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ROLE OF GLIAL CELLS IN PATHOPHYSIOLOGY OF DEMYELINATING DISEASES OF THE NERVOUS SYSTEM

ÚLOHA GLIOVÝCH BUNĚK V PATOFYZIOLOGII DEMYELINIZAČNÍCH ONEMOCNĚNÍ NERVOVÉHO SYSTÉMU

Bachelor's thesis

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Poděkování

Za odbornou konzultaci, čas strávený s touto prací a obrovskou preciznost při kontrolovaní bych chtěl z celého srdce poděkovat svému školiteli Mgr. Jánu Kriškovi Ph.D. a jeho kolegovi Mgr. Tomášovi Knotkovi, dále mé přítelkyni Sáře za pomoc s vizuální částí práce a své mámě Elišce za korekturu angličtiny.

Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

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Podpis:

Abstract: Glial cells, such as oligodendrocytes, Schwann cells, NG2 glia, astrocytes, and microglia, play a major role in the homeostasis of the nervous system, including the myelin sheath maintenance. Enveloping myelin sheaths produced by oligodendrocytes and Schwann cells, provide a mechanical, isolating, and trophic support to the axons. Importantly, a disruption of a certain component or a dysregulation of a specific process may lead to the collapse and the loss of the myelin sheath, known as demyelination. Axonal demyelination is a pathological condition characteristic of different neurological diseases, such as multiple sclerosis, acute disseminated encephalomyelitis, Charcot-Marie-Toth disease, or Lyme neuroborreliosis. Since, demyelinating diseases are still more prevalent in the population, a suitable and effective treatment is crucial for the patients. However, treatment is not available, which results from an insufficient understanding of pathological mechanisms, low permeability through the blood-brain barrier, and a limited regenerative capacity of the nervous system. Therefore, further research in the field of demyelinating diseases is necessary.

Key words: oligodendrocyte precursor cell, oligodendrocyte, Schwann cell, myelination,
acute disseminated encephalomyelitis, multiple sclerosis, remyelination

Abstrakt: Gliové buňky, ku příkladu oligodendrocyty, Schwannovy buňky, NG2 glie, astrocyty a mikroglie hrají důležitou roli v homeostáze nervového systému, včetně myelinového obalu. Myelinové obaly tvořené oligodendrocyty a Schwannovými buňkami zabezpečují mechanickou, izolační a trofickou podporu axonů. Navíc, poškození určitého stavebního prvku myelinu anebo narušení určitého procesu může vést ke zhroucení a ztrátě myelinového obalu, známého jak demyelinizace. Demyelinizace axonu je patofyziologický stav charakteristický pro mnoho onemocnění, například roztroušenou sklerózu, akutní diseminovanou encefalomyelitidu, Charcotův-Marieův-Toothův syndrom anebo limskou neuroboreliózu. Nakolik jsou demyelinizační onemocnění pořád více rozšířené v populaci, vhodná a efektivní léčba je pro pacienty rozhodující. Nicméně, tato léčba ale není dostupná pro každé demyelinizační onemocnění z důvodu nedostatečného porozumění patofyziologickým mechanismům, slabé prostupnosti hematoencefalické bariéry a limitované regenerační schopnosti nervové tkáně. Z těchto důvodů je další výzkum v oblasti demyelinizačních onemocněni je nevyhnutný.

Klíčové slova: prekurzor oligodendrocytu, oligodendrocyt, Schwannova buňka, myelinizace, akutní diseminovaná encefalomyelitida, roztroušená skleróza, remyelinizace

List of abbreviations:

AD	Alzheimer´s disease
ADEM	acute disseminated encephalomyelitis
AIDS	acquired immunodeficiency syndrome
ANAT	aspartate-N-acetyltransferase
APs	action potentials
APC	adenomatous polyposis coli
AQP-4	anquaporin-4
ASPA	aspartoacylase
ATP	adenosine triphosphate
BBB	blood-brain barrier
CK-1	casein kinase-1
CMT	Charcot-Marie-Tooth disease
CNP	2´,3´-cyclic nucleotide-3´-phosphodiesterasere
CNS	central nervous system
CSF	cerebrospinal fluid
CSF-1-R	colony stimulating factor-1-receptor
CSPG-4	chondroitin sulfate proteolglcan-4
Cx-32	connexin-32
ECCs	endothelial capillary cell
Fzd	Frizzled receptor
GalC	galactocerebroside
GABA	gamma-aminobutyric acid
GLUT-1	glucose transporter-1
GSK-3β	glycogen synthase kinase-3β
HIV	human immunodeficiency virus
IGF-1	insulin-like growth factor 1
IFN	interferon
JC virus	John Cunningham virus
K^+	potassium ion
Kir channel	inward rectifier potassium channel
LRP-5/6	low density lipoprotein receptor-related protein-5/6
MAG	myelin-associated glycoprotein

MBP	myelin basic protein
MHC	major histocompatibility complex
MOG	myelin oligodendrocyte glycoprotein
MS	multiple sclerosis
MSCs	myeloid stem cells
Na^+	sodium ion
NAA	N-acetyl-aspartate
NG2	neural-glial antigen 2
NO	neuromyelitis optica
NPCs	neural progenitor cells
OPCs	oligodendrocyte precursor cells
PDGFR-α	platelet-derived growth factor receptor-α
PLP	proteolipid protein
PMP22	peripheral myelin protein 22
PNS	peripheral nervous system
PNNs	perineural nets
Px	periaxin
TCF/LEF	T-cell factor/lymphoid enhancer factor
TF	transcription factor
TGF	transforming growth factor beta
Th cells	T-helper cells
TNF-α	tumor necrosis factor alpha
VCAM-1	vascular cell adhesion molecule-1

Contents

1 Introduction

The myelin sheath is a specialized dynamical membrane system enveloping axon of neurons with the processes composed of proteins and lipids. The axons are enveloped in the central nervous system (CNS) and peripheral nervous system (PNS) by different glial cells: oligodendrocytes in the CNS and Schwann cells in the PNS. The function of the myelin sheath is axonal isolation, which is crucial for the propagation of action potentials (APs). Due to the insulation property, the propagation of APs is faster and more effective. Importantly, the myelin structure in the CNS differs from its structure in the PNS, most significantly by the distribution of myelinating cells, thickness of the myelin sheath, and a number of cells enveloped by a single myelinating cell. (Liu et al*.,* 2019). Except many differences, the CNS and PNS share common features, such as horizontal interruptions of the myelin sheath by the nodes of Ranvier and the establishment of multiple lamellae formation, apposed proteolipid layers of the myelin sheath (Battefeld et al., 2019; Sun et al., 2016). The whole structure is characterized by the stability and complexity on the molecular level. There are myelin-specific components of the lipidic and protein origin. The most abundant proteins in the CNS are myelin basic protein (MBP) (Kompaneets et al., 2022) and proteolipid protein (PLP) (Steyer et al., 2020). Both proteins stabilize the myelin sheath by their incorporation to the membrane system, where they interact with lipidic molecules, such as cholesterol, galactocerebroside (GalC), and sphingomyelin (Barnes-Vélez et al., 2023). However, the stability and complexity of the myelin sheath cause difficulties in regeneration and reconstruction of the whole system following disorders. As a result of a vast variety of different factors triggering demyelination, suitable and effective treatment is still needed in this field.

2 Glial cells

The neural tissue consists of two types of cells: neurons and glial cells. Neurons provide electrochemical signals and glial cells maintain these processes. There are also several types of glial cells, which differ in their function, origin and localization within the neural tissue. Each type of glial cells, also called glia, have multiple functions important for the organization, protection, and regeneration of neurons and the whole neural tissue. Astrocytes, oligodendrocytes, neural-glial antigen 2 (NG2) glia, including oligodendrocyte precursor cells (OPCs), and microglia can be found in the CNS. Conversely, Schwann cells are the major type of glial cells in the PNS (Verkhratsky & Butt, 2008).

2.1 Astrocytes

Astrocytes, the most abundant glial cells in the CNS, have a large spectrum of functions. Depending on their localization within the CNS, they are divided into two morphological subtypes: protoplasmic and fibrous astrocytes (Mazumder et al., 2022). Protoplasmic astrocytes dominantly occur in the gray matter of the CNS, extend more processes than fibrous astrocytes (Miller & Raff, 1984). Fibrous astrocytes, on the other hand are more prevalent in the white matter and the main difference lies in their stretched shape along the axons (Kim et al., 2016). Undoubtedly, astrocytes play the most important role in maintaining the CNS homeostasis. These cells, together with pericytes and endothelial capillary cells (ECCs), form the blood-brain barrier (BBB), an interface between the neural tissue and circulatory system (J. Huang et al.,

2022). Tight junctions expressed by ECCs at this interface do not allow hydrophilic molecules to pass through this barrier. Specialized receptors are needed for transport of essential compounds, for instance glucose transporter-1 (GLUT-1) for glucose (Parra-Abarca et al., 2019). Moreover, neurotransmitter reuptake and recycling are processed through astrocytes, for instance glutamate reuptake by glutamate transporter-1 and subsequent metabolic transformation to glutamine (Andersen et al., 2022). Maintaining ionic concentration, especially the concentration of K^+, is another crucial function of astrocytes. This function is primarily provided by inward rectifier potassium channels (Kir) 4.1 (Tong et al., 2014). Moreover, the concentration of Na^+ and K^+ is also maintained by Na^+/K^+-ATPase. This enzyme controls ionic concentration by pumping sodium (Na^+) to the extracellular space and K^+ to the intracellular space, while the consumption of adenosine triphosphate (ATP) (Hertz & Chen, 2016). Since, astrocytes perform irreplaceable functions in the CNS, a plethora of pathologies are related to their dysfunction. For example, the mutations in the gene encoding glial fibrillary acid protein play an important role in the progression of Alexander disease (Hagemann, 2022).

2.2 Oligodendrocytes

The second most abundant glial type in the are oligodendrocytes. They envelop several axons and the perinodal space (extracellular space at the node of Ranvier) in the CNS is occupied by astrocytic processes (Lorenzo et al., 2020).The myelin envelopment of axons is not compact but rather interrupted by gaps, called nodes of Ranvier (**Figure 1**) (Lubetzki et al., 2020). The myelin sheaths are terminated by paranodal loops, angulations of the myelin membrane (Sun et al., 2016). There are sodium (Na^+) and potassium (K^+) voltage-dependent channels localized at the nodes of Ranvier, providing a rapid propagation of APs along axons (Gong et al., 2012). This type of acceleration of APs is called saltatory conduction (Jacak & Jacak, 2020). Oligodendrocytes are also characterized by a high density of ribosomes necessary for protein expression, active Golgi apparatus and extending processes (Iglesias-Rozas & Garrosa, 2013).

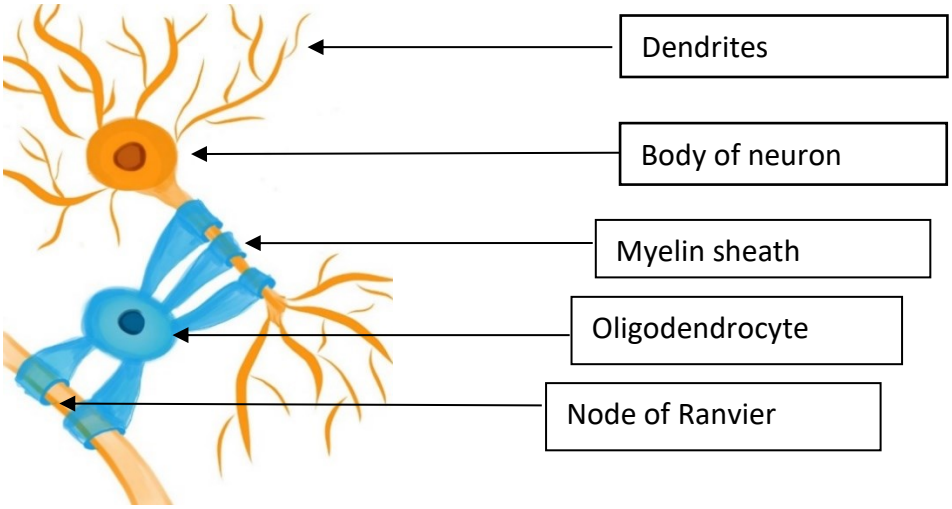

Figure 1 Oligodendrocyte enveloping axons with the myelin sheath. A single oligodendrocyte envelops several axons. The myelin sheath is interrupted by the nodes of Ranvier where Na^+ and K^+ voltage-dependent channels are localized. A figure inspired by original (istockphoto.com)

Unlike astrocytes, oligodendrocytes are divided into three morphological subtypes: interfascicular, perineural, and perivascular. Interfascicular oligodendrocytes are main myelinating cells in the CNS. The function of perineural oligodendrocytes stems from their remyelination capacity after injury, while perivascular oligodendrocytes provide mainly trophic support (Hayashi & Suzuki, 2019). The primary precursors of oligodendrocytes in the developing brain are radial glia. This population of undifferentiated cells differentiates to the stage called outer radial glia, and afterwards give rise to pre-oligodendrocyte precursor cells (Zonouzi et al., 2019). Outer radial glia and pre-oligodendrocyte precursor cells are specific only for the CNS development (Pollen et al., 2015). Pre-oligodendrocyte precursor subsequently differentiate to OPCs and pre-myelinating oligodendrocytes forming mature oligodendrocytes (Rivers et al., 2008). Fully differentiated oligodendrocytes are characterized by the expression of structural proteins, such as MBP and PLP (Di Gioacchino et al., 2020; Greer & Pender, 2008). A detailed description of proteins expressed by oligodendrocytes is included in further chapters. According to latest studies, a metabolic function of oligodendrocytes has been revealed (El Waly et al., 2022); oligodendrocytes express monocarboxylic transporter-1 for transport of compounds, e.g., lactate and pyruvate, to neurons. Any disruption of this metabolite flow causes severe neurodegeneration and is a symptom for demyelinating diseases, such as amyotrophic lateral sclerosis (Lee et al., 2012).

2.3 NG2 glia

Firstly, the use of terms “NG2 glia” and “OPCs” is often misunderstanding in many theses. Therefore, it is necessary to define the difference between OPCs and NG2 glia. Oligodendrocyte precursor cells are a subtype of NG2 glia with distinct differentiation capacity. While OPCs have only capacity to form mature myelinating oligodendrocytes, other NG2 glia differentiate to astrocytes in the developing brain and after stroke in the gray matter or even to neurons (Liu et al., 2021). The cell population of NG2 glia differentiating to oligodendrocytes is mainly determined by the expression of platelet-derived growth factor receptor-α (PDGFR-α) and NG2 proteoglycan, also known as chondroitin sulfate proteoglycan-4 (CSPG-4) (H. C. Wilson et al., 2006). Compared to the precursors of oligodendrocytes, NG2 glia precursors express interleukin-1β for their differentiation to astrocytes (Summers et al., 2010).

Oligodendrocyte precursor cells are an undifferentiated cell population in the CNS. In comparison to mature oligodendrocytes, they have fewer processes and do not envelop axons. As stated by Spitzer et al. (2019), OPCs are not a homogenous cell population, as they differ in the expression of Na^+ voltage-dependent channels, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate receptors during the process of their maturation (Spitzer et al., 2019). Same as oligodendrocytes, OPCs differentiate from their primary progenitor, radial glia (Zonouzi et al., 2019). Oligodendrocyte precursor cells primarily react to injury or inflammation by the process of proliferation and subsequent differentiation to mature oligodendrocytes (H. T. Zhang et al., 2010). Besides this function, OPCs also regulate the permeability of the BBB by the expression of transforming growth factor-β (TGF-β), which binds to its receptor on the brain ECCs, and inducing the expression of tight junction proteins, which decrease the permeability of the BBB (Seo et al., 2014). Importantly, OPCs are also involved in the pathology of Alzheimer´s disease (AD). According to Vanzulli et al. (2020),

an early progression of AD is associated with decreased numbers of OPCs (Vanzulli et al., 2020), while demyelination is one of typical symptoms of AD (Fornari et al., 2012).

Secondly, NG2 glia are totipotent cell population in the nervous system, receiving a lot of attention in the last years. The diversity of NG2 glia is responsible for different morphological features. NG2 glia are characterized by the change in their morphology after stimuli resulting in their activation. Short processes and indistinctive Golgi apparatus are typical for an activated state. In contrast to this description, resting NG2 glia have short processes, massive nucleus and Golgi apparatus necessary for the synthesis of NG2 proteoglycan (Jin et al., 2018). Like other glial cells, NG2 glia originate from radial glia located in the ventricular zone. Their migration into the grey and white matter is under the control of acheate-scute homolog 1 factor (Kelenis et al., 2018). In contrast to OLGs, NG2 glia form glutamatergic and gamma-aminobutyric acid (GABA) synapses with neurons in the *Hippocampus*, cerebral cortex and *Corpus callosum* (Mangin et al., 2012). Their involvement in injury and subsequent repair is crucial. A contribution to repairment of the nervous tissue after acute injury includes migration to the site of injury, structural changes, and an increased proliferation capacity (Hill et al., 2014). Importantly, the remyelination process provided by NG2 glia is more effective, if demyelination is acute and not chronic (H. C. Wilson et al., 2006). Acute phase of ischemic stroke, a pathophysiological state caused by hypoxic condition in the brain followed by a capillary defect, is an appropriate example, when NG2 glia are activated after injury. After stroke, angiogenesis and the white matter repair are needed, which is govern by NG2 glia. NG2 glia induce the proliferation of brain ECCs by the release of Wnt7a and Wnt7b factors and angiopoietin 1, forming new capillaries (Yuen et al., 2014). Besides that, NG2 glia participate also in several mechanisms involved in the white matter recovery, such as inducing oligodendrocytes maturation by glial growth factor 2 (Bengtsson et al., 2005; F. Li et al., 2020).

2.4 Microglia

Any damage to the CNS, including demyelination, is a stimulus for microglia to respond to the pathogenic event. They are a part of innate immunity, with their functions similar to macrophages. The main features shared with macrophages are an erythromyeloid lineage and the process of phagocytosis (Davies & Miron, 2018). Similarly to NG2 glia even microglia undergo a rapid morphological transformation after their activation. An inactive state is characterized by the process of ramification, which is described as a state when the prolongation of their processes occurs. Compared to the inactive state, in an active state, microglia have a compact shape with short processes (Young & Morrison, 2018). Microglia are not a uniform cell population. There are two main subtypes according to their activation state and the mechanisms they provide. M1 microglia are activated by lipopolysaccharide or interferon gamma (IFN-γ), which stimulate the production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β, and interleukin-6, resulting in the attraction of different immune cells, such as lymphocytes or M2 microglia in the CNS (Le et al., 2001; R. Li et al., 2004). After the recognition of pro-inflammatory cytokines, M2 microglia are activated by interleukin-4 and interleukin-13, mediating tissue reconstruction by phagocytosis of cell debris and support neurons by neurotrophic factor and insulin-like growth factor 1 (IGF-1) (Amo-Aparicio et al., 2021; Suh et al., 2013). Additionally, microglia play a role in the development

and reconstruction of the neural tissue by phagocyting OPCs and removing redundant synapses (Irfan et al., 2022). As stated by Schafer et al. (2012), the process of OPCs phagocytosis by microglia in the optic nerve is controlled by the complement cascade, a cascade that is activated by the direct interaction between OPCs and microglia. The phagocytosis of OPCs is provided by the recognition of fractalkine expressed on OPCs and its receptor expressed on microglia (Schafer et al., 2012).

2.5 Schwann cells

The most abundant glial cell type localized in the PNS are Schwann cells. They have the similar functions to oligodendrocytes in the CNS, enveloping axons with the myelin sheath. In comparison to oligodendrocytes, a Schwann cell enwraps only one axon (Zawadzka et al., 2010). Moreover, the perinodal space is occupied by Schwann cell microvilli (Scherer et al., 2001), which is an extended structure of the cell membrane stabilized by the actin cytoskeleton (Liu et al., 2019). Furthermore, Schwann cells are surrounded by the basement membrane, which coordinates the interactions with neurons, while Schmidt-Lanterman incisures, protrusions of the Schwann cell cytoplasm in the myelin sheath, facilitate the metabolic support between Schwann cells and their myelin sheaths (Tricaud et al., 2005). In contrast to the CNS, the most prevalent structural proteins in Schwann cells are P0 protein and peripheral myelin protein 22 (PMP22) (Marinko et al., 2021; Raasakka et al., 2019). Schwann cells are divided into two major subtypes: myelinating and non-myelinating. Myelinating Schwann cells are prolonged along a single axon, while non-myelinating Schwann cells form the Remak bundles, groups of axons surrounded by the cytoplasm of a single Schwann cell (Jessen & Mirsky, 2005). The development of Schwann cells is associated with the neural crest cells, their primary precursors, which migrate along the peripheral axons and form Schwann cell precursors. The whole process of neural crest cells differentiation to precursors of Schwann cell is regulated by Sox10 (Kuhlbrodt et al., 1998). The differentiation of the precursors to mature Schwann cells and the expression of related genes, e.g. *P0*, is under the control of Krox20 factor (Topilko et al., 1994). Not only the development, but also the maintenance of Schwann cells is essential. Any dysregulation of this system during the development or adult life affects their stability. Schwann cells can be impaired by various pathological conditions, including demyelination caused by mechanical damage, autoimmunity, or the formation of Schwann-cell-derived tumor called schwannoma (Houlden et al., 2008; Prabhakar et al., 2022; Yuki & Hartung, 2012). For instance, Charcot-Marie-Tooth (CMT), an example of an inherited demyelinating disease is caused by mutations in heat-shock protein gene, which is expressed as a response to cell stress (Houlden et al., 2008). Moreover, infiltration of Campylobacter jejuni, cytomegalovirus and Epstein-Barre virus into the PNS might induce the Guillain-Barré syndrome, a pathogen-induced demyelinating disease. Pathogens contain structurally and sequentially similar proteins to the PNS specific proteins that can be recognized by the immune system, with a subsequent production of antibodies binding even to innate proteins (Rodríguez et al., 2018).

3 Major protein and lipid components defining the myelin structure

Proteins and lipids are building units of the myelin sheath responsible for its stability, insulation of axons and response to immune stimuli. Improper functioning or destruction of a specific component may lead to a severe pathological condition. The myelin sheath contains up to 70% lipids and the rest is mostly formed by proteins (Verkhratsky & Butt, 2008). Lipids are mainly responsible for the insulation of the APs, whereas proteins stabilize the lamellae. Additionally, there are differences in the molecular composition between the CNS and PNS. On the other hand, certain similarities are present, including the presence of MBP and similar lipidic composition (Quarles et al., 2005).

3.1 Protein and lipidic composition of the myelin sheath in the CNS

The most abundant myelin-associated protein in the CNS is PLP. It has been identified also in another isoform, called DM20 (Yoshida & Colman, 1996). Both isoforms display a hydrophilic character, as they are localized in the extracellular space (**Figure 2**), providing a mechanical support inside the myelin lamellae (Greer & Pender, 2008). The protein is encoded by *PLP1* gene and mutations in this gene induce Perzeus-Merzbacher disease (Elitt et al., 2020).

Another highly prevalent protein in the CNS, MBP, is localized at the cytoplasmatic surfaces of myelin lamellae (**Figure 2**). The protein is basic and positively charged, which determines its solubility in the water environment of the cytoplasm, while it also electrostatically interacts with negatively charged fatty and amino acids. Due to its location, the protein is important for the stabilization of cytoplasmic surfaces of the myelin sheath (Sarmah & Kundu, 2023). Additionally, MBP might be a target of T-cells in multiple sclerosis (MS), which will be discussed in the next chapters (di Gioacchino *et al.,* 2020).

Other proteins, such as myelin oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), and 2´,3´-cyclic nucleotide-3´-phosphodiesterase (CNP), which are less prevalent in the myelin structure, play also an important role for myelin functions.

Firstly, MOG is exposed to the extracellular space (**Figure 2**) of the CNS formed by the perineuronal nets (PNNs) (Linington et al., 2021). The PNNs are mainly composed of CSPG and hyaluronic acid. Besides CSPG and hyaluronic acid, specific proteases are also localized in the PNNs responsible for the remodeling of the PNNs. Matrix metalloproteinases are the most abundant type of these proteases (Chaunsali et al., 2021). Myelin oligodendrocyte glycoprotein is also involved in MOG-associated diseases, autoimmune diseases based on the recognition of MOG by antibodies targeted against the pathogen's antigen. Optic neuritis and transverse myelitis are an example of MOG-associated diseases (Hacohen et al., 2018).

In comparison to MOG, MAG is localized on the other side of the myelin sheath, forming a connection between the axon and the inner mesaxon in the periaxonal space (**Figure 2**) (Vivinetto et al., 2022). Myelin-associated glycoprotein is expressed by oligodendrocytes while its receptor is localized on the periaxonal membrane. This interaction has a suppressive function on axonal regeneration (Vinson et al., 2003).

The protein specific for the myelin sheath in the CNS, CNP, is localized on the cytoplasmatic surfaces. In fact, it is found as an oppositely working protein to MBP, which is responsible for myelin compaction. This protein interacts with the actin cytoskeleton, rebuilds it, and forms cytoplasmic extensions (Snaidero et al., 2017). Inactivity of CNP is associated with degraded brain tissue and a loss of the myelin sheath (Iwamoto et al., 2008).

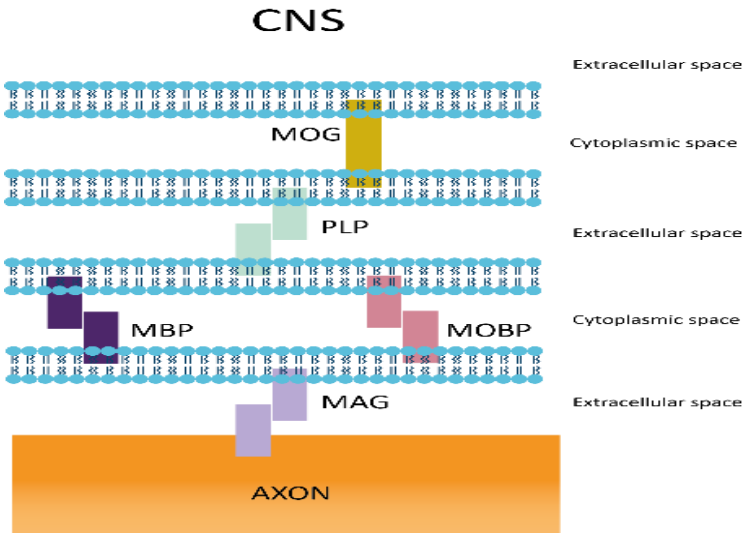

Figure 2 The protein composition in the central nervous system (CNS). The myelin sheath is formed by multiple proteolipid layers, called lamellae. Every protein has its specific localization within the myelin sheath. Therefore, myelin-associated glycoprotein (MAG) is extended into the periaxonal space, stabilizing the connection between the axon and outermost myelin layer, whereas myelin oligodendrocyte glycoprotein (MOG) is localized in the innermost layer. Myelin basic protein (MBP), the most abundant protein, is localized in the cytoplasmic space, while proteolipid protein (PLP) stabilizes the myelin sheath in the extracellular space. The figure was inspired by Verkhratsky and Butt, (2008).

Another major group of molecules forming the myelin sheath are lipids. Lipids contribute to the myelin stability by the interactions between lipid heads. The most abundant molecules of the lipidic origin in the myelin sheath are cholesterol, phospholipids, sphingomyelin, cerebrosides (composed of sphingosine, fatty acid, and sugar residue) and ceramides (composed of sphingosine, fatty acid, and polar head, such as ethanolamine or choline). Typical fatty acids localized in the myelin sheath are lignoceric (24:0) and nervonic acid (24:1) (Srinivasarao et al., 1997). The first number in the bracket represents the length of fatty acid chain and the second number determines the incidence of unsaturated bonds. Galactosylcerebroside is the most abundant sphingolipid within the myelin sheath (Poitelon et al., 2020). The myelin sheath is composed of various lipidic molecules with a specific prevalence: GalC and cholesterol represent about 35%, sphingomyelin represents 15%, and the rest consists of gangliosides and phospholipids (Poiteton et al., 2020). Cholesterol is incorporated into the myelin sheath in order to decrease membrane fluidity (Pinkwart et al., 2019).

3.2 Protein and lipidic composition of the myelin sheath in the PNS

The myelin structure in the PNS is distinct from its structure in the CNS because of the different protein composition. The most abundant proteins in the CNS, such as MBP and PLP, have their structurally similar partners in the PNS.

Starting from the most abundant constituents, myelin protein P0 is localized on the extracellular faces of the myelin membrane (**Figure 3**). The abundancy of the protein provides strong adhesion between the layers. Mutations in the P0 gene cause severe consequences to the membrane assembly, leading to a decreased myelination ability and CMT (Avila et al., 2010). Although, P0 is a minor protein in the CNS, the expression of its ortholog significantly increases after CNS injury. Therefore, the protein expression is controlled by various mechanisms under different conditions (Bai et al., 2014).

Another essential protein for the PNS architecture is PMP22. The protein is inserted into the myelin membrane with a large domain oriented to the extracellular space (**Figure 3**) (Marinko et al., 2020). The gene encoding PMP22 is localized on chromosome 17 and a deletion of 1.5 Mb fragment results in hereditary neuropathy with liability to pressure palsies. On the other hand, a duplication of this fragment induces CMT (Koike et al., 2022).

Connexin-32 (Cx-32) is a member of a large protein family exerting their functions in the whole body. This isoform is also expressed in NG2 glia, where its function is not fully understood, although according to Melanson-Drapeau et al. (2003), knock-out of Cx-32 gene resulted in an increased proliferation of NG2 glia (Melanson-Drapeau et al., 2003). Connexins generally facilitate transport of various molecules between two cells. In the myelin sheath, Cx-32 is mostly found at the paranodal loops and Schmidt-Lanterman incisures, where is facilitates this function. Mutations in the gene encoding Cx-32 are the cause of CMT (Ressot & Bruzzone, 2000).

The axon-myelin communication is provided in both the CNS and PNS by MAG (Tropak et al., 1988). Besides MAG, the interactions between myelin and axons are also mediated by periaxin (Px). This protein has two isoforms, L-Px, a large isoform and S-Px, a small isoform. The isoforms are localized in a different parts of Schwann cells: L-Px is localized in the outer and inner mesaxon, whereas S-Px is localized in the cytoplasm of Schwann cells. Studies suggest that Px is necessary for final stages of myelin membrane assembly. Knock-out of this gene allows for the myelin sheath formation, although the system is highly unstable (Gillespie et al., 2000).

Moreover, the PNS contains also major CNS proteins, such as MBP and MAG (**Figure 3**) and P2 protein stabilizing cytoplasmic surfaces and providing fatty acids transport (Zou et al., 1998).

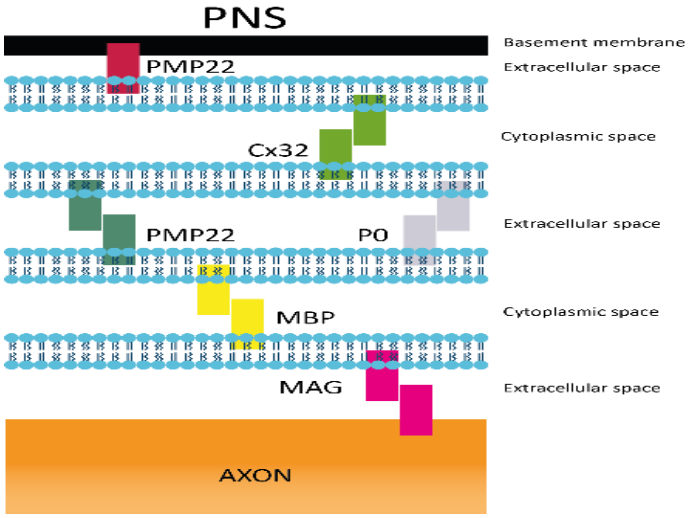

Figure 3 The protein composition in the peripheral nervous system (PNS). Similar to the central nervous system, the myelin sheath is formed by multiple proteolipid layers. The main difference is the basement membrane of Schwann cells and different protein composition. For instance, myelin basic protein (MBP) is present in the peripheral nervous system, although protein 0 (P0) is the most abundant protein. Connexin-32 (Cx-32) is a specific connexin isoform in the PNS localized the cytoplasmic spaces providing. The communication between axon and the myelin sheath is facilitated by myelin associated glycoprotein (MAG), whereas peripheral membrane protein 22 (PMP22) provides an interaction with the extracellular space. The figure was inspired by Verkhratsky and Butt, (2008).

The composition of myelin lipids in the PNS is highly analogous to the composition in the CNS. This means that PNS myelin contains cholesterol, glycerophospholipids, and sphingomyelin. The only difference represents a higher ratio of phosphatidylcholine and sphingomyelin in the PNS (Poitelon et al., 2020).

4 Demyelination stimuli and associated processes

The myelin sheath is a stabile structure, although a disruption of any component on the molecular or cellular level can be a stimulus for the myelin sheath collapse and demyelination. Demyelination is induced by stimuli from the inner and outer environment of various extent. Based on the range, demyelination is classified as primary and secondary. Primary demyelination is characterized solely by the loss of myelin and the secondary demyelination is a complex process of neural tissue degeneration, including degeneration of the myelin sheath (McKeever, 2010).

As mentioned in the previous paragraph, stimuli causing demyelination have variable causes. Inherited demyelination is a pathophysiological condition caused by a congenital mutation. The mutation can be incorporated in the gene that is essential for the proper myelin formation. This gene can code a structural protein or an enzyme responsible for the synthesis of a certain lipid, possibly an enzyme modifying a protein (Saba et al., 2020). This type of diseases is relatively rare, and a sufficient treatment is recently not available (Li et al., 2018). Diseases, such as Alexander disease, Canavan disease, Krabbe's disease, and metachromatic leukodystrophy belong to this type of diseases (Chao et al., 2022; Hordeaux et al., 2022; Li et al., 2018; Santhanakumaran et al., 2022).

Demyelinating diseases are mainly caused by acquired factors. The term "acquired disease" means that the disease is not manifested immediately after birth, instead it appears during the lifetime following a specific stimulus

(Wilson & Schooley, 2017). Therefore, multiple sclerosis causes the highest incidence of this demyelination type (Dehghan et al., 2021). The stimuli causing acquired demyelination include environmental and genetic factors (Ekundayo et al., 2022). An acquired disease is usually formed due to molecular mimicry, a process of the infiltration of a toxin and subsequent production of antibodies against innate proteins. The antibodies against the innate proteins are synthetized as a result of structural and sequential similarities with the proteins of the pathogen. The process has usually severe consequences, leading to an autoimmune response (Balbin et al., 2023). Besides MS, this category of diseases is also represented by, acute disseminated encephalomyelitis (ADEM), and MOG antibody-associated demyelinating encephalomyelitis (Wei et al., 2023).

Virus-induced demyelination can be perceived as a type of acquired demyelination. Viruses are intracellular parasites of a noncellular origin. They need a host cell for generating new virus particles (virions). After invading the host cell, its immune system is activated to eliminate the virus. If the process is not effective or the immune system cannot recognize the virus, the infected tissue is degenerated. This also occurs in the neural tissue, especially in the myelin sheath. John Cunningham (JC) virus, measles virus, and human immunodeficiency virus (HIV) can all invade the neural tissue and demyelinate axons (Haley et al., 2020; Liuzzi et al., 1994; Tucker & Paskauskas, 2008). On the other hand murine coronavirus and Theiler's encephalomyelitis virus, can be used for experimental research purposes to initiate demyelination (Dal Canto et al., 2000; Gonzales et al., 2004). The myelin sheath degradation by viral agents can either be direct, which means that infected oligodendrocytes undergo cell lysis, or indirect when the immune system activates an inappropriate response, resulting in myelin sheath loss (Perlman & Zhao, 2017). Once, the virus infiltrates the neural tissue, T-cells migrate to the inflammation zone and start to produce cytokines responsible for oligodendrocytes and myelin degradation. Degenerated oligodendrocytes represent myelin debris, which is a target for macrophages that remove cellular remains (Ryan et al., 2022).

All types of demyelination share a common feature, a need for tissue regeneration and reconstruction. This process is called remyelination and is described in the next chapter.

5 Remyelination of demyelinated axons and the formation of renewed myelin sheaths

Remyelination is a process of regenerating the myelin sheaths along demyelinated axons. The effectivity of remyelination rapidly decreases with age. The process of myelin sheath recovery is complicated and OPCs are not the only cell type participating in remyelination. According to the latest knowledge, microglia and astrocytes play also an important role (Hasan et al., 2023; Hong et al., 2023). Therefore, the treatment should not be focused just on OPCs.

Following neural tissue impairment leading to demyelination, OPCs are mobilized, they proliferate and afterwards migrate to the site of injury, where they differentiate to oligodendrocytes enveloping axons (**Figure 4**) (Moyon et al., 2015).

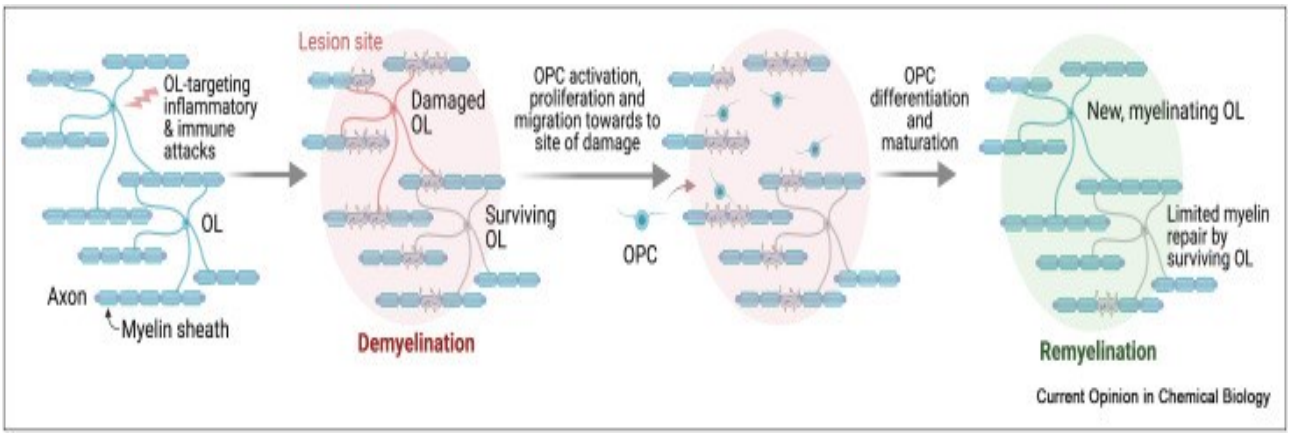

Figure 4 Lesion formation and subsequent response. Lesion is formed as a result of stimuli of various origin causes demyelination, which is recognized by oligodendrocyte precursor cells (OPCs). Due to their progenitor character, proliferation and differentiation to oligodendrocytes (OL) occur. The result of the whole process is the reestablishment of the myelin sheath. The figure was adopted from Beyer and Lairson, (2022).

Each stage of cell maturation is defined by the expression of different marker genes. Remyelination is primarily recognized by OPCs, which commence their proliferation and differentiation to premyelinating oligodendrocytes controlled mainly by fibroblast growth factor 21 (Kuroda et al., 2017). The stage of premyelinating oligodendrocytes and the maturation to enveloping oligodendrocytes is regulated by transforming growth factor beta 1. Moreover, premyelinating oligodendrocytes express O4 protein, CNP and GalC (**Figure 5**) (Beyer & Lairson, 2022; Hamaguchi et al., 2019). Lastly, differentiated oligodendrocytes express standard structural proteins, such as MBP and PLP (de la Fuente et al., 2020). Sox10 and Olig2 are the factors present at all stages (**Figure 5**) (Beyer & Lairson, 2022). On the other hand, high abundancy of hyaluronic acid and myelin debris may inhibit remyelination (Back et al., 2005; Natrajan et al., 2015).

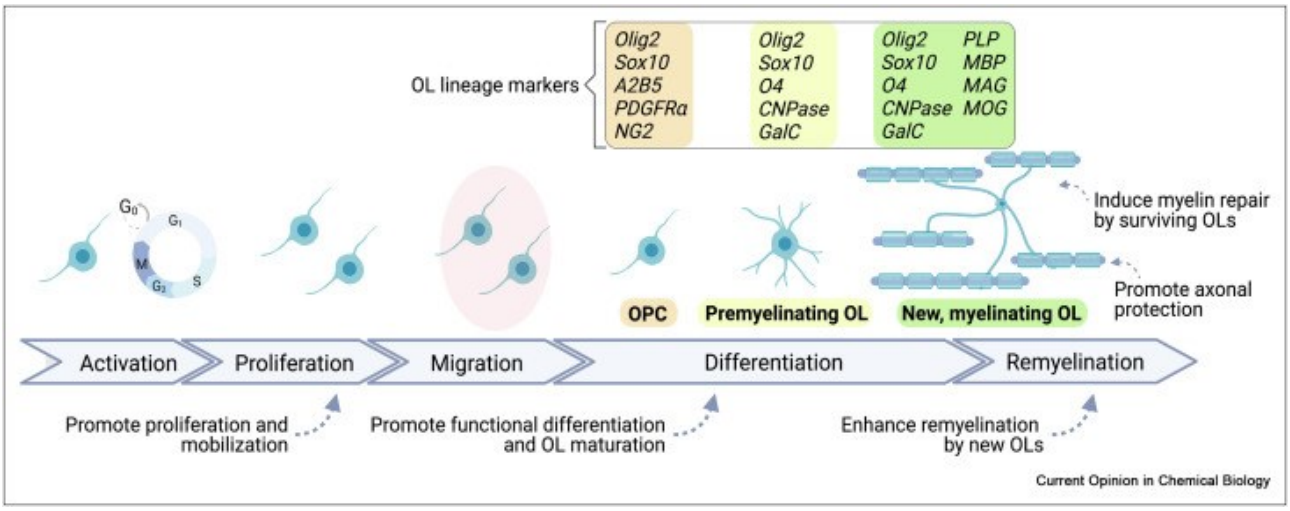

Figure 5 Scheme of processes crucial for remyelination by oligodendrocyte precursor cells (OPCs). After recognition of a lesion, OPCs cells are activated, they proliferate and migrate to the site of lesion. The cells afterwards differentiate to premyelinating oligodendrocytes and subsequently to mature oligodendrocytes enveloping axons. The whole process is coordinated by various factor. Olig2 and Sox10 are present in all differentiation stages. The figure was adopted from Beyer and Lairson, (2022).

The process of oligodendrocytes maturation from their progenitors is governed by Wingless-related integration site (Wnt)/β-catenin signaling (Fancy et al., 2009). This pathway is preserved among Metazoa, underlying its role in the formation of multicellular organisms (Rim et al., 2022). Thus, the Wnt/β-catenin signaling pathway is responsible for many processes related to tissue development and its homeostasis, including the neural tissue and the proliferation and differentiation of OPCs (Fancy et al., 2009). The canonical pathway operates in two modes (**Figure 6**). In the inactive mode, sclerostin and Dickkopf-1 protein bind to low-density lipoprotein-related protein-5/6 (LRP-5/6), which inhibits their association with Frizzled (Fzd) receptor and Kremens co-receptor. Additionally, secreted-frizzled-related protein blocks the interaction between Wnt protein and Fzd receptor needed for the cascade activation (Krause et al., 2010). In the intracellular space, the complex of adenomatous polyposis complex (APC) and Axin2 is crucial for the initial phosphorylation of β-catenin by casein kinase-1 (CK-1), followed by the phosphorylation by glycogen synthase kinase-3β (GSK-3β) (H. Huang & He, 2008). The complex of APC, Axin2, GSK-3β, and CK-1 is summarily called the degradation complex (J. Fan et al., 2017). The latter phosphorylation of β-catenin is a signal for β-Tcrp E3 ubiquitin ligase that binds ubiquitin tag to β-catenin and promotes its degradation in the proteasome complex (C. Liu et al., 2002). On the other hand, the active mode is characterized by binding of Wnt ligand to Fzd receptor, and LRP-5/6 (**Figure 6***)* (Zarkou et al., 2018). The association of Wnt proteins on the outer membrane causes a conformational modification in the cytoplasmatic domain of LRP-5/6, attracting p21-activated kinase-1 (Choi et al., 2006). Phosphorylated domains are subsequently recognized by Dishevelled protein and Axin2. The dissociation of Axin2 from the degradation complex initiates the collapse of the complex and the accumulation of β-catenin in the cytoplasm, and its subsequent translocation through the nuclear membrane. β-catenin binds to the T-cell factor/lymphoid enhancer factor (TCF/LEF) complex in the nucleus, which is inhibited by the TLE/Groucho complex and dissociates in the presence of β-catenin (Behrens et al., 1996). The β-catenin-TCF/LEF complex is a TF that activates Wnt-target genes (**Figure 6**). These encode secretory Wnt proteins essential for the development of different tissues (Fan et al., 2017).

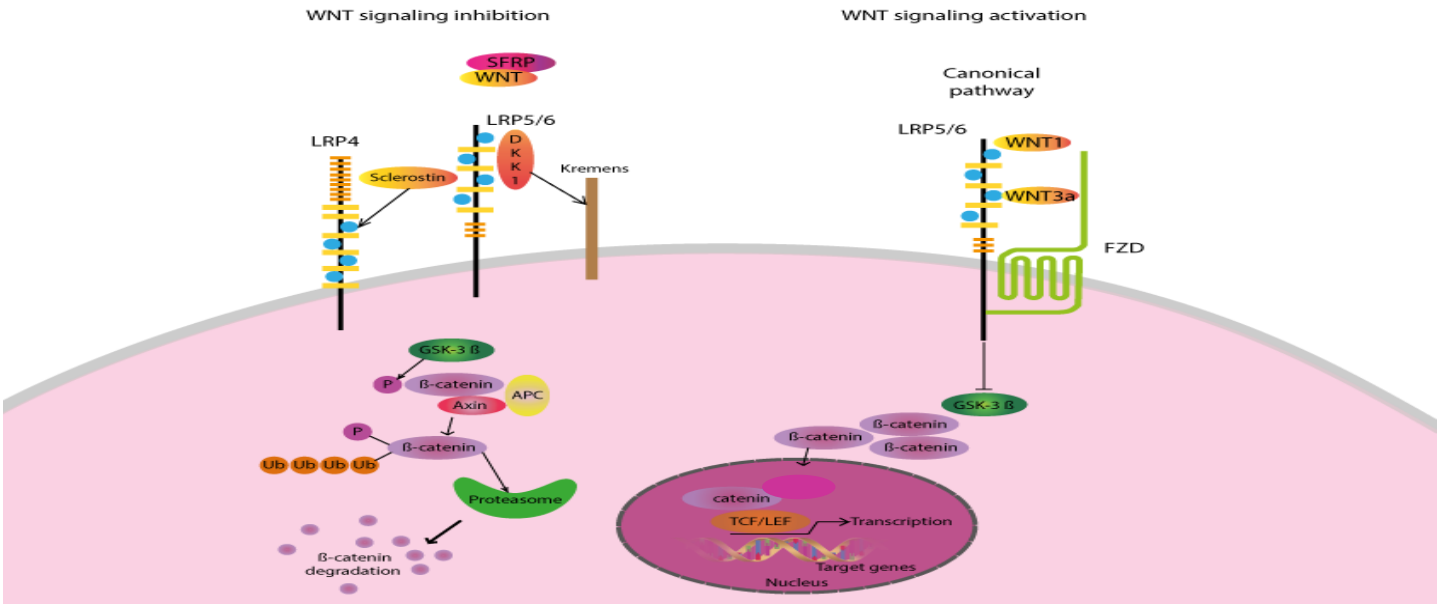

Figure 6 Wingless-related integration site (Wnt)/β-catenin signaling pathway. This signaling pathway operates in two modes: an active and inactive mode. The inactive mode is characterized by binding of sclerostin and Dickkopf-1 repressors to low-density lipoprotein-related protein-5/6 (LRP-5/6) and Kremens co-receptor. Moreover, secreted-frizzled-related protein blocks the interaction between Wnt protein and Frizzled (Fzd) receptor, which leads to the association of adenomatous polyposis complex (APC) and Axin2 with β-catenin in the cytoplasm. The complex of APC, Axin2, and β-catenin is recognized and phosphorylated by glycogen synthase kinase-3β (GSK-3β) and subsequently by casein kinase-1. Double-phosphorylated β-catenin is a signal for ubiquitination, which initiates its degradation in the proteasome. The presence of Wnt ligands, on the other hand, promotes its recognition by Fzd. This recognition is a signal for axin2, which dissociates from the complex with APC and β-catenin. Therefore, GSK-3β does not phosphorylate β-catenin that enters the nucleus and works as a transcription factor in the complex with T-cell factor/lymphoid enhancer factor (TCF/LEF). This transcription factor commences the expression of Wnt-target genes. The figure was inspired by Maeda et al., (2019).

As stated by Fancy et al., the white matter lesion is followed by the maturation of OPCs via Wnt signaling pathway (Fancy et al., 2009). Primarily, the population of OPCs was identified based on the expression of Olig2, a factor characteristic for oligodendrocyte lineage during the whole maturation process (Arnett et al., 2004). Moreover, the subpopulation of OPCs expressing NG2 and PDGFR-α, the factors specific for immature oligodendrocyte population, reacted to the white matter lesion by the expression of T-cell factor-4, whose expression was not present under the physiological conditions (Kitada & Rowitch, 2006). T-cell factor 4 is a TF, which forms a complex with β-catenin and commences a transcription of Wnt-target genes, such as *axin2* and represses the expression of *HYCCIN,* which encodes hyccin, a protein essential for the formation of lysosomes (Fancy et al., 2009).

Besides Wnt signaling, other mechanisms also contribute to the activation of NG2 glia. One of them is mediated via GABA signalization. OPCs express $GABA_A$ receptor on their cytoplasmic membrane (Zonouzi et al., 2015). The release and binding of GABA inhibits the maturation of NG2 glia. In contrast, according to Hamilton et al. (2017), the use of GABAzine, an inhibitor of $GABA_A$ receptors, disrupted GABA signalization, while increasing the number of NG2 glia (Hamilton et al., 2017). Moreover, recent study by Kirchhoff et al. (2019), suggested a participation of Kir channels in the process of remyelination after ischemic stroke (Hong et al., 2023). The specific isoform Kir4.1 localized in astrocytes and NG2 glia contributes to the preservation of the resting membrane potential and reuptake of K^+ to the intracellular space, which is crucial for remyelination (Tong et al., 2014). Additionally, a treatment with luteolin, a flavonoid extract with anti-oxidative and anti-inflammatory effects enhanced, current propagation through the Kir4.1 channels, and promoted the reconstruction of the myelin sheath (Jia et al., 2015). Therefore, the interactions between luteolin and Kir4.1 channels participate in the remyelination, although the full mechanism is still unknown (Hong et al., 2023).

Although, oligodendrocytes and NG2 glia play a prominent role during remyelination, different cell types, such as microglia and astrocytes, participate in the process as well. The remyelination state of microglia is defined by the expression of *Cybb* gene encoding nicotinamide adenine dinucleotide phosphatase-2, MHC-II genes and activin-A factor gene, whose target genes are still not fully understood (Dillenburg et al., 2018; Masuda et al., 2019). Microglia influence two main myelin-related functions: removing myelin debris by phagocytosis and initiating the proliferation of OPCs (Keough et al., 2016; Lampron et al., 2015; Williams et al., 2007). Microglia express triggering receptor expressed on myeloid cells-2 (TREM-2), which recognizes damage and pathogen-associated patterns, such as lipopolysaccharides. This

process is followed by microglial migration and the removal of cellular debris. There is also evidence that TREM-2 recognizes amyloid-β plaques characteristic of AD. (Ulland & Colonna, 2018). The other main role of microglia is the maturation of OPCs by the release activin-A, a member of TGF-β family. Activin-A initiates the recruitment of M2 microglia and the myelin regeneration, which was proved by increase in the expression of myelin proteins. Additionally, glatiramer acetate, a drug that contains acetylated glutamic acid, lysine, alanine, and tyrosine, increased the number of M2 microglia, and thus the formation of OPCs (Miron et al., 2013).

Astrocytes are also involved in remyelination by the release of factors stimulating the development of the glial scar and the maturation of OPCs. The glial scar is a structure in the impaired neural tissue established primarily by reactive astrocytes, but also by OPCs, and microglia (C. Zhang et al., 2022). The scar formation and the production of various factors by astrocytes can have both positive and negative effects on the tissue regeneration. For instance, chondroitin sulfate proteoglycans and hyaluronic acid produced by astrocytes inhibit the maturation of OPCs to myelinating oligodendrocytes and axonal reestablishment (Andrews et al., 2012). In contrast to these extracellular proteins, brain-derived neurotrophic factor and IGF-1 produced by astrocytes, stimulate the differentiation OPCs (Saitta et al., 2021).

6 Diseases associated with demyelination and their potential treatment

Demyelination diseases are a large group of neurological disorders, which can be triggered by genetical or pathogenic factors. Demyelination may occur in the CNS and PNS. The symptoms and the time of onset differ, depending on the patient's age and the stage of the disease (Usta et al., 2023). Generally, an effective treatment of demyelinating diseases and its administration to the neural tissue is complicated, mainly due to the impermeability of the BBB (Kanwar et al., 2012). Based on the factor responsible for the pathology of the disease, three categories of demyelinating diseases can be identified: inherited, autoimmune, and pathogen-induced demyelinating diseases.

6.1 Inherited demyelinating diseases

Charcot-Marie-Tooth disease is the most prevalent inherited type of polyneuropathy, a disorder characterized by dysfunction or impairment of peripheral nerves. This disease is divided into four subtypes according to the gene expressed by Schwann cells, where mutation is present: CMT-1A, CMT-1B, CMT-2A, and CMT-1X (Kitaoji et al., 2023). The most common subtype, CMT-1A, is developed due to the duplication of *PMP22* gene (Kitaoji et al., 2021). The mutations in another structural protein, protein P0 are responsible for the development of CMT-1B (Kochanski et al., 2004). Compared to CMT-1A and CMT-1B, CMT-2A is caused by the mutation in *MFN2* gene encoding MFN2 protein, which is localized in the outer mitochondrial membrane and mediates the interaction between two mitochondria or between mitochondria and endoplasmic reticulum (Shahin et al., 2023). All the subtypes of CMT already mentioned share a common feature, coding by autosomal chromosomes. In contrast to them, CMT-1X is X chromosome-linked disease and originates from the mutations.

in *GJB1* gene encoding Cx-32 (Xiao et al., 2015). Generally, the age of onset is approximately in 20th year of life, although it can differ according to the disease subtype. Similar to other polyneuropathies, CMT is displayed by deficiency in motor skills, scoliosis, and deafness, although *pes cavus,* a condition characterized by spiralized fingers on the feet, is specific for CMT (Beloribi-Djefaflia & Attarian, 2023). Up to date, there is no specific treatment of CMT, although the improvement of patient´s motoric functions can be provided by the rehabilitation and exercise. Additionally, pharmaceutic approach has been only tested on mice. For example, colony stimulating factor-1-receptor (CSF-1-R) expressed by macrophages is a tyrosine kinase with high affinity to colony stimulating factor-1 and interleukin-34. Both cytokines stimulate the proliferation of the CNS infiltrated macrophages that drive the degeneration of the nervous system, including demyelination (van der Wildt et al., 2022). As stated by Klein et al. (2015), the process of demyelination can be reduced by PLX5622 inhibitor of CSF-1-R in mouse model of CMT-1B and CMT-1X (Klein et al., 2015).

Metachromatic leukodystrophy, an inherited demyelinating disease, is caused by mutations in the gene of a lysosomal protein, arylsulfatase A. This protein is responsible for the removal of sulfate group from sphingolipids such as GalC (Matzner et al., 2009). Accumulated sulfated sphingolipids in oligodendrocytes, macrophages, neurons, and Schwann cells cause metachromatic leukodystrophy. This disease is mainly demonstrated by demyelination and overall collapse of the organ systems, including the nervous system (Santhanakumaran et al., 2022). However, metachromatic leukodystrophy is an extremely rare disease, an incidence in the European population is lower than two cases per 100000 residents (Berger et al., 1997). The most common outbreak of metachromatic leukodystrophy occurs between the 8th and 12th year of life (Fan et al., 2020). Patients exhibit symptoms, such as psychomotor relapse, spastic quadriplegia (a form of cerebral palsy caused by a dysfunction of brain structures controlling movement and senses), ataxia, dysphagia (a disability of swallowing), and deafness (Hyde et al., 1992; Santhanakumaran et al., 2022). The possibilities of treatment are limited, although few medical approaches have been established. One of them is a use of bone marrow transplantation. Bone marrow contains myeloid stem cells (MSCs), which can penetrate through the BBB. Modified MSCs that overexpress HoxB4 protein, a TF inducing a higher expression of hematopoietic stem cells, can pass through the BBB. The subsequent translocation of MSCs through the BBB induced the differentiation of a minor part to mature oligodendrocytes (Miyake et al., 2010).

Alexander disease, another inherited disease, is caused by mutations in glial fibrillary acidic protein (Vaia et al., 2023). The protein is expressed in astrocytes and the mutated form results in an increase in the production of Rosenthal fibers, amyloid structures in the cytoplasm. This pathophysiological condition leads to complex neurodegeneration, including demyelination (Li et al., 2018). In 2011, Prust et al. divided Alexander disease into two major types: I and II. The difference between these two types is the age of the first manifestation and disease development (Prust et al., 2011). Type I develops at an early age and is characterized by macrocephaly, seizures, and frontal leukodystrophy (a damage in white matter of frontal lobe); whereas type II is prevalent in an adult age, with the symptoms such as dysfunction of autonomic nervous system, dysphagia, dysphonia (abnormal speech function), and complications with breathing (Yoshida

& Nakagawa, 2012). Unfortunately, the mechanism of disease progression is still not fully understood and a proper way of treatment is not established (Vaia et al., 2023).

Krabbe's disease, also called globoid leukodystrophy, is another example of a lysosomal-related disorder. The cause of disease is induced by mutations in the gene for galactosylceramidase in both oligodendrocytes and Schwann cells (Iacono et al., 2022). Galactosylceramidase promotes the hydrolyzation of galactosylceramide to β-galactose and ceramide, and galactosylsphigosine to β-galactose and sphingosine, lipidic components of the myelin sheath (Belleri et al., 2020). The loss of enzymatic function results in the aggregation of galactosylceramide that is subsequently transformed by acid ceramidase to galactosylsphingosine, known as psychosine (Li et al., 2019). Increased concentrations of psychosine are toxic to myelinating cells and cause demyelination (Iacono et al., 2022). Similar to Alexander disease, Krabbe's disease can be divided into two types, depending on the age of the onset of the first symptoms. Type I is typical for infants with a minimal survival rate. Type II outbreaks after one year of life and patients have more positive predictions, although symptoms such as tremors (uncoordinated shaky movements) and leg weakness, are still present (Orsini et al., 1993; Pannuzzo et al., 2010). Unfortunately, no treatment for this disease is available, although novel approaches have emerged. The transplantation of human pluripotent stem cells from the bone marrow and umbilical-cord blood can slow down the disease progression, yet not fully cure the disease (Escolar et al., 200et al., 1998; Yoon et al., 2021). The latest therapy is based on targeting biosynthesis of galactosphingolipids, specifically the last reaction in this synthetic pathway. The reaction catalyzed by uridine diphosphate-galactose ceramide galactosyltransferase, mediates the attachment of β-galactose to ceramide. In 2022, Zaccariatto et al. discovered an inhibitor of this enzyme, RA 5557, which significantly decreases the concentration of psychosine and prevents mice from demyelination (Zaccariotto et al., 2022).

Canavan disease is triggered by a mutation in the gene encoding aspartoacylase (ASPA). This enzyme mediates the conversion of N-acetyl-aspartate (NAA) synthetized in neurons into aspartate and acetate in oligodendrocytes (Chao et al., 2022). In neurons, NAA is synthetized from L-aspartate and acetyl-CoA by aspartate-N-acetyltransferase (ANAT), and subsequently transported to oligodendrocytes (Zyśk et al., 2020). In oligodendrocytes, NAA is degraded to aspartate and acetyl-CoA by ASPA. Acetyl-CoA can be used for the synthesis of lipids crucial for the myelin sheath and aspartate is an amino acid which is a component of myelin proteins (Kołodziejczyk et al., 2009). The mutated gene of ASPA does not allow for the production of functional protein, and thus the accumulation of NAA in oligodendrocytes results in the lack of acetyl-CoA and aspartate, causing demyelination (Traka et al., 2008). The symptoms of Canavan disease are displayed between the 3rd and 5th postnatal month and include feeding complications, blindness, uncoordinated movement, paralysis, and mental deficiency. The most severe cases end in death in the first ten years of life, whereas the patients with less severe form survive up to 40 years (Bokhari et al., 2022). Despite the known cause of Canavan disease, the treatment is still sufficient. There is an effort to decrease the expression level of ANAT or to increase the acetate level by substituting with glyceryl triacetate or tripheptanoin diet, although both approaches still have not been introduced into clinical practice (Francis et al., 2014; Nešuta et al., 2021; Segel et al., 2011). The most innovative and complex experimental way of treating Canavan disease may be performed by the application of induced pluripotent stem cells which can be

obtained from dermal fibroblasts of patients with Canavan disease. After the isolation of cells, an insertion of lentiviral vector containing a wild-type sequence of *Aspa* gene followed. The vector was inserted under the promotor which initiates the division of neural progenitor cells (NPCs). The process of reprogramming was proved by an increased activity of TFs specific for the state of NPCs, such as PAX6 and Sox2. A minor part of the integrated cells was identified as OPCs due to higher levels of OLIG2, a permanently expressed marker in this cell population (Beyer & Lairson, 2022; Chao et al., 2022). A proper functioning of ASPA was detected by decreased concentrations of NAA, overall reconstruction of the myelin sheath, and an improvement in the health condition (Chao et al., 2022).

6.2 Autoimmune demyelinating diseases

Autoimmunity of the myelin sheath, an inappropriate reaction of the immune system characterized by elevated levels of cytokines and the production of antibodies against the myelin proteins, is the most common cause of demyelination (Netravathi et al., 2022; Sanak et al., 2023;). Various cell types, including B-cells, T-cells, macrophages, and microglia participate in the autoimmune response (Finsen & Owens, 2011; Griffin et al., 1992; Mayrhofer et al., 2021; Sanak et al., 2023). Autoimmune demyelinating diseases, such as MS, are recently an expanding type of demyelinating diseases as a result of more effective diagnostic approaches, rapidly spreading environmental factors, and prolonging life span (Feigin et al., 2019).

Multiple sclerosis, a frequent neurological disease associated with demyelination, is induced by $CD4^+$ T-helper (Th) cells migration through the BBB. These cells can attach to the ECCs in the brain and migrate along the capillary. The migration through the BBB is initiated by the recognition of very late antigen-4, an adhesion protein expressed on the surface of Th-cells, and vascular cell adhesion molecule-1 (VCAM-1) on the ECCs (Chigaev et al., 2011). After binding to VCAM-1 on the ECCs, Th-cells enter the CNS stimulated by the production of chemokines, co-binding molecules, and metalloproteinases (Chigaev et al., 2011; Zhao et al., 2022; Zhu et al., 2022). The production of TNF-α by activated microglia, IFN-γ by Th-cells, and interleukin-2 also by Th-cells disrupts tight junctions between the ECCs. Th-cells express also co-binding molecules, for example sphingosine 1-phosphate receptor. The up-regulation of this co-receptor by Th-cells is associated with enhanced permeability of the BBB and increased number of immune cells in the CNS (Scott et al., 2016). Moreover, matrix metalloproteinases degrade the extracellular proteins surrounding the BBB (Fernandes et al., 2009). Infiltrated $CD4^+$ Th-cells subsequently interact with an antigen presented on major histocompatibility complex-2 (MHC-II) of dendritic cells or macrophages. This interaction promotes the recruitment of other immune system components, especially different types of Th-cells, macrophages, B-cells, and microglia (El-Salem et al., 2021; Pokryszko-Dragan et al., 2012; Salloom, 2020). Besides, $CD4^+$ Th-cells, $CD8^+$ T-cytotoxic cells also infiltrate the CNS. $CD8^+$ T cytotoxic cells recognize antigens on MHC-I of neurons and oligodendrocytes, which is followed by the release of cytotoxic molecules, perforin and granzyme B. Perforin forms the pores in the cytoplasmic membrane in order to allow the entrance of granzyme B, which is a proteinase degrading intracellular proteins and the whole structure howe(Fransen et al., 2020; Howe et al., 2007). A higher disease incidence is mostly associated with civilized countries of the northern hemisphere.

For example, in the United States, there are 400,000 patients suffering from MS, which is one quarter of all cases globally (Garg & Smith, 2015; Kister et al., 2013). The most frequently employed method to diagnose MS is magnetic resonance imaging (MRI). A positive diagnosis can be made after the identification of myelin lesions or plaques, demyelination zones with higher signal transmission and lower density (Kolb et al., 2022). The lesions are mainly observable as pale areas in the periventricular (on the outer surface of the third ventricle) and juxtacortical (under the cortex) area of the brain (**Figure 7**) (Polman et al., 2011).

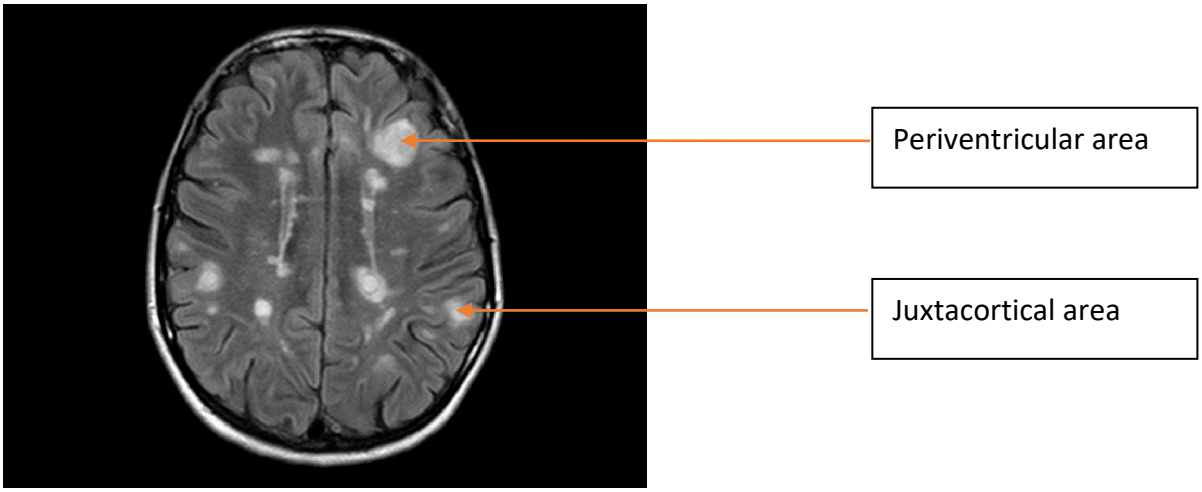

Figure 7 Magnetic resonance image of myelin lesions in periventricular and juxtacortical areas. The periventricular area is oriented into the lumen of the third ventricle, whereas the juxtacortical area is in the proximity to the cortex. The image was adopted from Essilfie et al., (2020).

Not only MRI, but also the analysis of cerebrospinal fluid (CSF) contributes to MS diagnosis. The method is based on the increased detection of immunoglobulin G in the CSF (Fenu et al., 2018). The recent therapeutic strategy has been based on the use of an immunomodulatory approach. This approach targets a specific reaction or the structure of the immune system in order to decrease its activity or function (Bock et al., 2022). This type of treatment is represented by a drug natalizumab, which is a laboratory-synthetized or monoclonal antibody interacting with alpha 4-integrin. This protein on the surface of Th-cells has an adhesive function and its blockage inhibits the migration of Th-cells into the CNS (Buron et al., 2023). Another widely used, however less effective therapy is presented by IFN-β, whose specific mechanism is unknown, although it recognizably stimulates the production of neural growth factor. An increased production of this factor suppresses the activity of T-cells and B-cells (Kieseier, 2011).

Acute disseminated encephalomyelitis is a disease that is barely distinguishable from MS and has the highest prevalence among children (Callen et al., 2009). This disease is characterized by acute inflammation and myelin degradation usually after a viral attack, vaccination, or exposure to a toxic factor (Daoud et al., 2011; Yazdanpanah et al., 2022). The recognition of antigen by T-cells stimulates the production of antibodies and cytokines that react to the inflammation (Gray et al., 2005). Generally, the response to an infiltrated pathogen is represented by components of the adaptive and innate immunity (Rossi et al., 1997). Similar to MS, the most intense myelin degradation occurs in the periventricular area of the white matter (Mikaeloff et al., 2004). The most common cause of ADEM, a viral infection, is

induced by influenza, rubella, measles and mumps virus (Lazibat & Brinar, 2013). On the onset of ADEM, no general neurological symptoms are expressed; however, headache and fever are present. After the initial phase, neurological symptoms, including ataxia, constant fatigue, or impairment of sensory functions appear. Moreover, the expression of certain symptoms, such as motoric dysfunction or speech disability corelates with the demyelinated areas in the brain (Dale et al., 2000). A full therapeutically achieved suppression of ADEM symptoms is still unavailable, although drugs such as corticosteroids and monoclonal antibodies can slow down and dilute the symptoms (Apak et al., 1999; Dale et al., 2000). The use of methylprednisolone, a corticosteroid drug, increases the expression of anti-inflammatory factors and regulates the activity of T lymphocytes (Kim et al., 2018). On the other hand, immunoglobulin G, the most abundant antibody in the blood serum, represents a treatment for ADEM as it paralyzes the toxins and induces cellular apoptosis in infected cells (Vidarsson et al., 2014).

An inflammatory condition of the optic nerve, affecting visual perception and resulting in demyelination, is called neuromyelitis optica (NO). The disease is developed due to the production of antibodies against MOG and aquaporin-4 (AQP-4) (Wingerchuk et al., 2015). Immunoglobulin G neutralizes recognized antigens and activates the complement cascade, a mechanism based on antigen recognition, resulting in cell lysis (Warwick et al., 2021). In comparison to MOG, which is incorporated in the myelin sheath, AQP-4 is expressed in astrocytes. This membrane channel participates in the processes of water transport in the CNS. This explains its localization on the processes extended to the BBB (Peng et al., 2023). The first symptoms of NO are usually displayed between the 30^{th} and 40^{th} year of life, mostly affecting the female population. On the onset of NO, characteristic symptoms of neurological disease, such as fatigue, sleep deprivation, headache, and depression, are present. After this stage, more specific symptoms appear, specifically pain associated with the eye movement (Min et al., 2023). An early diagnosis and timely treatment are the key for curing NO. Corticosteroids are a general medication for NO, although their efficacy is not always sufficient (Cree et al., 2019). More specific and effective treatment is represented by mycophenolate mofetil, a specific inhibitor of inosine monophosphate dehydrogenase, which is an essential enzyme for purine synthesis in lymphocytes (Liu et al., 2021). However, the lymphocytes must synthetize nucleotides always *de novo,* inosine monophosphate dehydrogenase plays a major role in their proliferation. Therefore, the use of mycophenolate mofetil decreases the number of lymphocytes, which decreases their immune response, as well (Park et al., 2023).

6.3 Viral and bacterial demyelinating diseases

The last category of diseases described in this thesis is dedicated to virus and bacterial-induced demyelinating diseases. A variety of viruses and bacteria, differs in the type of infected host cell (e.g. oligodendrocyte or Schwann cell), or penetration and replication mechanism (Eng et al., 2006). After infiltration the nervous system, the virus or bacteria can enter either the latent phase, a state when an infected cell does not react to its presence due to its low activity, or the lytic phase. This phase is characterized by the active replication accompanied by specific symptoms (Stohlman & Hinton, 2001).

The first virus-induced demyelinating disease reviewed in this thesis is progressive multifocal leukoencephalopathy identified by the presence of JC virus in the CNS, specifically in oligodendrocytes. Even though JC virus targets the CNS, it primarily attacks the kidneys and subsequently infiltrates the CNS through the bloodstream (Major et al., 2013). The majority of the identified cases are related to immunodeficient patients suffering from the diseases such as MS treated by natalizumab, acquired immunodeficiency syndrome (AIDS), or even after organ transplantation (Chatterjee et al., 2022; Major et al., 2013; Negishi et al., 2022). The patients with diagnosed progressive multifocal leukoencephalopathy display muscles weakness, the loss of senses, mental and visual deficiency. The disease diagnosis is recently provided only by one technique, which is the detection of anti-JC virus specific antibodies in the blood circulation (Negishi et al., 2022). Moreover, there is a lack of knowledge for implementing a general approach to treat progressive multifocal leukoencephalopathy, although single case reports have been published. For example, the use of pembrolizumab, an inhibitor of programmed cell death receptor-1 on T-cytotoxic cells, activating apoptosis in infected cells, suggests a possible way of treatment (Chatterjee et al., 2022).

Compared to progressive multifocal leukoencephalopathy, Lyme neuroborreliosis does not originate from a viral infection. The disease is caused by *Borrelia burgdorferi,* a bacterium that belongs to spirochetes, which are classified as bacteria with a prolonged and thin body, able to penetrate through the skin and characterized by high motility (Graña-Miraglia et al., 2020; Ramesh et al., 2015). The bacteria are a commensal with *Ixodes scapularis,* an infective tick. *Borrelia burgdorferi* invades the body of humans or domestic animals after the tick biting (Tardy et al., 2023). Approximately 20% of cases display an invasion to the CNS and PNS, followed by demyelination. According to Ramesh et al. (2015), the most visible demyelination is observed in the roots of the spine (Ramesh et al., 2015). Typical symptoms of Lyme neuroborreliosis are erythema migrans, a red spot at the place of biting, fever, headaches, and fatigue. The presented symptoms are a reason for the treatment with antibiotics, such as doxycycline that infiltrates the bacteria and binds to the ribosomes, which inhibits its reproduction (Bernardshaw et al., 2022).

7 Conclusion

Glial cells are an essential part of the nervous system, providing functions in the maintenance of the whole tissue. The myelin sheath, an important structure of the nervous system, is also formed and regenerated by glial cells. Oligodendrocytes in the CNS and Schwann cells in the PNS generate the myelin sheath in order to isolate axons, accelerate the propagation of APs and to nourish enveloped axons. Despite astrocytes and microglia do not form the myelin sheaths, their role in maintenance of the myelin is essential. Astrocytes primarily regulate the permeability of the BBB, together with the neurotransmitter homeostasis and cell metabolism homeostasis. Microglia are immune cells of the nervous system responsible for the response to pathogenic stimuli and removal of nonfunctional cellular structures. Generally, the myelin sheath is a membranous system characterized by high degree of organization. Therefore, any dysregulation of its complex structure or cellular processes involved in the myelin formation lead to a pathophysiological condition known as demyelination. Demyelination can be triggered by various factors: inherited, autoimmune, and pathogen-induced factors,

which can be accompanied with different reactions of glial cells. Each type of glial cells reacts to a demyelination stimulus by a specific mechanism. For instance, reactive astrocytes are essential for the formation of the glial scar after injury, microglia remove myelin debris, and OPCs migrate to the site of injury and differentiate to mature myelinating oligodendrocytes. On the other hand, the effectivity of protective mechanisms decreases with age; therefore, a suitable and effective treatment is needed, especially for the aged population. Unfortunately, current therapeutic approach in the majority of demyelinating diseases is not available or effective enough. The recent research in the field of demyelinating diseases has suggested therapeutical approaches based on immunomodulation or regenerative medicine. The target of the immunomodulatory treatment is a specific reaction which enhances or reduces the immune response. Especially, autoimmune diseases are treated with this type of medication. Another approach, in contrast, utilizes regenerative medicine to restore the nervous system. Transplantation of undifferentiated cell populations such as NSCs and MSCs, which can differentiate to OPCs in the nervous system and subsequently to myelinating oligodendrocytes, reestablishes the myelin sheath.

Altogether, the myelin sheath is a complex but dynamical cellular structure with an irreplaceable insulating and metabolic function. Its disruption results in serious consequences characteristic of the certain types of demyelinating diseases. The range of these diseases is wide; therefore, an effective treatment is not available for each type of disease, which opens space for further research in this field.

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9 Figure references

Figure 1: (istockphoto.com); 3.5. 2022 <Stock ilustrace Oligodendrocyty Nebo Oligodendroglia – stáhnout obrázek nyní - Nervová buňka, Anatomie, Biologie - iStock)>*

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