there is a growing appreciation that white matter abnormalities are involved in schizophrenia, and, in particular, that OLs play a role in the disease (recently reviewed in Karoutzou *et al.*[123]). The frontal and temporal lobes are the last cortical regions to be myelinated (reviewed in Stewart and Davis[124]) and this occurs in adulthood, during the time when the onset of schizophrenia commonly occurs. A DNA microarray study compared the prefrontal cortex of 12 schizophrenic and 12 control patients and examined expression levels of over 6000 genes. When the 89 genes with the largest expression differences were grouped by biological function, it was noted that a group of myelin-related genes (MAG, Transferrin, myelin and lymphocyte protein (MAL), CNP, Gelsolin and ErbB3) were found to be downregulated in schizophrenic brains compared to control. Moreover, this was the only gene group that was decreased in schizophrenic brains.[125] While many questions remain regarding the involvement of white matter loss in schizophrenia, OL apoptosis has been reported in schizophrenic brains.[126] It remains to be seen whether this is a cause or consequence of schizophrenia.[127]

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