Artykuł przeglądowy *Review*

Oligodendrocytes: Morphology, functions and involvement in neurodegenerative diseases

IZABELA KRAWCZYK-MARĆ, AGATA WAWRZYNIAK, IWONA ŁUSZCZEWSKA-SIERAKOWSKA*, MAREK BABICZ**, STANISŁAW ORKISZ

Department of Morphological Sciences, Faculty of Medicine, University of Rzeszów, ul. Leszka Czarnego 4, 35-615 Rzeszów, Poland
*Department of Human Anatomy, Medical University of Lublin, ul. Jaczewskiego 4, 20-090 Lublin, Poland
**Department of Pig Breeding and Production Technology, Faculty of Biology, Animal Sciences and Bioeconomy, University of Life Sciences in Lublin, ul. Akademicka 13, 20-950 Lublin, Poland

Received 31.10.2018 *Accepted 17.01.2019*

Krawczyk-Marć I., Wawrzyniak A., Łuszczewska-Sierakowska I., Babicz M., Orkisz S.
Oligodendrocytes: morphology, functions and involvement in neurodegenerative diseases

Summary

Oligodendrocytes (OLs) are myelinating cells of the central nervous system (CNS). They are a highly specialized type of glial cell in the CNS of vertebrates, which guarantee the transmission of action potentials over long distances by producing a myelin sheath that wraps adjacent axons. Although they are often credited merely with participation in myelination, recent research has led to a radical change in the understanding the role of these glial cells. OLs are currently understood to be plastic and adaptive cells, capable of responding quickly to changes taking place in the spatial neuronal network in the CNS. Due to their complex differentiation process and their physiology, OLs are among the most sensitive cells in the CNS. Finding answers about their interactions with other types of glial cells may result in benefits in the form of neuroprotection and axon plasticity. Damage to OLs and the myelin sheath is one of processes contributing to the development of crippling neurological diseases, although the role of these cells in neurodegeneration remains controversial. This article not only presents OLs as cells whose ultimate goal is to produce myelin sheaths, but also discusses their involvement in neurodegenerative diseases.

Keywords: oligodendrocytes, central nervous system, myelin, neurodegenerative diseases

The nervous system of humans and animals consists of two main cell types: neurons and neuroglia (21, 48). Research on the neuroglia has contributed to the understanding of interactions between neurons and glial cells. An important feature of neuroglial cells is their excitability, which enables communication with neurons and modulates their activity (5). Neurons, glia and blood vessels work closely together to control conduction functions. Impairment of this symbiosis results in neurodegenerative diseases involving cognitive dysfunctions, such as Alzheimer's disease (AD) (52). The central nervous system (CNS) of an adult mammal includes four types of glial cells: astrocytes, oligodendrocytes (OLs), microglial cells and ependymal glia (9). OLs, astrocytes and ependymocytes are derived from a common line of neuronal progenitor cells in the neuroectoderm, whereas microglial cells are CNS macrophages derived from monocytes (42). In the peripheral nervous system, glial cells are represented by Schwann cells and satellite glial cells (21). Glial cells were classified less than 100 years ago by Pio del Rio-Hortega, who correctly assumed that microglia play a defensive role in a pathological CNS (39). Although that research was remarkably accurate for that time, innovative technologies have revealed new molecular, cellular and physiological aspects of glial tissue in the CNS. In the normal CNS, astrocytes regulate neurotransmitters and neurovascular dynamics. In response to damage, they become reactive and, together with the microglia, form glial scars. Under the influence of infection or damage in the CNS, microglia promote axon growth and remyelination, but in the case of excessive activity, they exert a cytotoxic effect. OLs and their precursors in normal tissue accelerate axonal conduction and support axonal function, but they are extremely susceptible to damage. Astrocytes, microglia and OLs interact to influence the survival, differentiation and remyelination of neurons. Communication between glial cells and nerve fibres is present even in invertebrates, such as earthworms, shrimp and copepods, but OLs and Schwann cells that

produce myelin sheaths are present only in vertebrates (29). In vertebrates, the ratio of glial cells to neurons in the cortex increases with increasing brain size. Various authors have reported that the ratio of the number of neuroglia to neurons in the cerebral cortex is approximately 1.5-1.7 in humans, 0.3-0.4 in rodents, 1.1 in cats, 1.2 in horses, 0.5-1.0 in Rhesus monkeys, and 4.0-6.0 in elephants and whales (*Balaenoptera physalus*). The highest number of glial cells has been found in the cerebral cortex of dwarf whales (*Balaenoptera acutorostrata*), which contains about 12.8 billion neurons and about 98 billion glial cells. In this case, the ratio of the number of glia to neurons is 7.6 (56). The increase in the ratio of the number of neuroglia to neurons during the evolution of mammals is a reflection of the increase in energy expenditure by neurons. Human neurons need about 3.3 times as much energy as rodent neurons do (26).

Astrocytes

Astrocytes are specialized CNS glial cells that perform many functions. They are presumed to be formed indirectly from radial glia, whose functions include creating scaffolding for newly formed neurons. Astrocytes have a star-shaped cellular body with numerous branched processes. On the basis of morphological differences, astrocytes have been divided into two main classes: protoplasmic astrocytes (with short processes), present mainly in the grey matter of the CNS, and fibrous astrocytes (with many long processes), located primarily in the white matter (9, 49). Astrocytes are additionally classified according to their ability to react to CNS damage. Inactive, resting and reactive astrocytes have been distinguished. The resting type is present in normal, unchanged glial tissue in the CNS, while reactive astrocytes locate closer to the site of injury, and together with microglia participate in the formation of glial scars (32).

Microglia

Microglia are a population of resident mesenchymal CNS macrophages located near nervous structures and closely involved in brain homeostasis. This type of glial cells also plays a key role in the development and differentiation of neurons and in perinatal synapse formation. In the adult brain, microglial cells account for about 5-20% of all glial cells (1). They take the form of typical macrophages that multiply during inflammation or local damage to nervous tissue. They have a small oval cell body (about 4 μm) with numerous processes. CNS disorders caused by factors such as infection, trauma or ischemia result in the activation of microglia, which cause morphological changes in these cells, their proliferation, changes in receptor expression and changes in their function (42). The signal that initiates microglia activation has not been conclusively determined, but it seems that the main stimulus may be the depolarization of the neuronal cell membrane or signals of neuronal origin, such as pro-inflammatory cytokines, growth factors, complement system proteins, free radicals, neurotoxins, nitric oxide, prostaglandins, ATP or stimulating amino acids. Activated microglia can secrete numerous growth and inflammatory factors. These glia maintain the homeostasis of the neuronal microenvironment, supervise the survival of neurons within the CNS and act as immunologically competent cells (23).

Oligodendrocytes

In the CNS, OLs are glial cells responsible for the production of myelin. It is easy to forget that until the mid-1950s, many researchers believed the myelin sheath to be an axonal product, not a natural glial product. Neuroglia were often perceived only as 'glue', whose role was limited to supporting neurons. Only recently have scientists begun to analyse and understand this unique type of glial cell. Advances in imaging technology and model systems have provided researchers with access to the internal mechanisms of OLs, allowing them to investigate their role in axonal maintenance, survival and adaptation (14, 15, 25, 54), as well as in the formation of a complex spatial network of neuronal circuits (28).

Formation of oligodendrocytes. In vertebrates, the CNS myelination process begins during embryogenesis and continues after birth, with the time of its completion depending on the species of animal. In the initial stage of the neural tube, there is only one cell layer built of neuroblasts. This gives rise to neurons and spongioblasts, from which the remaining types of glial cells are formed, with the exception of microglia (12). The formation of OLs begins with O-2A (oligodendrocyte-type 2 astrocyte) bipotential glial precursor cells, from which all types of glia may develop. O-2A migrate very quickly and inhabit the white and grey matter of the CNS. During this migration, some of O-2A become precursor cells for OLs – oligodendrocyte precursor/progenitor cells (OPCs) (17). These cells show a high level of ganglioside recognition by the A2B5 antibody, the PDGF α receptor (PDGFαR) and the NG2 proteoglycan. Most OPCs proliferate in the CNS white matter in response to local mitogenic signals. Differentiation of OPCs is regulated in part by transcription factors, such as Olig1, Olig2, Mash, Myt1, Nkx2.2 and Sox10. Before birth, stem cells stop proliferating, which slows down the cell cycle associated with the growth, differentiation and death of the cell. At the target site, OPCs are transformed into immature OLs, characterized by the expression of monoclonal antibody O4. Cells with this antibody are transformed into mature OLs with their own specific antigenic marker, galactocerebroside (GC), on their surface. From that moment OLs are capable of producing myelin. The differentiation of OPCs in myelinating OLs is characterized by a rapid growth rate and profound morphological changes requiring a dynamic remodelling of the cytoskeleton. Excess or unnecessary OLs die in the early stages of differentia-

tion, leaving cells with the necessary components for myelin formation (9, 17).

Classification of oligodendrocytes. The Scottish pathologist W. Ford Robertson first described cells that are now known as OLs. Initially, OLs were unnoticed until the silver staining method used by Pio del Rio Hortega in 1919 led to their discovery (6). Pio del Rio Hortega classified OLs according to the size and shape of their soma, the number of processes, their distribution, and their manner of interaction with axons with which they are associated. As a result of these analyses, he grouped these glial cells into four subtypes (I to IV). Type I cells, present in the grey and white matter of the CNS, had a small round cell body (15-20 μm) and a large number of processes extending in multiple directions. Type II OLs were present only in the white matter and had a polygonal body shape (20-40 μm), with fewer and thicker processes, compared to type I OLs. Type III OLs, the least common, were present in the white matter and had 1-4 processes that myelinated the brainstem and spinal cord axons. Type IV OLs, present in the white matter, had a flattened soma and were located mainly at the axons of the brainstem and spinal cord (39).

Observations of animal brains at the level of the electron microscope have made it possible to distinguish three types of OLs according to the density of the cytoplasm: OLs with light, medium and dark cytoplasm (57). OLs with light cytoplasm have a large centrally located nucleus with distinct chromatin and a large nucleolus. This type of OL contains typical cellular organelles, such as the rough endoplasmic reticulum, the Golgi apparatus, mitochondria and microtubules. This type of OL has the most processes. OLs of the medium type, which are slightly smaller, have an oval nucleus with eccentrically arranged chromatin and a smaller nucleolus. The third type, with the most electron-dense cytoplasm, has a large number of mitochondria, the Golgi apparatus and the rough endoplasmic reticulum. The nucleus is spherical and centrally located, with chromatin located near the nuclear membrane. A few short electron-dense processes extend from the soma. Light OLs are assumed to be myelinating cells, while dark ones are their mature form, mainly involved in maintaining myelin. In young individuals, the forms with light and medium cytoplasm are predominant. With age, the number of OLs decreases, especially light ones, which transform into the form with dark cytoplasm. Light OLs are believed to be capable of continuous mitotic divisions (4, 30, 57). Many morphological characteristics distinguish OLs from astrocytes, in particular their smaller size, greater cytoplasm and nucleus density, lack of intermediate glial filaments and the presence of a large number of microtubules in their processes, which may be involved in maintaining their stability (5).

Formation of the myelin sheath

Recent years have seen advances in imaging technology and transgenic modelling which have provided significant insight into the physiology of OLs. The basic and best-known function of these cells is the formation of a myelin sheath around most axons in the CNS. Recent evidence suggests that the remodelling of myelin takes place not only de novo or by replacement of dying OLs, but also owing to the plasticity of the myelin sheath itself (15). The OL is an adaptive cell, capable of responding to changes in axonal number and size. Myelination is therefore a process of pruning and sculpting the myelin sheath (54).

The myelin sheath is composed of a modified cellular membrane of OL processes that surround axons, insulating them and ensuring fast and effective conduction of electric impulses along the long axis. Owing to this multilayer covering around axons, a nerve impulse is conducted 20-100 times faster than along non-myelinated axons of a similar diameter. This difference was undoubtedly the cause of evolutionary changes leading to the formation of myelinating cells in the nervous system (33). Myelin formation by OLs has been a phylogenetic success in vertebrates for 400 million years. The appearance of myelin significantly influenced the development of vertebrates, in particular their nervous system (58). Invertebrates and jawless fish could achieve rapid impulse transfer by increasing the axonal diameter. However, these species have only a few axons with huge diameters for specific reflexes. It should be noted that the equivalent of myelin also exists in some invertebrates (18, 33). For example, 'myelin' accelerates the escape response of small crustaceans *Calanoida caltrops*, which dominate in oceanic zooplankton. The 'myelin' of copepods is of axonal origin, not of glial origin as in vertebrates (59). The unique composition of myelin, i.e. its high lipid content and low water content, insulates axons. The dry mass of myelin contains 70% lipids and 30% proteins. Specific components of myelin – glycolipids and proteins – are formed in OLs (5). The lipids present in OLs and myelin include glycosphingolipids, mainly galactocerebrosides (GalC) and their sulphate derivatives – sulfatides (10). The most important are myelin basic protein (MBP) and proteolipid protein (PLP), which constitute about 80% of myelin proteins. Other proteins include 2'3'-cyclic nucleotide 3'-phosphodiesterase (CNP), myelin-associated glycoprotein (MAG), and myelin/oligodendrocyte glycoprotein (MOG). All the compounds described above play a key role in the formation of myelin (5). Myelination is a complex sequence of events that can be divided into successive stages: 1) proliferation and migration of OPCs, 2) recognition of target axons and axon-glial signalling, 3) differentiation of OPCs in myelinating OLs, 4) axonal wrapping, 5) transport of membrane components, 6) myelin compaction and 7) formation of the nodes of Ranvier. The myelination process requires the activation of numerous enzymes necessary for the synthesis of lipids and proteins and the transport of specific myelin protein components (3, 47).

Oligodendrocytes and neurodegenerative diseases

OL dysfunctions are features of demyelinating diseases, strokes, brain and spinal cord injuries and neurodegenerative diseases of the CNS in humans and animals (11). OL dysfunction has been reported in such neurodegenerative diseases as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease, although these diseases are not thought to be linked to the process of myelin sheath formation itself (25). There is increasing evidence that neurodegenerative diseases are complex nervous system disorders related mainly to glial cells.

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease of adulthood, characterized by the death of cortical and spinal motor neurons and a progressive loss of motor function. Patients are initially affected by muscle weakness and fasciculations, rapidly leading to paralysis and eventually death by respiratory failure. The disease pathology is characterized by abnormal accumulation of insoluble and misfolded proteins in degenerating motor neurons. The loss of these neurons results in progressive paralysis that is typically fatal. This degeneration has been linked to OL dysfunction.

The oligodendroglia pathology in ALS, including degeneration of OLs, impaired maturation of new OLs and OL involvement in neurodegeneration, shows some similarities to multiple sclerosis (MS). The main function of OLs is to provide support and insulation to axons in the CNS by creating the myelin sheath. They also provide metabolic support to neurons by supplying energy metabolites, such as glucose and lactate. Since the most abundant transporter of lactate in OLs is monocarboxylate transporter 1 (MCT1), their disruption results in axonal damage, leading to neural loss. OL progenitors (NG2+ cells) have been shown to undergo enhanced proliferation and differentiation. Although new OLs are being formed, they fail to mature, which results in progressive demyelination of axons (40, 53).

OLs have been implicated in the disease pathology of ALS using transgenic mouse models. There is still no human co-culture system to investigate the involvement of OLs in motor neurons in ALS. The toxicity of OLs occurs via soluble factors and contact between cells, so that numerous mechanisms of action and therapeutic options can be identified. OLs have been shown to be severely affected during ALS and to degenerate prior to motor neuron death. In an attempt to compensate for the loss of OLs, progenitor cells have been reported to be highly proliferative, but they fail to reach maturity. Motor fibres both in mouse models and in the spinal cords of ALS patients show signs of demyelination, but neither the ALS mouse model nor patients with ALS show defects in developmental myelination. Not only OLs are affected in ALS patients; NG2+ OL progenitor cells also show reactive changes. Once they differentiate into mature OLs, these cells provide axonal support and electrical insulation by forming the myelin sheath. The

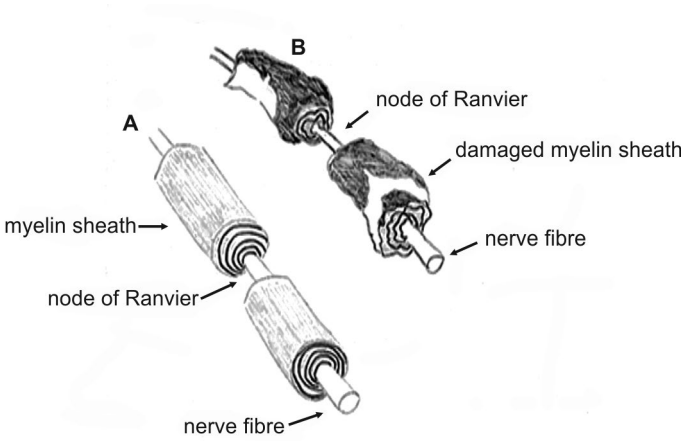

Fig. 1. The picture shows fibres with a normal myelin sheath (A) and a damaged myelin sheath in MS (B)

loss of or damage to OLs leads to the loss of the myelin sheath, which can lead to axon degeneration (22).

Abnormalities in OLs, such as pathological inclusions, have been observed in affected post-mortem tissue of ALS patients. In addition, the ALS-linked protein fused in sarcoma (FUS), has been found to be sequestered into inclusions in the cytoplasm of OLs from ALS patients with mutations in the FUS gene. The abundance of FUS inclusions in OLs seems to correlate with the age of onset. Early-onset patients have predominantly neuronal cytoplasmic FUS inclusions and very few oligodendroglia FUS inclusions, whereas patients with late-onset disease have highly abundant FUS inclusions in the cytoplasm of OLs, widespread throughout the CNS. In addition to the presence of inclusions, the grey matter of the ventral spinal cord of ALS patients also shows myelin abnormalities, demyelination and even OL degeneration. These abnormalities in the OLs of ALS patients are a strong indication that these cells could be implicated in ALS pathogenesis. OL pathology seen in ALS has several causes: damage that includes the presence of ALS-causing genes in the OLs; oxidative damage, which can be an additional trigger; and the damaging environment created by the degenerating motor neurons in combination with the deleterious effects of highly reactive microglia and astrocytes. The damaging environment also affects the differentiation capacity of NG2+ into new OLs, resulting in the presence of immature and dysfunctional OLs, which cannot properly sustain neurons and aggravate the vicious cycle of OL–motor neuron degeneration (36).

Multiple sclerosis (MS) is a chronic demyelinating CNS disease characterized by inflammatory and degenerative changes in the brain and spinal cord. This disease is the most common cause of non-traumatic disability in young people (37). In MS, the complex pathological process causes OL dysfunction and apoptosis, leading to demyelination and neurodegeneration. Permanent demyelination is the result of an imbalance between the dysfunction and loss of OLs and the reduction in OL generation from OPCs. This leads to insufficient remyelination of nerve fibres, accompanied by neuronal loss and axonal damage (11). MS is characterized by

lymphocyte perivascular accumulation, blood-brain barrier damage and axonal damage. The pathological hallmarks of MS are lesions known as plaques due to focal loss of myelin, with relative preservation of axons and astrocytic gliosis (41).

Two histological forms of OL dysfunction can be distinguished in MS: 1) OL dysfunction associated with the immune system, and 2) primary oligodendrogliopathy, in which the primary pathology is neurodegeneration, and stimulation of the immune system is a secondary reaction (11). *In vitro* and animal model studies have provided evidence that T-cytotoxic lymphocytes (24, 31) and activation of microglia and macrophages by pro-inflammatory molecules (13) directly affect myelin and OLs (35). In other studies of MS patients, various compounds present in OLs that may be targets of autoimmune responses, such as MBP, PLP, MAG, MOG, transaldolase, oligodendrocyte surface protein (OSP), oligodendrocyte myelin glycoprotein (OMgp), NG2 or glycolipids, were identified in serum and cerebrospinal fluid (19, 43, 50). One of the most important problems in the pathogenesis of MS is brain atrophy, which is the basis for irreversible neurological disability. Brain atrophy can be observed with the first appearance of clinical symptoms, and it progresses with the development of the disease (20). The disease leads to focal inflammatory demyelination in the white matter of the brain and spinal cord and to axonal degeneration.

Necroptosis is involved in the pathology of MS, and treatment targeting necroptosis may provide OLs with a protective strategy. Tumour necrosis factor α (TNF-α) is a pro-inflammatory cytokine involved in MS and may activate OL necroptosis regulated by receptor-interacting protein kinase 1 (RIPK1) and receptor-interacting protein kinase 3 (RIPK3) in the absence of caspase 8. TNF-α levels are elevated in the serum and cerebrospinal fluid of MS patients, which is correlated with the severity of the lesions and disease progression. Caspase-8-regulated apoptosis has an antagonistic relationship with RIPK1-regulated necroptosis. The activity of RIP1 and RIP3 kinases is indispensable in the mechanism of necroptosis. In the necroptosis process, the two kinases undergo mutual phosphorylation and form a pro-necrotic RIPK1/RIPK3 complex. Activated RIPK3 phosphorylates the pseudokinase MLKL, inducing its oligomerization and introduction into the cell membrane, which initiates necroptosis. Inhibition of RIPK1 kinase activity blocks necroptosis induced by TNFα by inhibiting its interaction with RIPK3. Inhibition of RIPK1 has been shown to protect OLs from cell death (38).

Alzheimer's disease (AD) is a neurodegenerative, multi-factorial disorder that affects brain neurons. Its cause remains unknown. AD is also the most common form of dementia in people over the age of 65. Once symptoms are manifested, the disease process is essentially irreversible, due to the loss of neurons, which generally lack the capacity to regenerate. Loss of cells leads to disease symptoms, such as memory impairment, language difficulties, inability to perform motor activities and general cognitive decline (44).

In physiological conditions, the amyloid precursor protein (APP) is one of the components of the neuronal cell membrane. As a result of normal α-secretase enzyme activity, APP is cleaved into soluble fragments. During abnormal transformations involving β- and γ-secretases, it is fragmented into insoluble β-amyloid forms, which accumulate intracellularly and then extracellularly in the form of amyloid plaques (Aβ). The presence of insoluble forms of β-amyloid leads to hyperphosphorylation of the tau protein, which binds to microtubules to stabilize them (60).

Tau mutations in the microtubule-associated protein tau gene (MAPT) lead to the formation of an easily phosphorylated tau protein with altered microtubule affinity, containing numerous β-sheet structures and aggregated in the form of double helical fibres. The incorrect structure and function of the tau protein is the cause of disturbances in intra-axonal transport. Hyperphosphorylated tau protein is deposited in a form referred to as neurofibrillary tangles (NFTs), leading to neuronal death (2). Other neuropathological changes found in AD include Hirano acid-absorbing bodies, which contain actin (16). Much of the recent research on AD has been focused on neurons, but recent studies suggest that glial cells, i.e. microglia, astrocytes, OLs and oligodendrocyte progenitor cells, are linked to the pathogenesis of AD (34).

Scientific studies have shown significant changes in the overall pattern of myelination and OL status before the onset of β-amyloid and tau protein pathology. It has been demonstrated that β-amyloid-mediated toxicity in OLs and myelin can occur through inflammation of nerve fibres, oxidative stress and/or apoptosis. OL dysfunction and the formation of neurofibrillary tangles seem to be induced by inflammation and oxidative stress as a common pathophysiological basis (7).

High levels of Aβ are observed in the white matter of AD patients. Aβ aggregates are responsible for the degeneration of neurons and vessels in the brains of AD patients. Although the molecular mechanism of cell death mediated by Aβ is not fully understood, it is probably associated with oxidative stress. OLs are particularly susceptible to reactive oxygen species because of their reduced content of glutathione (GSH), while on the other hand they have a high iron concentration, which together impairs the ability to capture oxygen radicals. In addition, Aβ has damaged cholesterol-rich membranes, such as those found in OLs and included in the myelin (45).

Parkinson's disease (PD) is a neurological disorder characterized by the progressive loss of the dopaminergic neurons (pars compacta) in the substantia nigra. In PD, there is a gradual loss of brain cells that make and store dopamine. The loss of neurons is associated with a glial response involving mainly activated glial cells.

Dopamine is a neurotransmitter in the brain that sends messages controlling movement. As PD progresses, more dopamine neurons in the brain are lost. The primary symptoms of PD are movement-related, and include resting tremors, rigidity and slowness of movement. However, many patients also experience non-movement related symptoms, such as cognitive impairment, mood changes, constipation and blood pressure problems. The causes of PD remain unknown, although researchers believe the disease may be brought on by a combination of environmental and genetic factors (51).

This glial response may be a source of trophic factors and can protect against reactive oxygen species and glutamate. Aside from these beneficial effects, the glial response can mediate a variety of deleterious events associated with the production of reactive species and pro-inflammatory prostaglandins and cytokines. The glial reaction is generally considered to be a consequence of neuronal death in neurodegenerative diseases, such as PD. It is believed that toxic substances released by glial cells may be involved in the propagation and perpetuation of neuronal degeneration. Glial cells can release compounds, such as pro-inflammatory cytokines [(TNF-α), interleukin-1β (IL-1β) and interferon-γ (IFN-γ)], which may act by stimulating nitric oxide production in glial cells or may exert a more direct effect on dopaminergic neurons by activating receptors involved in apoptosis. Activation of proteases, such as caspase-3 and caspase-8, which are known effectors of apoptosis, has been reported in PD. Caspase inhibitors do not protect dopaminergic neurons against degeneration in models of the disease, suggesting that manipulation of a single signalling pathway may not protect dopaminergic neurons. In contrast, anti-inflammatory drugs have been shown to reduce glial activation and protect the substantia nigra in an animal model of the disease. Inhibition of the glial reaction and inflammatory processes may thus represent a therapeutic target to reduce neuronal degeneration in PD (55).

OLs are highly vulnerable to ischemia and other forms of energy deprivation. During myelination, energy deprivation damages the immature OLs before signs of pathology appear in the neurons, and mature myelinating OLs in adult brains are also highly sensitive to energetic insults. OLs are capable to internalizing α-synuclein. There are at least two mechanisms through which altered OLs may stimulate neurodegeneration. OLs are involved in myelination, and their modification may dysregulate myelination, leading to axonal degeneration and synaptic loss. OLs are the predominant cells for glutamate clearance in human white matter, and alteration of OLs may underlie accumulation of high extracellular glutamate and increase the risk of glutamate excitotoxicity. Since multiple system atrophy (MSA) is histologically characterized by α-synuclein-immunoreactive cytoplasmic inclusions in OLs, the pathogenic mechanism of MSA may be attributable to alteration of OLs by accumulation of α-synuclein. MSA mouse models have been established with expression of mutant α-synuclein under control of oligodendroglia-specific promoters, such as 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP), myelin basic protein (MBP) and proteolipid protein (PLP). These α-synuclein transgenic mice develop extensive α-synuclein-immunoreactive inclusions in OLs in various brain regions (the neocortex, basal ganglia, cerebellum and brainstem), which are accompanied by myelin and neuronal damage and by motor deficits, recapitulating features of MSA. However, the role of OLs in PD remains poorly understood. In addition, multiple anti-inflammatory agents have been shown to possess neuroprotective properties (46).

Similarly to humans, animals also suffer from neurodegenerative diseases, such as AD in dogs, Huntington's disease (HD) in sheep or PD in dogs, horses and pigs (8). Most of the OLGs-related studies on AD, MS, PD or MSA have been carried out on a transgenic mouse model (27).

The last few years have seen enormous changes in our understanding of the biology of OLs, largely due to advances in technology and imaging. Importantly, the perception of these glial cells has changed, as they were previously believed to participate only in myelination. OLs are currently perceived as dynamic, adaptive and plastic cells that are fully capable of responding to a changing environment – from the emergence of new populations of these cells to changes in the existing, previously produced myelin sheath. The biology of OLs, myelination and regeneration of myelin sheaths are very complex processes whose impairment is associated with serious diseases of the nervous system. Intensive research carried out over the last few decades has explained the basic principles of these processes and offered new possibilities for therapeutic interventions. Much less, however, is known about the exact role of these cells in various diseases of the nervous system. Answering these questions will be the main challenge in the near future. Improved technology and renewed interest in glial tissue, and especially in OLs, will allow researchers to find answers to these questions.

References

1. *Arcuri C., Mecca C., Bianchi R., Giambanco I., Donato R.*: The Pathophysiological Role of Microglia in Dynamic Surveillance, Phagocytosis and Structural Remodeling of the Developing CNS. Front. Mol. Neurosci. 2017, 19, 10, 191, doi: 10.3389/fnmol.2017.00191.
2. *Ballatore C., Lee V. M., Trojanowski J. Q.*: Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. Nat. Rev. Neurosci. 2007, 8, 663-672.
3. *Barateiro A., Brites D., Fernandes A.*: Oligodendrocyte Development and Myelination in Neurodevelopment: Molecular Mechanisms in Health and Disease. Curr. Pharm. Des. 2016, 22, 656-679.
4. *Bauer N. G., Richter-Landsberg C., Ffrench-Constant C.*: Role of the oligodendroglial cytoskeleton in differentiation and myelination. Glia 2009, 57, 1691-1705.
5. *Baumann N., Pham-Dinh D.*: Biology of Oligodendrocyte and Myelin in the Mammalian Central Nervous System. Physiol. Rev. 2001, 81, 871-927.
6. *Boullerne A. I.*: The history of myelin. Exp. Neurol. 2016, 283, 431-445.
7. *Cai Z., Xiao M.*: Oligodendrocytes and Alzheimer's disease. International Journal of Neuroscience 2016, 126, 97-104.

8. *Danek M., Danek J., Araszkiewicz A.*: Large animals as potential models of human mental and behavioral disorders. Psychiatr. Pol. 2017, 51, 1009-1027.
9. *Domingues H. S., Portugal C. C., Socodato R., Relvas J. B.*: Oligodendrocyte, Astrocyte, and Microglia Crosstalk in Myelin Development, Damage, and Repair. Front. Cell Dev. Biol. 2016, 28, 4:71, doi: 10.3389/fcell.2016.00071.
10. *Ducić T., Quintes S., Nave K. A., Susini J., Rak M., Tucoulou R., Alevra M., Guttmann P., Salditt T.*: Structure and composition of myelinated axons: a multimodal synchrotron spectro-microscopy study. J. Struct. Biol. 2011, 173, 202-212, doi: 10.1016/j.jsb.2010.10.001.
11. *Dulamea A. O.*: Role of Oligodendrocyte Dysfunction in Demyelination, Remyelination and Neurodegeneration in Multiple Sclerosis. Adv. Exp. Med. Biol. 2017, 958, 91-127.
12. *Durand B., Raff M.*: A cell intrinsic timer that operates during oligodendrocyte development. Bioessays 2000, 22, 64-71.
13. *Felts P. A, Woolston A. M., Fernando H. B., Asquith S., Gregson N. A., Mizzi O. J., Smith K. J.*: Inflammation and primary demyelination induced by the intraspinal injection of lipopolysaccharide. Brain 2005, 128, 1649-1666.
14. *Fünfschilling U., Supplie L. M., Mahad D., Boretius S., Saab A. S., Edgar J., Brinkmann B. G., Kassmann C. M., Tzvetanova I. D., Möbius W., Diaz F., Meijer D., Suter U., Hamprecht B., Sereda M. W., Moraes C. T., Frahm J., Goebbels S., Nave K. A.*: Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature 2012, 29, 485, 517-521.
15. *Gibson E. M., Purger D., Mount C. W., Goldstein A. K., Lin G. L., Wood L. S., Inema I., Miller S. E., Bieri G., Zuchero J. B., Barres B. A., Woo P. J., Vogel H., Monje M.*: Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. Science 2014, 344, 1252304, doi: 10.1126/science.1252304.
16. *Griffin P., Furukawa R., Piggott C., Maselli A., Fechheimer M.*: Requirements for Hirano body formation. Eukaryot Cell 2014, 13, 625-634.
17. *Hardy R., Reynolds R.*: Proliferation and differentiation potential of rat forebrain oligodendroglial progenitors both in vitro and in vivo. Development 1991, 111, 1061-1080.
18. *Hartline D. K., Colman D. R.*: Rapid conduction and the evolution of giant axons and myelinated fibers. Curr. Biol. 2007, 17, 29-35.
19. *Hecker M., Fitzner B., Wendt M., Lorenz P., Flechtner K., Steinbeck F., Schröder I., Thiesen H. J., Zettl U. K.*: High-Density Peptide Microarray Analysis of IgG Autoantibody Reactivities in Serum and Cerebrospinal Fluid of Multiple Sclerosis Patients. Mol. Cell Proteomics 2016, 15, 1360-1380.
20. *Jaworski J., Psujek M., Janczarek M., Szczerbo-Trojanowska M., Bartosik-Psujek H.*: Total-tau in cerebrospinal fluid of patients with multiple sclerosis decreases in secondary progressive stage of disease and reflects degree of brain atrophy. Ups. J. Med. Sci. 2012, 117, 284-292.
21. *Jessen K. R.*: Glial cells. Int. J. Biochem. Cell Biol. 2004, 36, 1861-1867.
22. *Kang S. H., Li Y., Fukaya M., Lorenzini I., Cleveland D. W., Ostrow L. W., Rothstein J. D., Bergles D. E.*: Degeneration and impaired regeneration of gray matter oligodendrocytes in amyotrophic lateral sclerosis. Nat. Neurosci. 2013, 16, 571-579.
23. *Kettenmann H., Hanish U. K., Noda M., Verkhratsky A.*: Physiology of Microglia. Physiol. Rev. 2011, 91, 461-553.
24. *Lassmann H.*: Multiple sclerosis: lessons from molecular neuropathology. Exp. Neurol. 2014, 262, 2-7.
25. *Lee Y., Morrison B. M., Li Y., Lengacher S., Farah M. H., Hoffman P. N., Liu Y., Tsingalia A., Jin L., Zhang P. W., Pellerin L., Magistretti P. J., Rothstein J. D.*: Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature 2012, 487, 443-448.
26. *Lennie P.*: The cost of cortical computation. Curr. Biol. 2003, 13, 493-497.
27. *Liu Y., Zhou J.*: Oligodendrocytes in neurodegenerative diseases. Front. Biol. 2013, 8, 127-133, doi: 10.1007/s11515-013-1260-4.
28. *McKenzie I. A., Ohayon D., Li H., Paes de Faria J., Emery B., Tohyama K., Richardson W. D.*: Motor skill learning requires active central myelination. Science 2014, 346, 318-322.
29. *Miller R. H.*: Regulation of oligodendrocyte development in the vertebrate OUN. Prog. Neurobiol. 2002, 67, 451-467.
30. *Mori S., Leblond C. P.*: Electron microscopic identification of three classes of oligodendrocytes and a preliminary study of their proliferative activity in the corpus callosum of young rats. J. Comp. Neurol. 1970, 139, 1-29.
31. *Na S., Cao Y., Toben C., Nitschke L., Stadelmann C., Gold R., Schimpl A., Hünig T.*: Naive CD8 T-cells initiate spontaneous autoimmunity to a sequestered model antigen of the central nervous system. Brain 2008, 131, 2353-2365.
32. *Nash B., Ioannidou K., Barnett S. C.*: Astrocyte phenotypes and their relationship to myelination. J. Anat. 2011, 219, 44-52.
33. *Nave K. A., Werner H.*: Myelination of the Nervous System: Mechanisms and Functions. Annu. Rev. Cell. Dev. Biol. 2014, 30, 503-533.
34. *Nirzhor S. S. R., Khan R. I., Neelotpol S.*: The Biology of Glial Cells and Their Complex Roles in Alzheimer's Disease: New Opportunities in Therapy. Biomolecules 2018, 10, 8, pii: E93.
35. *Nitsch R., Pohl E. E., Smorodchenko A., Infante-Duarte C., Aktas O., Zipp F.*: Direct impact of T cells on neurons revealed by two-photon microscopy in living brain tissue. J. Neurosci. 2004, 24, 2458-2464.
36. *Nonneman A., Robberecht W., Van Den Bosch L.*: The role of oligodendroglial dysfunction in amyotrophic lateral sclerosis. Neurodegener. Dis. Manag. 2014, 4, 223-239.
37. *Noseworthy J. H., Lucchinetti C., Moses Rodriguez M., WeinshenkerB. G.*: Multiple Sclerosis. N. Engl. J. Med. 2000, 343, 938-952.
38. *Ofengeim D., Ito Y., Najafov A., Zhang Y., Shan B., DeWitt J. P., Ye J., Zhang X., Chang A., Vakifahmetoglu-Norberg H., Geng J., Py B., Zhou W., Amin P., Berlink Lima J., Qi C., Yu Q. Trapp B., Yuan J.*: Activation of necroptosis in multiplesclerosis. Cell Rep. 2015, 24, 10, 1836-1849.
39. *Pérez-Cerdá F., Sánchez-Gómez M. V., Matute C.*: Pío del Río Hortega and the discovery of the oligodendrocytes. Front. Neuroanat. 2015, 7, 9:92, doi: 10.3389/fnana.2015.00092.
40. *Philips T., Bento-Abreu A., Nonneman A., Haeck W., Staats K., Geelen V., Hersmus N., Küsters B., Van Den Bosch L., Van Damme P., Richardson W. D., Robberecht W.*: Oligodendrocyte dysfunction in the pathogenesis of amyotrophic lateral sclerosis. Brain 2013, 136, 471-482.
41. *Popescu B. F., Pirko I., Lucchinetti C. F.*: Pathology of multiple sclerosis: where do we stand? Continuum (Minneap Minn) 2013, 19, 901-921.
42. *Prinz M., Priller J.*: Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. Nat. Rev. Neurosci. 2014, 15, 300-312.
43. *Ramanathan S., Dale R. C., Brilot F.*: Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun. Rev. 2016, 15, 307-324.
44. *Rohn T. T.*: The triggering receptor expressed on myeloid cells 2: "TREMming" the inflammatory component associated with Alzheimer's disease. Oxid. Med. Cell. Longev. 2013, 2013:860959, doi: 10.1155/2013/860959.
45. *Roth A. D., Ramírez G., Alarcón R., Von Bernhardi R.*: Oligodendrocytes damage in Alzheimer's disease: beta amyloid toxicity and inflammation. Biol. Res. 2005, 38, 381-387.
46. *Sekiyama K., Sugama S., Fujita M., Sekigawa A., Takamatsu Y., Waragai M., Takenouchi T., Hashimoto M.*: Neuroinflammation in Parkinson's Disease and Related Disorders: A Lesson from Genetically Manipulated Mouse Models of α-Synucleinopathies. Parkinsons Dis. 2012, doi: 10.1155/2012/271732.
47. *Simons M., Nave K. A.*: Oligodendrocytes: Myelination and Axonal Support. Cold Spring Harb. Perspect. Biol. 2015, 22, 8, a020479, doi: 10.1101/cshperspect.a020479.
48. *Simons M., Trajkovic K.*: Neuron-glia communication in the control of oligodendrocyte function and myelin biogenesis. J. Cell Sci. 2006, 119, 4381-4389.
49. *Sofroniew M. V., Vinters H. V.*: Astrocytes: biology and pathology. Acta Neuropathol. 2010, 119, 7-35.
50. *Sun X., Bakhti M., Fitzner D., Schnaars M., Kruse N., Coskun Ü., Kremser C., Willecke K., Kappos L., Kuhle J., Simons M.*: Quantified CSF antibody reactivity against myelin in multiple sclerosis. Ann. Clin. Transl. Neurol. 2015, 2, 1116-1123.
51. *Sveinbjornsdottir S.*: The clinical symptoms of Parkinson's disease. J. Neurochem. 2016, 1, 318-324.
52. *Takano T., Han X., Deane R., Zlokovic B., Nedergaard M.*: Two-photon imaging of astrocytic Ca^{2+} signaling and the microvasculature in experimental mice models of Alzheimer's disease. Ann. N Y Acad. Sci. 2007, 1097, 40-50.
53. *Tognatta R., Miller R. H.*: Contribution of the oligodendrocyte lineage to CNS repair and neurodegenerative pathologies. Neuropharmacology 2016, 110, 539-547.
54. *Tomassy G. S., Berger D. R., Chen H. H., Kasthuri N., Hayworth K. J., Vercelli A., Seung H. S., Lichtman J. W., Arlotta P.*: Distinct profiles of myelin distribution along single axons of pyramidal neurons in the neocortex. Science 2014, 344, 319-324.
55. *Vila M., Jackson-Lewis V., Guégan Ch., Chu Wu D., Teismann P., Choi Dong-Kuga T. K., Przedborski S.*: The role of glial cells in Parkinson's disease. Neurology 2001, 14, 483-489.
56. *Wawrzyniak A.*: Analiza porównawcza oligodendrocytów w wybranych obszarach mózgowia u norki amerykańskiej (Neovison vison), lisa rudego (Vulpes vulpes), konia domowego (Equus caballus) i bydła domowego (Bos taurus). Praca hab., Wydz. Medycyny Weterynaryjnej UP, Lublin 2017.
57. *Wawrzyniak-Gacek A.*: Distribution of various types of oligodendrocytes and cellular localization of iron in the frontal cortex of the adult rat. Folia Morphologica 2002, 61, 115-121.
58. *Werner H. B.*: Do we have to reconsider the evolutionary emergence of myelin? Front. Cell. Neurosci. 2013, 15, 7:217, doi: 10.3389/fncel.2013.00217.
59. *Wilson C. H., Hartline D. K.*: Novel organization and development of copepod myelin. ii. nonglial origin. J. Comp. Neurol. 2011, 519, 3281-3305.
60. *Yankner B. A., Lu T.*: Amyloid beta-protein toxicity and the pathogenesis of Alzheimer disease. J. Biol. Chem. 2009, 20, 284, 4755-4759.

Corresponding author: Izabela Krawczyk-Marć, DVM, ul. Leszka Czarnego 4, 35-615 Rzeszów, Poland; e-mail: izkrawczyk@ur.edu.pl