

Review

# Environmental and nutritional “stressors” and oligodendrocyte dysfunction: role of mitochondrial and endoplasmatic reticulum impairment

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**Abstract:** Oligodendrocytes are myelinating cells of the central nervous system, which are generated by progenitor oligodendrocytes as a result of maturation processes. The main function of mature oligodendrocytes is to produce myelin, a lipid-rich multi-lamellar membrane that wraps tightly around neuronal axons, isolating them and facilitating nerve conduction through saltatory propagation. The myelination process requires the consumption of a lot of energy and a high metabolic turnover. Mitochondria are essential organelles which regulate many cellular functions including the energy production through oxidative phosphorylation. Any mitochondrial dysfunction impacts cellular metabolism and negatively affects the health of the organism. If the functioning of the mitochondria is unbalanced the myelination process is impaired. At the end of myelination, oligodendrocytes synthesize about 40% of the total lipids present in the brain. Since lipid synthesis occurs in the cellular endoplasmic reticulum, the alteration of this organelle can lead to partial or deficient myelination, triggering numerous neurodegenerative diseases. In this review the main dysfunctions of oligodendrocytes caused by exogenous or endogenous stimuli will be investigated. Furthermore, the oligodendrocyte reactions to excessive mitochondrial oxidative stress and an altered regulation of the functioning of the endoplasmic reticulum will be discussed.

Keywords: Oligodendrocytes; Myelination; Oxygen Reactive Species; Endoplasmic Reticulum; Unfolded Protein Response; Heavy metals; alcohol

## 1. Introduction

Oligodendrocytes are one of the main types of glial cells of the Central Nervous System (CNS) in addition to microglia and astroglia. They are the myelinating cells of the CNS and derive from progenitor cells following extremely regulated processes of proliferation, differentiation and migration. Oligodendrocytes have very important functions in brain development by dealing not only with producing myelin but also with covering neuronal axons with the myelin itself electrically isolating the axons and consequently allowing for a rapid and easy transmission of the nerve impulse. In addition, oligodendrocytes offer essential trophic and metabolic support to neurons, with which they come into close contact [1-3]. Astrocytes also participate enormously in the support and maintenance of CNS homeostasis, through physical interactions and secreted compounds. In particular, glia-astrocytes belong to astroglia and are perfectly integrated in the neural network where they deal with the transport of the main ions, the release of many neurotransmitters, the energy maintenance of neurons, through the synthesis of glycogen, to control the stability of the blood brain

barrier (BBB) [4,5] and to remove, together with microglia, reactive oxygen species (ROS) [6,7]. During neural development, oligodendrocytes are initially present in progenitor forms (OPC) and appear, structurally, like bipolar cells. The newly formed OPCs, and during their development, are characterized by the expression of some specific markers that unite them to future mature oligodendrocytes (OLs). Among these it is worth mentioning the expression of DM-20 mRNA, which produces one of the isoforms of the protein-lipid protein (PLP), which is the most abundant protein in myelin. [8] Another typical marker of OPC is Platelet-Derived Growth Factor Receptor  $\alpha$  (PDGFR $\alpha$ ), a receptor located on the surface of many cell types. This receptor binds to some Platelet-Derived Growth Factor isoforms, activating and acting as a mitogen and survival factor in OPCs, which, in this way, increase their number [9]. As development continues, OPCs transform into pre-oligodendrocytes which interact with a target neuronal axon, lose their immobile bipolarity and begin to build filamentous myelin growths. The pre-oligodendrocytes express two important markers arranged on the cell surface: O4 and O1. While O4 is already expressed in a late phase of OPCs, O1 is characteristic of pre-oligodendrocytes [10]. The next step involves the complete maturation of the pre-oligodendrocytes into mature oligodendrocytes, which change their morphology, from bipolar cells to highly branched cells, and produce myelin and associated proteins. This phase of oligodendrocyte development is easily identifiable because mature cells express the Olig2 marker [11]. Although mature oligodendrocytes have long been thought to be a homogeneous class of cells, there is currently a lot of information about their heterogeneity. In particular, three types of oligodendrocytes are known which reside in different regions and perform specific functions [3]:

- Interfascicular oligodendrocytes, which myelinate neuronal axons in white matter tracts;
- Perivascular oligodendrocytes which have the function of a metabolically supporting axons;
- Perineuronal oligodendrocytes which constitute a cell reserve for remyelination processes, if necessary and regulate neuronal excitability;

Myelin, produced by mature oligodendrocytes, is a predominantly lipid membrane that wraps itself tightly around neuronal axons and induces their electrical isolation, promoting a jumpy propagation of the nerve impulse in points not covered by myelin and called Ranvier Nodes. In this way, impulse propagation is efficient and faster than that which occurs in unmyelinated axons [12]. The counterpart of oligodendrocytes, at the level of the Peripheral Nervous System (PNS), is constituted by Schwann cells which provide for the isolation and neuronal metabolic support but, unlike oligodendrocytes, can myelinize one neuronal axon at a time [13].

The lipid composition of myelin is very rich and differs from all other eukaryotic plasma membranes; in particular, the lipid content constitutes about 70-75% of the dry weight of myelin and the lipids, cholesterol, phospholipids, galactolipids (galactolipid) and plasmalogen are present in the ratio 2: 2: 1: 1 [14]. Reduced myelin lipid levels have been associated with axonal and oligodendrocyte degeneration. In addition, a reduction in white matter was found. Finally, the change in the lipid component falls, ending an altered interaction between lipids and proteins and an incorrect packaging of the myelin [15]. Major proteins present in myelin include myelin basic protein (MBP, 30%), trans membrane protein (PLP, 50%), myelin associated glycoprotein (MAG) and myelin-oligodendrocyte glycoprotein (MOG) [16]. All the mentioned proteins are essential to compact myelin and make it functional: the localization of these macromolecules moves on the plasma membranes during the development process that goes from pre-oligodendrocytes to mature oligodendrocytes. This shift is also enabled by an intact and functional cell cytoskeleton. The subsequent adhesion between the oligodendrocyte and the neuronal axon is mediated by the myelinated proteins MBP and PLP. The proteins, therefore, are not static and inert molecules because, in addition to mediating the interactions between the intracellular sheets of myelin, they are responsible for guiding the assembly of myelin. The loss of structural proteins has shown an altered stability of myelin up to the onset of demyelinating diseases [17]. Also myelin, like all cellular components, undergoes turnover and proteins and lipids, which compose it, are replaced by newly formed molecules. The replacement of myelin has been defined as "myelin plasticity" just as "synaptic plasticity"[18]. The process of myelination is finely regulated and, from many studies reported in the scientific literature, it would appear that the mechanistic Target Of Rapamycin (mTOR) coordinates

the synthesis of myelin proteins and lipids [19]. In particular, mTOR and its components, (mTORC1 and mTORC2), promote the synthesis of lipids through the processing and maturation of the transcription factors SREBPs which are normally responsible for the formation of lipids. When the SREBPs are mature, therefore, they induce the expansion of numerous enzymes involved in the synthesis of fatty acids and cholesterol. mTORC1 signaling is also involved in the production of MBP; in fact, its alteration reduces the levels of its mRNA, highlighting that the translation of this protein, and probably of other myelinated proteins, is induced by mTORC1 [20]. What has been studied shows that the loss of mature oligodendrocytes or their structural and functional alteration can easily lead to incorrect myelination and the onset of neurodegenerative diseases. The oligodendrocytic loss of the ability to migrate and communicate with other types of cells also leads to the same result [21]. Mitochondria are basically involved in energy support and the endoplasmic reticulum is site of lipid synthesis, both being fundamental for the maintenance of oligodendrocyte-neuron functionality [22,23].

## 2. Mitochondria and endoplasmic reticulum in oligodendrocytes

In order to function at its best and perform all its functions properly the intricate neuronal network requires a significant amount of energy. These tasks include the absorption of neurotransmitters, the maintenance of ion gradients, action potentials, the transport of organelles, the recycling of synaptic vesicles and axonal growth. For this reason, the brain consumes 20-25% of our daily energy budget [24]. The white matter of the brain comprises about half of its volume and this is characterized by myelin-coated tissue. It is therefore evident how important is the production of energy at the level of oligodendrocytes. Mitochondria are essential organelles which regulate many cellular functions through oxidative phosphorylation. Mitochondrial organelles have been found to be fundamental in every moment of the development of oligodendrocytes: in fact, during the formation of myelin, they provide the substrates to generate the necessary and sufficient energy for the synthesis of lipids; during the development of brain functions, the production of ATP will be used to contribute to the support of axonal function; finally, in the case of pathological changes the mitochondria are able to buffer excess calcium ion or to induce the activation of apoptosis [25]. Neuronal axons can extend several feet in length and, for this reason, may require higher amounts of energy than is supplied by the glia [22]. One hypothesis suggests that oligodendrocytes can transport glucose and pyruvate to neuronal axons to allow subsequent oxidative phosphorylation. The veracity of this theory has recently been demonstrated following experiments using coronal slices of mouse corpus callosum in a glucose deprivation model. These experiments highlighted that oligodendrocytes provide neuronal metabolic support under conditions of energy stress by transferring glucose via gap junction [26]. Furthermore, another form of energy support could be the release of exosomes containing proteins, many of which are involved in energy metabolism [27]. Nonetheless, further evidence would need to be collected to determine whether oligodendrocyte glucose is subsequently metabolized by neurons. Recent scientific studies have described the presence of mitochondria in oligodendrocytes in the brains of rodents. In particular, oligodendrocytic mitochondria are found in narrow channels of the myelin sheath and are endowed with movement. However, the mitochondria of oligodendrocytes appear smaller, less abundant and with less mobility than the mitochondria found in neurons and astrocytes. These data report that ATP production in oligodendrocytes can contribute to myelin formation by maintaining lipid metabolism [28]. Any mitochondrial dysfunction impacts cellular metabolism and negatively affects the health of the organism. In particular mitochondrial dysfunction, at the level of neurons, involves oxidative damage that can lead to cell death generating neurodegeneration [29]. In these cases, supplementation with antioxidant compounds, of an exogenous or endogenous nature, has been shown to reduce the severity of many neurodegenerative diseases [30]. What happens when mitochondrial dysfunction occurs in the glia? Today it is known that if the functioning of the mitochondria is unbalanced the myelination process is impaired; the main consequences are oligodendrocyte degeneration and the onset of CNS pathologies, such as ischemia and neurodegeneration [31]. Glutamate-induced excitotoxicity, which precedes oxidative stress, caspase-3 activation and apoptotic death, is well known in neuronal cells

[32-34]. Oligodendrocytes are also sensitive to glutamate excitotoxicity since expressing the ionotropic  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite receptors, which are responsible for the overproduction of calcium ion, activation of the intrinsic mitochondrial pathway Bax- caspase 3 and apoptotic cell death [35].

At the end of myelination, oligodendrocytes synthesize about 40% of the total lipids present in the brain. Since lipid synthesis occurs in the cellular endoplasmic reticulum (ER), the alteration of this organelle can lead to partial or deficient myelination, triggering numerous neurodegenerative diseases. Several myelin proteins in the CNS and PNS are synthesized on ER-linked ribosomes, modified following translation and sent to myelin through vesicular traffic [36]. The consequence is that the production of lipids and proteins, during myelination, greatly increases the load of the secretory pathway which is very susceptible to ER stress [37]. The altered production of myelin by oligodendrocytes leads, as already mentioned, to the death of these cells and the onset of demyelinating diseases; in many of these pathologies a correlation with ER stress has been demonstrated [38]. ER stress is caused by the accumulation of unfolded or misfolded proteins, by the alteration of lipid synthesis, by the loss of calcium deposits; in these conditions the cell responds with the activation of a pathway called Unfolded Protein Response (UPR) which heals ER stress by decreasing the protein load, the increased protein folding capacity and the induction of cytoprotective genes. UPR protects the cell by reducing or eliminating ER stress. If UPR is unable to resolve the stressful events, the cell undergoes apoptosis [39,40]. For example, ER stress is visible in oligodendrocytes of patients with multiple sclerosis, an autoimmune neurodegenerative disease which involves the formation of auto-antibodies to myelin and gradually disabling. In fact, activation of UPR was found in oligodendrocytes of these patients with the involvement of the transmembrane transducers involved in this process [41]. Pelizaeus-Merzbacher disease (PMD) is a pathology linked to the X chromosoma that causes dysmyelination of the CNS due to a mutation in the gene that codes for the myelin protein PMD. The severity of this pathology depends on both the severity of the mutation and the ability of PLP to escape from the ER [42]. There are also PMD-like forms in which mutations of genes that code for other myelin proteins, such as MAG. Also in this case there is the involvement of ER with an increase in UPR [43]. Charcot-Marie-Tooth disease encompasses a group of genetic pathologies caused by a mutation for a gene of peripheral myelin proteins; mutations can be expressed by Schwann myelinating cells in PNS [44] As in the case of PMD, the severity of these pathologies depends on how much the proteins are retained in the ER. Furthermore there is a marked activation of UPR in Schwann cells [45]. To date, numerous scientific evidences promote UPR as a therapeutic target for numerous neurodegenerative diseases that include myelin disorders [46]. These new therapies focus on the use of compounds that selectively modulate UPR transducers [47].

### 3. Environmental and nutritional “stressors” and oligodendrocytes impairment

Mature oligodendrocytes are very sensitive cells that can easily be damaged. From this point of view, habits and lifestyle are essential to maintain a condition of oligodendrocyte balance. In the next section we will deepen two aspects in which oligodendrocytes and/or OPCs can suffer: chronic alcohol consumption and heavy metal intake.

#### 3.1. Chronic consumption of alcohol and oligodendrocytes

It has been widely demonstrated that chronic alcohol intake constitutes a huge public health problem all over the world and is a major cause of the onset of diseases and premature death. The effects of alcohol can vary greatly in relation to the daily amount and type of consumed drink. To date, the adverse effects of alcohol consumption on various parts of the body are known including the cardiovascular system, immune system, liver, intestine, and nervous system [48-54]. In particular, alcohol is regarded as a negative CNS modulator since it acts on various brain regions. In fact it has been shown that prolonged alcohol consumption can induce neuronal death and impaired brain development [55]. Scientific data conducted in recent years have shown that alcohol consumption was related to the reduction of white matter and to an incorrect composition and myelin functionality [56]. Obtained findings from post-mortem studies of alcoholics confirmed a reduction in brain weight

and increased demyelination [57]. Furthermore, under the same experimental conditions, alterations of the myelin structure with a reduced presence of sphingolipids and phospholipids, an increased presence of vacuoles and mitochondrial alterations were highlighted [58]. There are many scientific relevances on the basis of which the consumption of large quantities of alcohol determines myelin changes also in the fetus [59]. In fact, *in vivo* studies have shown, in a mouse model exposed to the alcoholic quantities corresponding to those of an alcoholic subject, that the fetuses in the third trimester showed a 58% reduction of mature oligodendrocytes and 75% of OPC. These findings correlate well with OPC's greater vulnerability to toxic damage than mature oligodendrocytes [60]. Moreover studies conducted *in vitro* on OPCs have shown that treatment with EtOH negatively modulated the expression of PDGFR $\alpha$  which has a fundamental role in the differentiation of OPC, in mature and myelinating oligodendrocytes [61]. Finally it is important to report that a prolonged abstinence from alcohol was able to positively modify the structure of myelin: in this case it was possible to observe a new increase in the expression of the MBP myelin protein in rats [62]. Scientific evidence has shown that oxidative stress, ER stress and apoptotic-caspase3-dependent death were increased in the brain in a model of mice which were given free access to ethanol and water (in the ratio 1: 9 respectively) for seven months [63]. In order to investigate this topic, further studies should be conducted.

### 3.2. Intake of heavy metals and oligodendrocytes

Heavy metals are normally present in the earth's crust and they are released spontaneously in concentrations that don't affect human health. However, any metal can be considered a "contaminant" if its concentration causes a harmful effect on humans or the environment [64]. To date, the presence of heavy metals in the environment has increased exponentially as a result of human activity, which includes industrialization, anthropogenic waste, the use of fertilizers and pesticides. It is also worth mentioning the occupational exposure to heavy metals that occurs in the workplace [65]. The main metals considered dangerous if present in abundant concentrations are lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), chromium (Cr), copper (Cu), nickel (Ni), aluminum (Al), cesium (Cs), cobalt (Co), molybdenum (Mo), strontium (Sr), and uranium (U). [66] Heavy metals are very resistant to biological and chemical decomposition processes, due to their non-degradable nature; the consequence is their accumulation in the food chain through the process of bio-magnification [67]. Heavy metals can accumulate in various organs, including the liver, heart, kidney and brain, and greatly affect their function. In the last decades, the presence of neurological damage following acute and chronic exposure to heavy metals has been increasingly evident [68-70]. In particular it has been shown that the accumulation of some metals can alter the process of myelination, possibly leading to neurodegeneration [71,72]. An important scientific work, conducted in our research group and recently published, has been carried out *in vitro* on mature oligodendrocytes and human neurons grown individually and in co-culture; cell lines were exposed to non-toxic concentrations of several essential (Cu<sup>2+</sup>, Cr<sup>3+</sup>, Ni<sup>2+</sup>, Co<sup>2+</sup>) and non-essential (Pb<sup>2+</sup>, Cd<sup>2+</sup>, Al<sup>3+</sup>) heavy metals. The choice to use sub-toxic concentrations of heavy metals was motivated by the desire to reproduce a model in which cells were in contact with the concentrations to which humans are exposed daily and unknowingly [73]. The results of this study showed that oligodendrocytes are more susceptible than neurons to exposure to heavy metals when the two cell lines have grown in direct contact. In addition, exposure to heavy metals showed a reduced oligodendrocyte expression of the MBP myelin protein and a massive dysregulation of the calcium ion in the endoplasmic reticulum. With this scientific study, the interruption of the cross-talk between oligodendrocytes and neurons has been demonstrated when cells are exposed to some heavy metals. The continuation of this work has shown, under the same experimental conditions, a direct involvement of the endoplasmic reticulum. In fact UPR was studied and inositol-requiring enzyme 1 pathway (IRE1 $\alpha$ ) was found to be activated. In particular IRE1 $\alpha$  carries out a protective action against the insult generated by the treatment with heavy metals. In fact the silencing of IRE1 $\alpha$  determined an increased mortality in both neurons and oligodendrocytes compared to the mortality observed in the absence of silencing. Furthermore a consequence of the silencing of IRE1 $\alpha$  was the increase of ROS and index

of lipid peroxidation not observed in the absence of silencing. Finally, the administration of subtoxic concentrations of heavy metals demonstrated the involvement of SREBP1 in both neurons and oligodendrocytes [23].

It has been shown that heavy metals may be responsible for the induction of oxidative stress, with the production and accumulation of ROS, increased cytotoxicity and genotoxic stress that involves physical or chemical alterations to the DNA [74]. Furthermore, experiments conducted on fetuses and embryos have shown that exposure for a short time to cadmium (25-100  $\mu\text{M}$ ) alters the stability of oligodendrocytes and induces apoptotic-mitochondria-dependent death in OPCs. In this cell line nuclear condensation, DNA fragmentation, mitochondrial release of cytochrome c and activation of caspase 3 and 9 were evaluated. Cadmium, therefore, is responsible for an altered myelination resulting from mitochondrial suffering [75]. Mercury also acts negatively on the correct functioning of the brain: the best known model of multiple sclerosis (autoimmune encephalomyelitis, EAE) was experimentally induced in groups of mice. Following the administration of mercury, the animals showed neurobehavioral alterations; following the sacrifice of the animals the brain was taken and analyzed. The obtained results showed high mitochondrial toxicity with accumulation of ROS, morphological alterations, release of cytochrome c and cell apoptotic death. In this case, therefore, repeated exposure to mercury accelerated the progression of multiple sclerosis through oxidative damage [76]. Lead is a well known heavy metal for its neuro-toxic properties. In fact, high intakes of this metal cause cognitive, neuro-behavioral and motor disorders dependent on the absorbed and accumulated quantities. These deleterious effects are particularly present if lead is accumulated during childhood or in the age of development [77]. The tolerated levels of lead in the blood of adults are 70  $\mu\text{g} / \text{dL}$  and higher values are the cause of encephalopathy. In these cases, magnetic resonance imaging (MRI) can detect macroscopic brain abnormalities [78]. Numerous experimental studies, conducted *in vitro* and *in vivo*, have highlighted the toxicity of lead both in neurons and in glia. In mature oligodendrocytes, lead alters the expression of genes essential for the formation of myelin, induces a delayed differentiation of OPCs and promotes an altered structure of mature oligodendrocytes. Finally, disintegration of the multi-lamellar structure were highlighted [79]. The functional alteration of mature oligodendrocytes and OPC is known following the massive uptake of all heavy metals, although a greater amount of data should be produced.

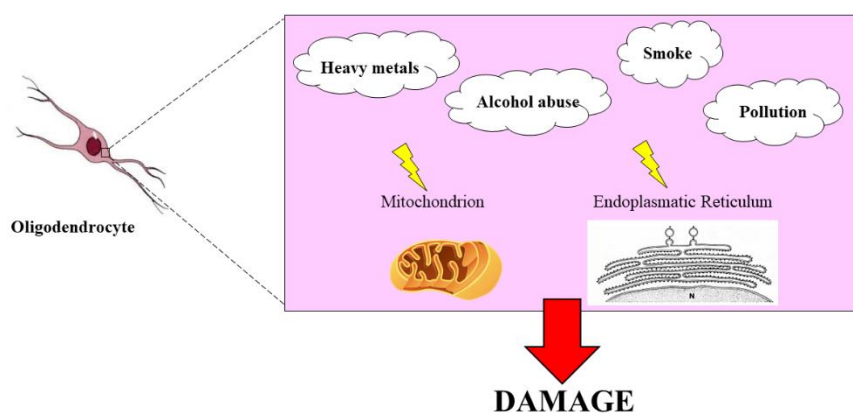
#### 4. Discussion and Conclusions

In this review, the fundamental role played by oligodendrocytes in all phases of their life was investigated. The integrity of these cells guarantees the development and correct functioning of the CNS [80-82]. Embryological studies have confirmed that oligodendrocytes, in order to become mature and functional, need to evolve from OPCs and these maturation steps are extremely and finely regulated. In this regard, the latest scientific findings have correlated the maturation of oligodendrocytes to some pathways which include epigenetics [83, 84] and the intestinal microbiota [85,86].

Although this argument is continuously updated, many doubts still exist and it would seem that there is no single mechanism to regulate the maturation process of oligodendrocytes. Once this development is completed axonal myelination by oligodendrocytes takes place and this process must also be finely regulated in order to avoid dysmyelination, demyelinating diseases and neurodegeneration.

In this delicate period of time any oligodendrocyte dysfunction can be responsible for structural and functional alterations [87,88]. Numerous scientific studies have shown how a correct lifestyle is essential for the purpose to protect the good health of oligodendrocytes. This habit should be followed by every adult person, in order to maintain and not alter the oligodendrocyte balance already formed [89,90]. Furthermore, an adequate lifestyle should also be followed by pregnant women since this period coincides with the initial formation and development of the nervous system of the fetus [91,92]. Finally, it is also important that correct habits are maintained during childhood, since this age group is important for the continuation of a correct development of the system nervous [93]. Altered habits that lead to damage to oligodendrocytes include chronic alcohol abuse and

exposure to heavy metals. These two aspects have been deepened, but there are other deleterious factors such as smoking, excessive exposure to environmental pollution and the use of drugs. In particular, tobacco smoke increases the extent of inflammatory processes, participating in the destruction of the main myelin proteins, mainly including MBP. It has also been shown that smoking worsens the course of demyelinating diseases, such as multiple sclerosis [94-96]. Even exposure to pollution has been shown to have deleterious effects on oligodendrocytes and myelination [97,98]. Finally, drug abuse with psychotic effects on the central nervous system, can interact with oligodendrocytes even if this aspect remains controversial [99,100]. In this review we have highlighted how the main damages and malfunctions of oligodendrocytes are related to the dysfunction of two fundamental cellular organelles: the mitochondrion and the endoplasmic reticulum. A graphic cartoon of this topic is shown in figure 1.



**Figure 1.** Graphic representation of the involvement of mitochondria and endoplasmic reticulum in the damage of oligodendrocytes.

In light of what has been deepened and described, there are two directions in which research in this area could continue:

Begin to consider mitochondria and the endoplasmic reticulum as the main targets of oligodendrocyte dysfunction, trying to restore their conditions in order to evaluate any positive modulations in various neurological pathologies;

Change the direction in which neurological pathologies are observed: from the oligodendrocyte to the neuron instead of from the neuron to the oligodendrocyte. In this way, oligodendrocytes, astrocytes and microglia could be considered as the reference point of the neuron in health and disease conditions.

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