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Review article

Oligodendrogliopathy in neurodegenerative diseases with abnormal protein aggregates: The forgotten partner

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ABSTRACT

Oligodendrocytes are in contact with neurons, wrap axons with a myelin sheath that protects their structural integrity, and facilitate nerve conduction. Oligodendrocytes also form a syncytium with astrocytes which interacts with neurons, promoting reciprocal survival mediated by activity and by molecules involved in energy metabolism and trophism. Therefore, oligodendrocytes are key elements in the normal functioning of the central nervous system. Oligodendrocytes are affected following different insults to the central nervous system including ischemia, traumatism, and inflammation. The term oligodendrogliopathy highlights the prominent role of altered oligodendrocytes in the pathogenesis of certain neurological diseases, not only in demyelinating diseases and most leukodystrophies, but also in aging and age-related neurodegenerative diseases with abnormal protein aggregates. Most of these diseases are characterized by the presence of abnormal protein de-

Abbreviations: 5-HT, 5-hydroxytryptamine; Aβ, β-amyloid; ABCA8, ATP binding cassette subfamily A member 8; AD, Alzheimer's disease; ADP, adenosine diphosphate; AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; AMBRA-1, autophagy and beclin 1 regulator 1; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid glutamate receptor; ANG, angiogenin; ARTAG, aging-related tau astrogliopathy; ATP, adenosine triphosphate; ATXN2, ataxin 2; BDNF, brain-derived neurotrophic factor; BIN1, bridging interactor 1; C9Orf72, chromosome 9 open reading frame 72; Caspr, contactin-associated proteins; CBD, corticobasal degeneration; CHMP2B, charged multivesicular body protein 2B; CJD, creutzfeldt-Jakob's disease; CNP, 2',3'-cyclic nucleotide-3'phosphodiesterase; CNTF, ciliary neurotrophic factor; COX, cytochrome c oxidase; Cx30, Cx32, Cx40, Cx47, connexins 30, 32, 43, 47; DARPP32, protein phosphatase 1 regulatory inhibitor subunit; DLB, dementia with Lewy bodies; Elk1, Elk1, ETS transcription factor; FACS, fluorescence-activated cell sorting; FBXO7, F-box protein 7; FGF, fibroblast growth factor; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; FUS, fused-in-sarcoma; Fyn kinases, FYN proto-oncogene, Src family yrosine kinase; GABA, γ-aminobutyric acid; GalC, galactocerebroside (galactosylceramide); GDNF, glial-derived neurotrophic factor; GGT, globular glial tauopathy; Gm4, ganglioside 4; GPR17, G-protein coupled receptor 17; GRN, granulin; GSK3, glycogen synthase kinase-3; Gsx2, GS homeobox 2; GLUT1, glial glucose transporter 1; HDAC, histone deacetylase; HSP, heat shock protein; HtrA2/OMI, HtrA serine peptidase 2; IGF-1, insulin-like growth factor 1; iPSC, induced pluripotent stem cell; KCNQ2/3, potassium voltage-gated channel subfamily Q member 2/3; Kv3.1, Kv1.1/1.2, potassium-gated channels; LB, Lewy body; LBD, Lewy body disease; LINGO-1, leucine-rich repeat and Ig domain containing 1; LRRK2, leucine-rich repeat kinase 2; MAG, myelin-associated glycoprotein; MAP, microtubule-associated protein; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; MAPT, microtubule-associated protein tau; MBP, myelin basic protein; MCT, monocarboxylate transporter; MOBP, myelin/oligodendrocyte basic protein; MOG, myelin oligodendrocyte glycoprotein; MOSP, myelin/oligodendrocyte specific protein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSA, multiple system atrophy; MYRF, myelin regulatory factor; Nav1.6, Nav1.1, voltage-gated sodium channels; NBR1, NBR1 autophagy cargo receptor; N-CAM, neural adhesion molecule 2; NFT, neurofibrillary tangle; NG2, proteoglycan GSPG4; Nkx.2, Nk2 homebox; Nkx.6, Nk6 homebox; NMDA, N-methyl-D-aspartate receptor; NT-3, neurotrophin 3; NUB-1, negative regulator of ubiquitin like proteins 1; Olig1, oligodendrocyte transcription factor 1; Olig2, oligodendrocyte transcription factor 2; OMgp, oligodendrocyte-myelin glycoprotein; OPC, oligodendrocyte precursor cells; OPTN, optineurin; P38, tau kinase p-38; p62, sequestosome 1; PACRG, parkin coregulated; PART, primary age-related tauopathy; PDGF, platelet-derived growth factor; PD, Parkinson's disease; PDI, protein disulfide isomerase; PiD, Pick's disease; PLP, proteolipid protein; PRNP, gene coding for prion protein; PrP, prion protein; PP2A, protein phosphatase 2A; PSD93/95, postsynaptic density protein 93/95; PSP, progressive supranuclear palsy; Rab5, member Ras oncogene family; SAPK/JNK, stress-activated kinase/c-Jun N-terminal kinase; SHH, sonic hedgehog; SLC, solute carrier; SOD1, superoxide dismutase 1; Sox2, Sox8, Sox9, Sox10, SRY-box2, box8, box9, box10; SQTM1, sequestosome 1 p62; SUMO-1, small ubiquitin modifier 1; TARDBP, transactive response (TAR) DNA binding protein of 43 kD: TDP-43; TDP-43, TAR DNA binding protein; TPPP/p25, tubulin polymerization promoting protein; UBQLN, ubiquilin 2; VAL, valosin; VAMP, vesicle associated membrane protein; Wnt, Wnt family; XIAP, X-linked inhibitor of the apoptosis; Znf488, Znf536, zinc finger proteins 488 and 536.

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TDP-43
Prion

posits, forming characteristic and specific inclusions in neurons and astrocytes but also in oligodendrocytes, thus signaling their involvement in the disease. Emerging evidence suggests that such deposits in oligodendrocytes are not mere bystanders but rather are associated with functional alterations. Moreover, operative modifications in oligodendrocytes are also detected in the absence of oligodendroglial inclusions in certain diseases. The present review focuses first on general aspects of oligodendrocytes and precursors, and their development and functions, and then introduces and updates alterations and dysfunction of oligodendrocytes in selected neurodegenerative diseases with abnormal protein aggregates such as multiple system atrophy, Lewy body diseases, tauopathies, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration with TDP-43 inclusions (TDP-43 proteinopathies), and Creutzfeldt-Jakob´s disease as a prototypical human prionopathy.

1. Oligodendrocytes: general aspects

In addition to neurons and astrocytes, other cells, smaller in size, are present in the nervous system. These cells, called the "third element" turned out to be two different cell types after pioneering studies by Del Rio-Hortega (1921); one of these was microglia, the other oligodendroglia. The two cell types have different origins, morphology and functions; processes in some subtypes of oligodendroglial cells run in parallel to myelin thus suggesting a relationship between oligodendroglia and myelin (Penfield, 1924; Boullerne, 2016). Four different types were described by Pio del Rio-Hortega as detailed in a recent review (Perez-Cerda et al., 2015). Type I have small round cell bodies and large numbers of very fine cellular processes associated with thin myelinated fibers in the grey matter and interfascicular white matter; Type II are cuboidal with few and thick processes which trap axons longitudinally in the white matter; Type III have one or two long cellular processes and they are present in the brain stem and spinal cord; Type IV have an elongated cell body and unique long processes running in parallel to thick axons in the white matter of the brain stem and spinal cord. Perineuronal oligodendroglial cells are called "perineuronal satellites" whereas another subtype includes oligodendroglial cells localized in the proximity of small blood vessels and are called, for this reason, "perivascular satellites". Functions of perivascular oligodendrocytes are barely known although endothelial cell-oligodendrocyte interactions are altered in small vessel disease and aging (Rajani and Williams, 2017). Oligodendrocytes represent 75% of glial cells in the adult human brain (Pelvig et al., 2008).

Substantial knowledge about oligodendroglia and myelin in the central nervous system came out of electron microscopy observations and made it clear that oligodendrocytes are the only cells producing myelin in the central nervous system (Bunge, 1968; Raine, 1984; Hildebrand et al., 1993). Individual axons are myelinated by consecutive oligodendrocytes arranged in line; eachsegment or internode is separated from the next by a node of Ranvier. The myelin sheath is made up of thick membrane bi-layers of about 12 nm in periodicity formed by alternating electron-dense (major dense line of myelin) and electron-light (intra-period line of cytoplasm) tightly connected at their edges by thigh junctions between the electron-dense layers (Baumann and Pham-Dinh, 2001; Sherman and Brophy, 2005; Ozgen et al., 2016; Li and Richardson, 2016). This structure is not homogeneous along the internode but has non-compact regions such as the outer and inner periaxonal lips, the paranodal loops and interconnected cytoplasmic pockets (Pedraza et al., 2001; Traka et al., 2002; Poliak and Peles, 2003; Möbius et al., 2008; Hartline, 2008; De Monasterio-Schrader et al., 2012; Velumian et al., 2011; Aggarwal et al., 2011a; Nave and Werner, 2014).

Myelin sheaths protect the axonal membrane, promote the spread of electric signal along the axon, and decrease the capacitancy thus increasing the speed of the action potential with more efficiency (Rosenbluth, 2009; Bakiri et al., 2011; Harris and Attwell, 2012; Babbs and Shi, 2013). The nodes of Ranvier separate internodes. Axons at the site of nodes are enriched in voltage-gated sodium channels and potassium-gated channels Nav 1.6, Nav 1.1, KCNQ2/3, Kv 3.1, Kv1.1/1.2; and postsynaptic density protein 93/95 (PSD 93/95) which are all crucial for saltatory nerve conduction. In addition, cytoskeletal scaffolding proteins ankyrin G and B, αII/βII-spectrin and βIV-spectrin participate in the transport of ion channels and contribute to the assembling of axonal proteins at the node of Ranvier (Rosenbluth, 1976; Rasband et al., 1999; Rios et al., 2003; Devaux et al., 2003, 2004; Chen et al., 2004; Hartline and Colman, 2007; Duflocq et al., 2008; Susuki et al., 2013; Battefeld et al., 2014; Arancibia-Carcamo and Attwell, 2014; Barry et al., 2014). Astrocytes are often located at the vicinity of the nodes of Ranvier (Hildebrand, 1971a, b), but their role is not known.

Oligodendrocytes can generate between 20 and 60 myelinating processes with internodal lengths of about 20 μm–200 μm (Hildebrand et al., 1993). The estimated surface area of one oligodendrocyte, once the myelin membrane is "unfolded", is $5–50 \times 10^3\ \mu m^2$ (Baron and Hoekstra, 2010). Therefore, oligodendrocytes are one of the cell types in the body with the largest surface membrane.

Oligodendrocytes are connected with each other and with astrocytes through gap junctions thus forming a glial syncytium in the white matter tracts (Bedner et al., 2012; Nualart-Marti et al., 2013).

Myelin is composed of cholesterol (26%); glycosphingolipids, in particular galactocerebrosides and sulphatides (31%); plasmalogens (20%); phospholipids and gangliosides, particularly GM4; and proteins (30%) (Kursula, 2001, 2008; Chrast et al., 2011; Saher and Stumpf, 2015; Schmitt et al., 2015). The principal proteins are myelin basic protein (MBP), proteolipid protein (PLP) and its isoform DM20, 2',3'-cyclic nucleotide-3'phosphodiesterase (CNP), myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), myelin/oligodendrocyte specific protein (MOSP), myelin/oligodendrocyte basic protein (MOBP), oligodendrocyte-myelin glycoprotein (OMgp), transferrin, carbonic anhydrase, claudin 11, connexins 32 and 47 (Cs32 and Cx47) and tetraspan-2, among other minority proteins (Chen et al., 2006; Jahn et al., 2009; Harauz et al., 2009; Llorens et al., 2011; Raasakka and Kursula, 2014; McKerracher and Rosen, 2015). MBP and PLP represent 80% of the total myelin protein.

Nodes of Ranvier are enriched in certain myelin- and axon-derived proteins—netrin, contactin 1 and 2, neurofascin 155, neurofascin 186, contactin-associated proteins (Caspr 1 and 2)—which interact to bind the myelin sheath to the axon at the free borders of myelin, together with extracellular matrix proteins such as brevican, versican and N-CAM variant (Rasband, 2011; Thaxton et al., 2011; Susuki et al., 2013; Arancibia-Carcamo and Attwell, 2014; Griggs et al., 2017).

Because of the large area of oligodendrocytes and cellular processes including myelin, these cells would be very vulnerable to energy metabolism deficiencies. Oligodendrocytes and myelin in the developing brain are indeed very vulnerable to hypoxia. However, mature oligodendrocytes are equipped with metabolic mechanisms that can cope with metabolic insults. These include high levels of glutathione which protects oligodendrocytes from oxidative damage, switching from an oxidative to a glycolytic metabolism; myelin compaction and low turn-over of myelin proteins; and axon-myelin interactions which are mutually supportive (Back et al., 1998; Brown et al., 2001; Morland et al., 2007; Funfschilling et al., 2012; Toyama et al., 2013; Hirrlinger and Nave, 2014; Roth and Núñez, 2016).

Oligodendrocytes have an elaborate network of microtubules composed of microtubule-associated proteins MAP2 and tau whose assembly depends on the interaction of several kinases including Fyn kinases and microtubule-severing proteins such as stathmin (Richter-Landsberg, 2000). Alteration of the cytoskeleton in oligodendroglial cells occurs in tauopathies in which hyper-phosphorylated tau is accumulated and disrupts oligodendroglial microtubules (Richter-Landsberg, 2008). Since the oligodendroglial microtubules participate in the translocation and sorting of MBP and CNP, their alteration may render myelin vulnerable (Bauer et al., 2009). Abnormal tau inclusions in glial cells in tauopathies have functional consequences (Kahlson and Colodner, 2016).

2. Development of oligodendroglia and myelin

Oligodendrocyte precursor cells (OPCs) proliferate in the neuroepithelium of the subventricular zone and migrate to the future white matter through extending and retracting cell processes until their definitive placements (Baumann and Pham-Dinh, 2001; Kirby et al., 2006; Miller and Mi, 2007; Hughes et al., 2013). This process is modulated by self-repulsive movements which allow a certain separation between neighboring cells (Jarjour et al., 2003; Hughes et al., 2013). Oligodendrocytes during development are called pre-oligodendrocytes, immature oligodendrocytes, myelinating and mature oligodendrocytes, each one characterized by very specific morphological and biochemical properties. Differentiation of OPCs to oligodendrocytes depends on the availability of certain growth and survival factors such as platelet-derived growth factor A (PDGF)-A, fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1 (IGF-1), ciliary neurotrophic factor (CNTF) and neurotrophin 3 (NT-3); some cells remain as OPCs whereas redundant cells are eliminated by apoptosis (Barres et al., 1992; Raff et al., 1993; Barres and Raff, 1993; Trapp et al., 1997; Miller, 2002).

Although OPCs can differentiate into oligodendrocytes in the absence of axons (Abney et al., 1981; Raff et al., 1985), axons control the development of oligodendroglia *in vivo* (Wender et al., 1980; Privat et al., 1981; David et al., 1984; Valat et al., 1988; Barres and Raff, 1993, 1999). Moreover, axon signals mediated by certain transcription factors and selected microRNAs, histone deacetylases and the Wnt/-β-catenin pathway modulate myelin gene expression and myelination (Fancy et al., 2009; Emery, 2010; Piaton et al., 2010; Taveggia et al., 2010; Budde et al., 2010; Dugas et al., 2010; Zhao et al., 2010; Kim et al., 2010; Nave, 2010; Twak et al., 2011).

Myelination is also triggered by functional activity of neurons, mediated by ATP and adenosine signals which regulate cross-information between axons, astrocytes and oligodendrocytes, in parallel with down-regulation of PSA-NCAM and LINGO-1 (Demerens et al., 1996; Charles et al., 2000; Mi et al., 2005; Ishibashi et al., 2006; Brinkmann et al., 2008; Gyllensten and Malmfors, 2009). Synaptic activity contributes to the regulation of myelination (Kukley et al., 2007; Ziskin et al., 2007; Gibson et al., 2014; Hines et al., 2015; Mensch et al., 2015; Koudelka et al., 2016).

Myelination is a complex phenomenon which wraps the axon with concentric bilayers (Pedraza et al., 2001; Ffrench-Constant et al., 2004; Simons and Trotter, 2007; Bauer et al., 2009). The process of axon myelination is not uniform but varies along the segment of the involved axon. MBP is produced in the distal parts of oligodendrocytes closest to axons and then MBP progresses from the outside to the inside (Ainger et al., 1993, 1997; Snadeiro et al., 2014). PLP is transported to myelin by vesicular transport and interacts with MBP in the presence of neuronal signals; interaction between the neuron and MBP is necessary for myelin protein clustering (Fitzner et al., 2006). Galactocerebroside (galactosylceramide: GalC) is also incorporated at the same time; thus, neuron-oligodendroglial interactions are mandatory for proper myelin biogenesis (Trajkovic et al., 2006; Simons and Trajkovic, 2006).

Myelin compaction is regulated by several factors, among them CNP, the deficiency of which leads to increased myelin compaction (Snaidero et al., 2014). Conversely, over-expression of CNP leads to focal areas of loose myelin compaction (Gravel et al., 1996). MBP then aggregates and modifies its conformation, resulting in a very stable and resistant protein which limits the entry of other molecules (Aggarwal et al., 2011a, b; Aggarwal et al., 2013; Bakhti et al., 2013a, b). Myelin connects at their edges by tight junctions enriched in claudin-11 (Gow et al., 1999; Morita et al., 1999).

During myelination, molecular clustering occurs at the nodes of Ranvier which involves axonal adhesion molecule neurofascin 186, βIV spectrin, βII spectrin, ankyrin G, voltage-gated sodium channels, voltage-gated potassium channels, TAG-1 and actin, together with glial cell adhesion molecule neurofascin 155, axonal contactin and Caspr (Pan and Chan, 2017). Ankyrin deficiency alters the structure of the nodes of Ranvier and results in axonal degeneration (Saifetiarova et al., 2017). Caspr deficiency manifests by nodal disruption, disorganization of the microtubules and axonal swellings (Garcia-Fresco et al., 2006).

In addition to neuron-glia interactions, other extrinsic and intrinsic factors modulate OPC differentiation and myelination; these include hormones acting on specific receptors, cytokines and enzymes, some of them stimulators and others repressors (McTigue et al., 1998; Noble et al., 1988; Wang et al., 1998; Stolt et al., 2002; Calza et al., 2002; Valerio et al., 2002; Klein et al., 2002; Larsen et al., 2006; Kotter et al., 2006; Fancy et al., 2009; Emery et al., 2009; Meijer et al., 2012; Bankston et al., 2013).

3. Diversity of OPCs/NG2-glia

OPCs are also called NG2-glia because of their expression of proteoglycan GSPG4 (NG2). These cells are not only found during the development of the nervous system; OPCs are present in the adult brain and show particular features distinct from those seen in embryonic OPCs (Káradóttir et al., 2008; Tripathi et al., 2011; Clarke et al., 2012; Vigano et al., 2013; Crawford et al., 2016). OPCs/NG2-glia is considered the fourth element in the adult central nervous system constituting about 5–10% of the total cell population (Scolding et al., 1998; Horner et al., 2000; Dawson et al., 2003; Peters, 2004). Adult OPCs have the capacity to produce myelinating oligodendrocytes (Tripathi et al., 2010; Zawadzka et al., 2010), thus contributing to oligodendrocyte and myelin repair in the adult CNS (Tognatta and Miller, 2016). Indeed, NG2-glial cells are stem cells as they represent the major proliferative cell population in the adult CNS and have the capacity to differentiate into different cell types in addition to oligodendrocytes (Psachoulia et al., 2009; Simon et al., 2011; Dimou and Gotz, 2014; Crawford et al., 2016). OPCs can also generate astrocytes (Zhu et al., 2008,

2011; Vigano et al., 2016). For example, a subset of OPCs in the CA1 region of the mouse hippocampus expresses S100β, thus suggesting that these cells may act as precursors of astrocytes (Moshrefi-Ravasdjani et al., 2017). Human OPCs are also able to transform into astrocytes (Windrem et al., 2004; Sim et al., 2006, 2011). In addition, one NG2 can divide asymmetrically producing an oligodendrocyte and one NG2-glia (Hill et al., 2014). Whether adult OPCs are able to generate neurons is a matter of controversy. However, OPCs have been reported to be a source of pyriform pyramidal neurons in the adult rodent brain (Rivers et al., 2008; Guo et al., 2010), and adult OPCs removed from brain can transform into neurons *in vitro* or when inoculated into developing brains (Battefeld et al., 2014; Nunes et al., 2003). Furthermore, NG2 immunoreactivity is not restricted to a subpopulation of glial cells since pericytes also express NG2 (Ozerdem et al., 2001).

OPCs in the developing mouse brain arise from three waves and from different regions; progeny of the second and third waves persists until adulthood with a certain overlap and reconstructive capacities of the last generated OPCs (Kessaris et al., 2006; Dimou et al., 2005; Rowitch and Kriegstein, 2010; Tomassy et al., 2014). Regional heterogeneity of OPCs implies a different response to particular growth factors and sensitivity to determined signaling pathways even in close areas such as the ventral and dorsal spinal cord of the mouse (Cai et al., 2005; Fogarty et al., 2005; Vallstedt and Kullander, 2013). Important differences also exist between spinal, and cortical and white matter OPCs (Hildebrand et al., 1993; Chong et al., 2012; Hill et al., 2013; Vigano et al., 2013; Eugenin-von Bernhardi and Dimou, 2016; Naruse et al., 2017).

The region of origin also determines future functional capacities of the progeny as responses to demyelination and susceptibility to age-associated functional decline (Crawford et al., 2016; Ornelas et al., 2016). OPCs have the capacity to proliferate, migrate and differentiate following distinct insults, and they play some role in axon regeneration (Tan et al., 2005; Hughes et al., 2013). However, OPCs in the white matter differ from those of the grey matter in many ways including proliferation capacities, response to certain growth factors and plastic properties among others (Dimou et al., 2008; Kang et al., 2010; Young et al., 2013; Hill et al., 2013; Vigano et al., 2013; Serwanski et al., 2017; Hill et al., 2014; Dimou and Gotz, 2014). Certain OPCs express the G-protein coupled receptor 17 (GPR17) (Chen et al., 2009; Boda et al., 2011; Fumagalli et al., 2011) which is associated with higher capacity of differentiation into mature oligodendrocytes following cerebral injury (Vigano et al., 2016; Bonfanti et al., 2017).

Neurons can establish synaptic-like structures with NG2-glia, at least in particular regions and species (Bergles et al., 2000; Lin et al., 2005a, b), whose activation produces bursts of miniature potentials in NG2-glia mediated by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors (Bergles et al., 2000; Ziskin et al., 2007). In addition to AMPA receptors, NG2-glia expresses N-methyl-D-aspartate (NMDA) receptor, acetylcholine, γ-aminobutyric acid A ($GABA_A$) and other receptors (Williamson et al., 1998; De Angelis et al., 2012; Dzamba et al., 2013). NG2-glia also expresses the post-synaptic density protein 95 (PSD-95) (Sakry et al., 2011). Therefore, neurons can regulate proliferation and differentiation of NG2-glia through synaptic signals (Lin et al., 2005a, b; Kukley et al., 2010; Mangin et al., 2012; Sun and Dietrich, 2013; Hill et al., 2014; Gibson et al., 2014; Dimou and Gallo, 2015).

4. Expression of neurotransmitter, hormone receptors and ion channels in oligodendrocyte lineage

A plethora of neurotransmitter and other receptors are expressed in OPCs and at different stages of oligodendroglial differentiation and maturation; these modulate, after specific ligand binding, various stages of oligodendrocyte development (Marinelli et al., 2016). $GABA_B$ receptors are expressed at early stages and their activation induces proliferation and migration of OPCs (Luyt et al., 2007). NMDA, AMPA and kainate receptors are expressed in immature and myelinating oligodendrocytes favoring differentiation and myelination in physiological conditions but also contributing to oligodendroglial damage in ischemia and excitotoxic injury (Salter and Fern, 2005; Micu et al., 2006; Káradóttir et al., 2005).

5-hydroxytryptamine (5-HT) receptor subtypes 1 A and 2 A are expressed in immature and myelinating oligodendrocytes (Fan et al., 2015). Its activation after exposure to serotonin interferes with oligodendroglial differentiation and myelinogenesis (Persico et al., 2000; Fan et al., 2015). Curiously, depression is accompanied by reduced oligodendroglia, expression of myelin-related genes and decreased MBP levels in various brain regions (Aston et al., 2005; Yamazaki et al., 2007; Regenold et al., 2007). Dopamine receptors D2 and D3 are expressed in oligodendrocyte precursors where they are probably involved in the regulation of differentiation and myelin formation (Bongarzone et al., 1998). Adult oligodendrocytres in rats also express D2 and D3 receptors but their function is not known (Rosin et al., 2005). Pre-oligodendrocytes express α- and β-adrenoreceptors whose activation inhibits their proliferation (Ghiani et al., 1999). Cholinergic receptors are present in OPCs and oligodendrocytes at different phases; acetylcholine via muscarinic receptors potentiates proliferation (De Angelis et al., 2012).

OPCs exhibit opioid receptors (Knapp et al., 1998). Dinorphin and pro-encephalin-derived peptides are produced at different stages of oligodendrocyte maturation, thus suggesting an autocrine/paracrine effect on cell survival and development (Knapp et al., 2011). However, perinatal exposure to methadone and bupremorphine alter myelination in the developing rat brain (Eschenroeder et al., 2012; Vestal-Laborde et al., 2014).

ADP and ATP stimulate OPC migration through specific receptors (Agresti et al., 2005) but ATP may also facilitate calcium-mediated excitoxicity and oligodendrocyte damage (Butt, 2006).

Prolactin activates proliferation, maturation and myelination of oligodendrocytes (Gregg et al., 2007). Dexametasone enhances myelination at early stages but reduces myelin formation at advanced stages of development (Almazan et al., 1996). Increased proliferation and oligodendroglial death, suggesting decreased lifespan, and increased oligodendroglial turnover are found in female and castrated male rats (Cerghet et al., 2009). Thyroid hormones activate the expression of myelin-related genes (Farsetti et al., 1991; Tosic et al., 1992; Rodriguez-Peña et al., 1993). Other factors influencing oligodendrocyte development are cannabinoids, liver X receptor, retinoic acid, prostaglandins and peroxisome proliferator activated receptor γ (Marinelli et al., 2016).

Finally, different ion channels are expressed in OPCs and oligodendrocytes including voltage-gated sodium channels (Tong et al., 2009), voltate-gated calcium channels (Verkhratsky et al., 1990) and diverse potassium channels (Buttigieg et al., 2011; Wang et al., 2011; Hawkins and Butt, 2013; Moroni et al., 2015; Battefeld et al., 2016; Livesey et al., 2016; Fang et al., 2017; Brasko et al., 2017; Larson et al., 2018) which participate in glial cell proliferation, regeneration, oligodendroglia/neuronal and axonal interactions, and

which modulate oligodendroglial responses to ischemia, excitotoxicity and seizures, among other pathological settings.

5. Diversity of oligodendrocytes

Transcriptomic profiles of neurons, astrocytes and oligodendroglia have been identified using high-throughput methods (Cahoy et al., 2008; Zhang et al., 2014; Moyon et al., 2015; van Bruggen et al., 2017). Single-cell RNA sequencing revealed different subpopulations of oligodendrocytes from several brain regions of juvenile and adult mouse brain (Zeisel et al., 2015; Marques et al., 2016). A single cluster of OPCs was found in the first studies (Marques et al., 2016; Hochgerner et al., 2017). However, several OPC clusters were recognized thereafter in the adult murine spinal cord (Habib et al., 2016). Likewise, several clusters of oligodendrocytes have been described in the mouse CNS (Tasic et al., 2016; Habib et al., 2017; Hochgerner et al., 2017).

Gene expression studies have also identified subpopulations of OPCs in human adult white matter and fetal forebrain (Sim et al., 2006, 2011), and in human (and murine) ventral midbrain during development (La Manno et al., 2016). Similar analysis has been extended to human oligodendrocytes, further confirming different clusters of oligodendrocytes and precursors in human brain (Darmanis et al., 2015; Spaethling et al., 2017; Habib et al., 2017; Lake et al., 2017).

All this information supports pioneering observations by Pio del Rio-Hortega describing different types of oligodendroglial cells. However, available information is not uniform and it is difficult, at present, to consolidate clear-cut profiles for different clusters/types of oligodendrocytes. There is probably a more complex scenario because transcription is modifiable depending on the function and physiological state of the cells.

6. Signals involved in OPC generation, oligodendroglia differentiation and myelination

Major knowledge of OPC generation comes from the study of the mouse spinal cord and forebrain. In the spinal cord, the first wave of generation occurs at embryonic day 12, originates from the ventral neural tube and depends upon sonic hedgehog (SHH) and *Nkx6.1* and *Nkx6.2* regulation of Olig 1 and Olig2 transcription (Orentas et al., 1999; Lu et al., 2000; Vallstedt et al., 2005). A second wave originates at embryonic day 15 from the dorsal spinal cord; it is not dependent on SHH but it is regulated by *Dbx1* and *As11* and requires fibroblast growth factor enhancement and decreased bone morphogenic protein signaling (Vallstedt et al., 2005; Cai et al., 2005; Fogarty et al., 2005; Sugimori et al., 2008). A third wave occurs at birth (Rowitch and Kriegstein, 2010).

In the forebrain, the first wave comes from the medial ganglionic eminence upon SHH and *Nkx.2* mediation (Nery et al., 2001; Tekki-Kessaris et al., 2001; Kessaris et al., 2006), and it spreads to the entire forebrain (Kessaris et al., 2006; Klambt, 2009). The second wave comes from the lateral ganglionic eminence under the control of *Gsx2* (Chapman et al., 2013) and it populates all the forebrain (Kessaris et al., 2006; Klambt, 2009). The third wave occurs at birth, and derives from dorsal and outer subventricular zones through *Emx1* extending to the corpus callosum and capsular white matter (Kessaris et al., 2006).

Such detail in human brain is not available although OPCs first appear approximately at nine weeks of gestation and proliferate until about 18 weeks of gestation; oligodendroglia start to differentiate until about 27 weeks of gestation (Back et al., 2001; Jakovcevski et al., 2009; Sim et al., 2011)

Early oligodendroglial differentiation, at least in the murine brain, is mediated by activation of transcription factors *Znf488* and *Znf536*, down-regulation of *Sox2*, up-regulation of *Sox8*, *Sox9*, *Sox 10*, *Olig1* and *Olig 2* (Kuhlbrodt et al., 1988; Wegner and Stolt, 2005; Yang et al., 2013; Wang et al., 2014). At early stages, human and murine cells also express platelet derived growth factor receptor α (PDGFα), gangliosides (as revealed by the antibody A2B5) and NG2 (Hart et al., 1989; Noble et al., 1988; Wolswijk and Noble, 1989; Richardson et al., 1988; Roy et al., 1999; Chang et al., 2000; Dawson et al., 2000; Levine et al., 2001; Sim et al., 2006, 2011; Wang et al., 2014). The transition of OPCs to post-mitotic oligodendrocytes is characterized by chromatin condensation with heterochromatin formation (Huang et al, 2015), up-regulation of selected microRNAs and silencing of genes involved in cell proliferation including PDGF, FGF and Wnt, among other factors (Yu et al., 2010, 2013; Zhao et al., 2010; Dugas et al., 2010; Ackerman et al., 2015; Giera et al., 2015; Barca-Mayo and Lu, 2012; Magri et al., 2014; Mitew et al., 2014; Fitzpatrick et al., 2015). Wnt/β-catenin pathways play different roles in oligodendrocyte development and myelination in different brain regions and at different stages (Guo et al., 2015). These transcription factors are controlled by epigenetic remodeling of the chromatin by histone acetylation and methylation. Histone deacetylases 1 and 2 (HDAC 1 and 2) actively participate in this process (Marin-Husstege et al., 2002; Shen et al., 2005; Liu et al., 2007a, 2015).

Early stages of oligodendrocyte lineage are identified by the expression of Olig1, Olig2 and Nkx2.2 (Liu et al., 2007b). PDGF-Rα, NG2, Olig1, Olig 2, Sox 10 and A2B5 are OPC differentiation and pre-oligodendrocyte markers. Loss of PDGF-Rα and NG2, and increased expression of surface lipid sulfatide, galactocerebroside and CNP, together with Olig 1 and Olig 2, are characteristic of immature oligodendrocytes (Marinelli et al., 2016).

After oligodendrocyte differentiation, myelination is triggered by myelin regulatory factor (MYRF) which is expressed in post-mitotic oligodendrocytes (Cahoy et al., 2008). This is accompanied by increased expression of MBP, MAG, PLP1, MOG and CNP which have MYRF binding motivs in their promoters (Emery et al., 2009; Koenning et al., 2012; Bujalka et al., 2013; McKenzie et al., 2014; Emery and Lu, 2015). At this time, oligodendrocytes also produce sulfatides and galactocerebrosides as main lipid components of myelin. MBP, MAG, MOG and PLP are mainly found in myelin under physiological conditions in the mature brain; carbonic anhydrase II, CNP and galactocerebroside can be identified in oligodendrocytes in brain tissue sections; surface lipid sulfatide, Olig1, Olig2 and Sox 10 are additional markers expressed in myelinating oligodendrocytes (Bradl and Lassmann, 2010; Marinelli et al., 2016).

The role played by neurons and axons during myelinogenesis has been detailed before. Whether oligodendroglial subtypes depend on the type of axons and the type of neurons is a matter for study (Ludwin, 1979; Tauber et al., 1980; Tomassy et al., 2014; Battefeld et al., 2016; Micheva et al., 2016).

7. Oligodendroglia and axon integrity

In addition to studies showing the role of axons in the development of oligodendroglia, several *in vitro* and *in vivo* experimental models have demonstrated that oligodendroglia are involved in support of axonal transport and axon integrity (Nave and Trapp, 2008; Lee et al., 2012; Saab et al., 2013; Beirowski, 2013; Morrison et al., 2013; White and Krämer-Albers, 2014; Simons et al., 2016). Axon outgrowth is also sustained in part by growth factors such as GDNF and BDNF produced by oligodendrocytes (Du and Dreyfus, 2002; Wilkins et al., 2003; Dai et al., 2003)

Oligodendrocyte cell death is produced by diphtheria toxin in mice selectively expressing diphtheria toxin receptor in oligodendoglia or by conditionally targeting diphtheria toxin to PLP-CrER mice (Ghosh et al., 2011; Oluich et al., 2012). In all these settings, oligodendroglial cell death is accompanied by axonal damage with little if any myelin destruction and with the absence of secondary immune reaction (Pohl et al., 2011; Oluich et al., 2012).

Mice with altered expression of PLP, a protein primarily affected in certain forms of Pelizaeus-Merzbacher disease, is manifested by demyelination and axonal damage (Sidman et al., 1964; Griffiths et al., 1981; Schneider et al., 1992; Gotow et al., 1999; Al-Saktawi et al., 2003; Karim et al., 2007; Mayer et al., 2011). However, axonal damage, mainly or exclusively, is found in PLP1 null mice (Griffiths et al., 1998; Edgar et al., 2004), presumably due to altered axonal transport (Edgar et al., 2004, 2010). Axonal mitochondrial dysfunction via altered metabolic coupling occurs in PLP-deficient mice (Yin et al., 2016).

Mice lacking CNP show early axonal damage and disruption of the paranodal architecture, followed by axonal degeneration and myelin damage (Lappe-Siefke et al., 2003; Rasband et al., 2005; Edgar et al., 2009). This may be due to increased myelin compaction interfering with oligodendrocyte metabolic effects on axons (Edgar and Nave, 2009).

Finally, transgenic mice lacking MAG have subtle changes in myelin structure accompanied by reduced axon caliber, reduced neurofilament phosphorylation and progressive axon loss (Fruttiger et al., 1995; Yin et al., 1998; Pan et al., 2005).

In addition to the involvement of particular myelin proteins in the maintenance of axon stability, other data provide strong support for the notion of metabolic interaction between oligodendrocytes and axons. During development, oligodendrocytes import glucose and lactate (Rinholm et al., 2011). However, mature oligodendrocytes can survive only with glycolysis. Conditional Cox10 mutant mice in which oligodendroglia (and Schwann cells) fail to assemble mitochondrial complex IV (cytochrome c oxidase: COX) show peripheral but not central myelin abnormalities. These alterations are accompanied by increased brain lactate concentrations, thus suggesting that enhanced glycolysis in oligodendroglia, aimed at preserving energy supply, may maintain axon integrity in spite of altered mitochondrial metabolism in oligodendrocytes (Funfschilling et al., 2012).

Blood-derived glucose taken up by oligodendrocytes through glial glucose transporter 1 (GLUT1) is metabolized via glycolysis to produce piruvate and lactate which are delivered to the axons through specific solute carriers, the monocarboxylase transporters (Saab et al., 2013). Solute carrier (SLC) protein family 16 includes monocarboxylate transporters (MCT) located in cell membranes (Pierre and Pellerin, 2005). MCT1 is mainly expressed in oligodendrocytes (Rinholm et al., 2011; Lee et al., 2012). Inhibition of MCT1 in organotypic cultures of the spinal cord in glucose-deprived media is toxic to neurons but not to oligodendroglial cells; the effects on neurons are reversed with the addition of lactate into the medium (Lee et al., 2012). *in vivo* experiments geared at inducing reduction of MCT1 activity result in axonal damage (Lee et al., 2012). Together, these observations suggest that MCT1 serves as intermediate transporter of metabolites necessary to energy metabolism in neurons.

Oligodendrocyte and axon interactions are not only bi-directional; astrocytes also participate as crucial players. Oligodendrocytes are connected with astrocytes through gap junctions composed of connexins (Cx); Cx32 and Cx47 are synthesized by oligodendrocytes, and Cx30 and Cx43 by astrocytes (Orthmann-Murphy et al., 2007). Mice lacking either Cx47 or Cx32 are viable but transgenic mice lacking both Cx32 and Cx47 show thin or absent myelin sheaths, vacuolation, enlarged periaxonal collars, oligodendrocyte cell death, and axonal loss (Menichella et al., 2003). Double mutations of Cx30 and Cx47, affecting oligodendroglial and astrocytic components of gap junctions, show severe vacuolization and myelination defects in all white matter tracts of the CNS, accompanied by decreased numbers of oligodendrocytes, severe astrogliosis and microglial activation in white matter tracts (Tress et al., 2012). Cx47 is also expressed in OPCs and its expression increases in co-cultures with astrocytes which induce proliferation of oligodendrocytes via Cx47-mediated activation of the ERK/Id4 pathway and sphingosine-1-phosphate receptors 3 (Liu et al., 2017a, b; Xu et al., 2017). Cx26 is localized in individual gap junctions between astrocytes and in heterotypic gap junctions between astrocytes and oligodendrocytes (Nagy et al., 2011).

8. Oligodendrocytes in brain aging

Human myelination is uniquely expanded and vulnerable to aging (Tse and Herrup, 2017). White matter lucencies with age were discovered by neuroimaging studies (Hachinski et al., 1987; Meyer et al., 1992). Progressive white matter decline in human brain, as revealed by magnetic resonance imaging (MRI), starts at about 45 years of age (Bartzokis et al., 2001, 2003; Sperling et al., 2014) and it is enhanced in Alzheimer's disease (Bartzokis et al., 2003). This is accompanied by white matter hyperlucencies which correspond either to areas of poor perfusion, areas of myelin pallor, or periventricular edema (Barber et al., 1999; Young et al., 2008; Black et al., 2009; Holland et al., 2008; Erten-Lyons et al., 2013; Liu et al., 2017a, b), thus indicating that age-related white matter alterations are multifactorial.

Small blood vessel disease is not uncommon from middle-age onwards and it is likely causative of variegated lesions in the white matter including hypoperfusion, status cribosus, small infarcts or lacunes, and diffuse white matter demyelination (so called Binswanger encephalopathy when clinically manifestesd as cognitive impairment) (Kalaria et al., 2015).

All these changes may be silent depending on the degree and localtion of lesions but they are also causative of cognitive impairment once certain thresholds are reached (Ferrer, 2010)

The time of OPC division is increased in old age and therefore oligodendrocyte repair is delayed (Lasiene et al., 2009; Psachuolia et al., 2009; Zhu et al., 2011). Moreover late oligodendrocyte progenitors are particularly vulnerable to hypoxia (Back et al., 2002). HDCA1 and Olig2 are downregulated in the aging brain (Shen et al., 2008a, b) thus limiting rates of remyelination.

Oligodendroglial nuclei in the aging white matter show signatures of oxidative DNA damage which increase in Alzheimer's disease (Al-Mashhadi et al., 2015). Oxidative damage likely involves RNA, proteins and lipids, as in other cells and regions. Whether specific oligodendroglial proteins are oxidatively damaged in old age deserves study. Likewise, further information is needed to learn about the functional integrity of oligodendrocyte glucose and monocarboxylate transporters in old age.

9. Oligodendrogliopathy

The term astrogliopathy refers to alterations of astrocytes occurring in diseases of the nervous system, includes reactive astrogliosis (mainly manifested as an increase in the amount of GFAP and in the number of astrocytes containing GFAP), and stresses the cardinal role of astrocytic dysfunction in the pathogenesis of neurological diseases (Seifert et al., 2006; Pekny and Pekna, 2014; Pekny et al., 2016; Osborn et al., 2016; Verkhratsky et al., 2017a, b). Astrocytopathy refers to decrease in the number of astrocytes,

atrophy/degeneration and loss of function occurring as a primary cause of a disease or as a factor contributing to the development and progression of a particular disease (Pekny et al., 2016; Ferrer, 2017).

The term oligodendrogliopathy has developed more recently (Wenning et al., 2008; Bleasel et al., 2016) to stress the prominent role of altered oligodendrocytes in the pathogenesis of certain neurological diseases (Fellner and Stefanova, 2013; Tognata and Miller, 2016; Ettle et al., 2016a, b). Oligodendrogliopathy is crucial in demyelinating diseases and most leukodystrophies. Indeed, the term oligodendrogliopathy was initially coined by Lassman et al. in the context of myein-associated glycoprotein deficiency (Lassmann et al., 1997), and astro- and oligodendrogliopathy are early events in CNS demyelination (Zhang et al., 2013; Rone et al., 2016). Yet disturbances of oligodendrocyte function have also emerged as determining factors in apparently distant diseases such as psychiatric disorders including schizophrenia and major depression (Miyata et al., 2015; Birey et al., 2017).

Here, we review oligodendrogliopathy in relevant neurodegenerative diseases with abnormal protein aggregates.

9.1. Multiple system atrophy

Multiple system atrophy (MSA) is a sporadic adult-onset degenerative disease manifested clinically by parkinsonism, cerebellar symptoms and autonomic dysfunction, and neuropathologically by degeneration of the olivopontocerebellar system, substantia nigra and autonomous nervous system, together with the presence of oligodendroglial and neuronal inclusions containing abnormal α-synuclein (Holton et al., 2011). MSA is a prototypic oligodendroglioneural synucleinopathy (Jellinger, 2018) (Fig. 1).

Four stages or grades of neuropathology have been proposed in MSA. However, differences in the main forms of clinical presentation—nigro-striatal degeneration and olivopontocerebellar atrophy, as well as individual variations—make practical use of the proposed classification at advanced stages of the disease difficult (Jellinger et al., 2005; Ozawa et al., 2004).

Reduced white matter and myelin staining, together with altered lipid levels, is found in the striatum, cerebellar white matter, fascicles of the pons and medulla oblongata, and, often, white matter of the cerebral hemispheres and internal capsule (Matsuo et al., 1998; Schocke et al., 2002; Shiga et al., 2005; Blain et al., 2006; Paviour et al., 2007; Brooks and Seppi, 2009; Prodoehl et al., 2013; Don et al., 2014). These lesions are accompanied by characteristic oligodendroglial inclusions called Papp-Lantos inclusions which are the hallmark of the disease (Papp et al., 1989).

Early studies showed the presence of ubiquitin and tau in these inclusions (Abe et al., 1992; Murayama et al., 1992; Papp and Lantos, 1994; Papp et al., 1989; Takeda et al., 1997). Subsequent inquiries revealed α-synuclein as the main component of oligodendroglial inclusions in MSA (Spillantini et al., 1998; Tu et al., 1998;

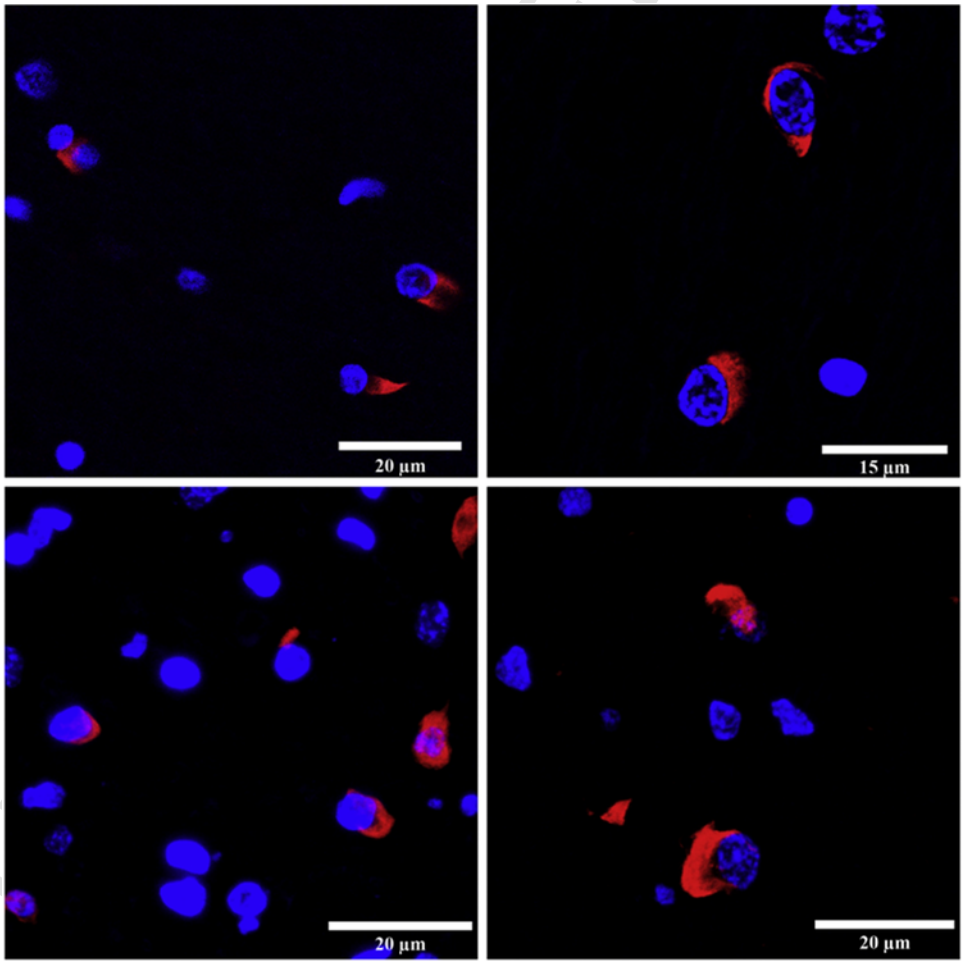

Fig. 1. α-synuclein-immunoreactive (red) oligodendroglial inclusions in the cerebellar white matter (A, B) and pons (C, D) in multiple system atrophy (MSA). Paraffin sections, nuclei stained with DRAQ5™(blue); A, C, D, bar = 15 µm; B, bar = 20 µm.

Wakabayashi et al., 1998; Gai et al., 2003; Jellinger and Lantos, 2010).

The distribution of α-synuclein deposits correlates with the main pathological lesions, and the number of inclusions increases with disease progresion (Papp and Lantos, 1994; Inoue et al., 1997; Halliday et al., 2011). Abnormal α-synuclein deposits are also found less numerously in the cytoplasm and nuclei of neurons (Papp and Lantos, 1992; Wenning and Jellinger, 2005).

The source of α-synuclein in MSA oligodendrocytes is controversial. From very little to nearly no α-synuclein mRNA is expressed in adult control and MSA oligodendrocytes (Solano et al., 2000; Ozawa et al., 2001; Miller et al., 2005). However, one study reported mRNA α-synuclein expression in oligodendrocytes, although it is not clear whether the expression is increased in α-synuclein-containing oligodendroglial inclusions in MSA (Asi et al., 2014). Other surveys showed the presence of α-synuclein protein in cultured oligodendrocytes (Richter-Landsberg et al., 2000). Moreover, α-synuclein has been demonstrated in oligodendroglial cell lineage derived from induced pluripotent stem cells (iPSCs) from human healthy cases and patients with Parkinson's disease and MSA with decreased α-synuclein expression during oligodendrocyte maturation; transcripts are also detected in human and rodent oligodendrocytes isolated by fluorescence-activated cell sorting (FACS) (Djelloul et al., 2015).

As an alternate proposal, α-synuclein in oligodendrocytes may originate in neurons and then become trapped by oligodendrocytes. Monomeric, oligomeric and fibrillar forms of α-synuclein uptake occur in oligodendrocytes *in vitro* and *in vivo*; α-synuclein can transfer to grafted oligodendroglial cells from host rat brain neurons overexpressing human α-synuclein (Reyes et al., 2014). Neuronal to oligodendroglia α-synuclein transfer is further supported in transgenic mice expressing A53 T human α-synuclein enhanced by docosahexaenoic acid (Kisos et al., 2012). α-synuclein uptake in both neurons and oligodendroglia seems to be mediated by endocytosis as dynamin GTPase suppression decreases α-synuclein uptake in neurons and oligodendrocytes (Konno et al., 2012). Finally, slow degradation of α-synuclein in oligodendroglial cells has been suggested as an accompanying factor in the generation of Papp-Lantos inclusions (Fellner et al., 2011).

α-synuclein in MSA is abnormally nitrated, phosphorylated and oxidized, and has anomalous solubility (Dickson et al., 1999; Giasson et al., 2000; Duda et al., 2000; Campbell et al., 2001; Fujiwara et al., 2002; Hasegawa et al., 2002; Pountney et al., 2004; Tong et al., 2010; Ubhi et al., 2011).

In addition to abnormal α-synuclein, MSA inclusions contain several proteins including synphilin-1, SUMO-1, ubiquitin, FBXO7, dorfin, PACRG, NUB-1, HtrA2/OMI, XIAP, αB-crystallin, proteasome subunits, HSP70, HSP90, PDI, p62, NBR1, LRRK2, clusterin, methallothionein-III, cyclin-dependent kinase 5, mitogen-activated protein kinase, P39, Elk1, tubulin polymerization-promoting protein p25α (TPPP/p25α), tau, γ-tubulin, MAP5, histone deacetylase 6, DARPP32, midkine, Rab5, rabaptin-5, 14-3-3 and AMBRA-1, among others (Abe et al., 1992; Murayama et al., 1992; Takeda et al., 1997; Spillantini et al., 1998; Gai et al., 1999; Nakamura et al., 1998, 2000; Piao et al., 2001; Honjyo et al., 2001; Iwata et al., 2001; Kato et al., 2000; Sasaki et al., 2002; Wakabayashi et al., 2002; Kawamoto et al., 2002; Hishikawa et al., 2003; Kovács et al., 2004; Pountney et al., 2005a, b; Tanji et al., 2007; Song et al., 2007; Taylor et al., 2007; Kovács et al., 2007; Wenning et al., 2008; Kawamoto et al., 2008; Honjo et al., 2008, 2011; Pountney et al., 2011; Chiba et al., 2012; Odagiri et al., 2012; Zhao et al., 2013; Wong et al., 2013; Kawamoto et al., 2014; Miki et al., 2018). Impaired protesome function and autophagy play key roles in the pathogenesis of protein aggregates in oligodendrocytes in MSA (Schwarz et al., 2012).

The meaning of the great number of proteins trapped in oligodendroglial inclusions is not known, but some of these proteins are implicated in particular functions. p25α is re-localized in oligodendrocytes in MSA before the appearance of oligodendroglial inclusions, and the interaction of p25α with MBP is altered (Song et al., 2007). Moreover, p25α induces α-synuclein aggregation (Lindersson et al., 2005; Kragh et al., 2009). Therefore, p25α seems to have a double effect, enhancing α-synuclein aggregation and impairing myelination.

Oligodendroglia inclusions also contain tubulin β-III which co-localizes with α-synuclein in abnormal inclusions in certain MSA transgenic mice (Nakayama et al., 2009). Interactions of tubulin β-III and other cytoskeletal proteins, such as tau, with abnormal α-synuclein have deleterious effects on the microtubules (Nakayama et al., 2012; Ota et al., 2014).

Immunoprecipitation studies have also shown abnormal α-synuclein interactions with Rab3a in the cerebellum and pons in MSA, thus suggesting alterations in membrane and synaptic vesicle trafficking in MSA (Dalfó and Ferrer, 2005).

The expression of several proteins is increased in the white matter of affected regions in MSA. For example, ABCA8, an ATP-binding cassette lipid transporter, which promotes sphingomyelin production in oligodendrocytes, is increased in white matter in MSA (Bleasel et al., 2013). Transfected human oligodendrocytes with ABCA8 produce an increase in α-synuclein and p25α (Bleasel et al., 2013), thus suggesting that ABCA8 is involved in MSA pathogenesis although not necessarily present in oligodendroglial inclusions. In the same line, the endoplasmic reticulum stress response is activated at early stages of the disease in areas with oligodendroglial inclusions (Makioka et al., 2010).

It has been reported that the volume of the nuclei of oligodendrocytes is reduced in MSA in regions devoid of inclusions (Uyama et al., 2009). Yet it is not clear whether the same applies to the nuclei of oligodendroglia bearing inclusions. Moreover, the number of oligodendrocytes seems to be preserved in the white matter in MSA (Ettle et al., 2016a, b; Nykjaer et al., 2017). On the other hand, the number of OPCs is increased in MSA, and some OPCs contain α-synuclein inclusions (Ahmed et al., 2013a; May et al., 2014).

Several animal and cell models have been developed to gain understanding about MSA. Expression of oligodendroglial α-synuclein has been generated following intrastriatal injection of chimeric viral vectors expressing α-synuclein under the control of MBP; interestingly, phosphorylated and proteinase-resistant α-synuclein is detected in the striatum and substantia nigra, indicating, in addition, the capacity for seeding (Bassil et al., 2017). Other viral vector models are currently assessed in rodent and nonhuman primates (Mandel et al., 2017).

Transgenic models reproduce α-synuclein overxpression and phosphorylation in oligodendroglia under the control of myelin gene promoters, either MBP, PLP or CNP (Kahle et al., 2002; Yazawa et al., 2005; Shults et al., 2005; Tank et al., 2014; Fernagut et al., 2014; Fellner et al., 2015; Bleasel et al., 2016; Overk et al., 2018). All of them show, albeit with particularities, clinical phenotype and neuropathology reminiscent of MSA (Kuzdas et al., 2013; Boudes et al., 2013; Flabeau et al., 2014). Myelin loss occurs in every model, and reduced numbers of oligodendroglia are reported in some of them (Yazawa et al., 2005; Stemberger et al., 2010; Stefanova et al., 2012). The number of OPCs is increased in transgenic mice generated with MBP promoter (May et al, 2014). Additional evidence shows that α-synuclein overexpression impairs the maturation of OPCs and reduces the production of MBP (Ettle et al., 2014), and that α-synuclein overexpres-

sion in oligodendrocytes in primary and stem cell-derived oligodendrocytes impairs myelin formation (Ettle et al., 2016a, b).

Other factors condition α-synuclein alterations and oligodendrocyte deterioration in MSA. α-synuclein pathology and myelin damage are enhanced following mitochondrial inhibition and oxidative stress in transgenic mice (Stefanova et al., 2005; Ubhi et al., 2009). This is reproduced *in vitro* when oxidative stress induces α-synuclein aggregation in cultured oligodendroglia (Riedel et al., 2011; Pukaβ and Richter-Landsberg, 2014; Pukaß et al., 2015). α-synuclein accumulation is also attained following proteasomal inhibition (Stefanova et al., 2012). This is further supported by studies *in vitro* demonstratring altered autophagy and proteasomal activity in oligodendrocytes following α-synuclein expression (Schwarz et al., 2012). The effects of α-synuclein uptake and mitochondrial damage have been sustained in astrocytes after uptake of α-synuclein monomers (Lindström et al., 2017); no similar studies are available regarding oligodendrocytes. Interestingly, oxidative and proteolytic stress also induces the recruitment of tau in oligodendrocytes overexpressing α-synuclein (Riedel et al., 2009).

Finally, transgenic mice expressing oligodendroglial α-synuclein under the MBP promoter show reduced GDNF protein expression and preserved GDNF mRNA, suggesting that abnormal α-synuclein brings about post-translational effects on GDNF expression. Normalization of GDNF levels ameliorates behavior and neuropathological deficits in these mice (Ubhi et al., 2010, 2012).

Mechanisms of disease progression are not known but *in vitro* α-synuclein uptake studies, α-synuclein accumulation in oligodendrocytes in certain murine paradigms, and more importantly, transmission studies of MSA to transgenic mice are in line with the concept of cell-to-cell transmission of abnormal MSA α-synuclein. *in vitro* studies demonstrate α-synuclein uptake by oligodendrocytes and formation of intracellular aggregates reminiscent of oligodendroglial inclusions in MSA (Kisos et al., 2012; Konno et al., 2012). α-synuclein transmission to oligodendrocytes and precursors, in addition to neurons, occurs in embryonic rat brain tissue grafted to mice producing human α-synuclein under a viral vector (Reyes et al., 2014). Redistribution of α-synuclein from neurons to oligodendrocytes is observed in double-transgenic mice (Rockenstein et al., 2012). Most clear evidence of α-synuclein transmission comes from the observation that MSA homogenates inoculated into the brain of mice produce a neurodegenerative disease characterized by the accumulation of abnormal α-synuclein in neurons and oligodendroglia similar to that seen in human MSA (Watts et al., 2013). The same results are obtained after inoculation of homogenates obtained from other series of MSA cases thus replicating first studies; importantly, no similar oligodendroglial inclusions are found after inoculation of homogenates from cases with Lewy body disease, thus suggesting the existence of specific MSA strains (Prusiner et al., 2015). These findings together with propagation of MSA-derived α-synuclein in cultured cells (Woerman et al., 2015) suggest that MSA has the properties of a prion-like disease with the capacity to propagate to oligodendroglail cells (Woerman et al., 2017).

Interestingly, α-synuclein induces fibrillization of tau, and co-incubation promotes fibrillization of both proteins (Giasson et al., 2003). Double-transgenic mice expressing both α-synuclein and tau show synergistic fibrillization of these two proteins (Fillon and Kahle, 2005). Concurrence of α-synuclein and tau in abnormal neurites and less commonly in neurons in the Contursi kindred of familial PD rarely co-localizes with almost complete spatial disparity (Duda et al., 2002). Rare tau granular deposits are seen in oligodendrocytes in MSA which do not co-localize with α-synuclein deposits thus suggesting that tau aggregation might be another pathway of oligodendroglial degeneration in this disease (Nigashi et al., 2011; Jellinger, 2012). Oxidatively modified α-synuclein is degraded by the proteasome and it plays a pro-aggregative role for tau in oligodendroglial cells exposed to particular settings (Riedel et al., 2009).

9.2. Lewy body diseases

Lewy body diseases (LBD) include Parkinson's disease (PD) and Dementia with Lewy bodies (DLB). Both are characterized by distinct premotor symptoms followed by parkinsonism due to the involvement of the autonomic nervous system, selected nuclei of the medulla oblongata and pons, and eventually the substantia nigra pars compacta, respectively. Cognitive deficits may appear with disease progression in PD, whereas dementia is an early symptom in DLB. Involvement of the cerebral cortex, although with differences in PD and DLB, is causative of cognitive impairment and dementia. The term LBD comes from the presence of intraneuronal inclusions named Lewy bodies composed of abnormal α-synuclein which is nitrated, phosphorylated, abnormally conformed and aggregated, and with altered solubility; abnormal α-synuclein is also accumulated in aberrant neurites (Jellinger, 2011; Ince, 2011; Revesz et al., 2015).

The putative progression of PD has been classified into six stages from the medulla oblongata (and olfactory bulb) to the pons, midbrain, limbic system, diencephalic nuclei and neocortex (Braak et al., 2003, 2004). Involvement of the autonomic nervous system is also considered an early stage of PD pathology. Cases without clinical symptoms or with pre-motor symptoms (without parkinsonism) and with Lewy bodies and neurites in the lower parts of the brain stem are categorized as pre-motor or incidental PD (Dickson et al., 2008; Ferrer et al., 2012). Yet some incidental LBD cases have LBs in the cerebral cortex and these cases have been categorized as putative preclinical stages of DLB (Frigerio et al., 2011).

White matter involvement in PD is limited, whereas white matter involvement in DLB is variable, mainly affecting the posterior lobes, and often linked with associated Alzheimer's disease (AD) pathology (Bohnen and Albin, 2011; Nedelska et al., 2015; Firbank et al., 2016; Joki et al., 2018). Decreased size of oligodendroglial nuclei has been described in LBD independently of the concomitant AD pathology (Gagyi et al., 2012). The reasons and functional consequences are not known.

α-synuclein-positive inclusions in astrocytes and oligodendroglia are found in the midbrain in PD; they are composed of filamentous structures about 25–40 nm in diameter, and their presence correlates with neuronal loss, at least in the substantia nigra (Wakabayashi et al., 2000). Oligodendroglial inclusions containing abnormal α-synuclein have also been reported in many nuclei and fiber tracts of the brain stem containing Lewy bodies or Lewy neurites (Seidel et al., 2015).

Oligodendrocytosis occurs in the substantia nigra and striatum following acute and chronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment in mice and macaques, respectively, used as models of PD (Annese et al., 2013). This suggests that oligodendrocytes are vulnerable to this treatment although its implication in LBDs is not known. The meaning of reported auto-antibodies against MAG in parkinsonian patients without correlation with disease severity (Papuć et al., 2016) deserves further study.

There is a bulk of information regarding prion-like propagation of neuronal α-synuclein in several in vivo and vitro paradigms of LBDs (Ulusoy et al., 2015; Rey et al., 2016; Shimozawa et al., 2017; Choi et al., 2018; just to include additional references to those signaled in previous paragraphs).

As already mentioned in MSA, oligodendrocytes can take up recombinant α-synuclein monomers, oligomers and, to a lesser extent, fibrils, and α-synuclein can be transferred to grafted oligoden-

droglial cells from host rat brain neurons overexpresing α-synuclein (Reyes et al., 2014). Curiuosly, no oligodendroglial α-synuclein-immunoreactive inclusions are produced after inoculation of brain homogenates from cases with LBD in striking contrast with the inoculation of MSA homogenates, which have the capacity to transfer abnormal α-synuclein to oligodendrocytes in addition to neurons, and to generate oligodendroglioneural α-synucleinopathy (Watts et al., 2013; Prusiner et al., 2015).

9.3. Tauopathies

Tauopathies are adult-age neurodegenerative diseases defined by the accumulation of abnormally phosphorylated tau in neurons and glial cells. Tau proteins are encoded by microtubule associated protein tau gene, *MAPT,* the transcription of which by splicing produces six isoforms in the brain. Some tauopathies are identified as 4R-tauopathies, and others as 3R-tauopathies depending on the axon 10 splicing. Sporadic tauopathies include Pick's disease (PiD), a 3R tauopathy; and progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and argyrophilic grain disease (AGD), all of them 4R-tauopathies, each with particular clinical, neuropathological and biochemical traits (Dickson et al., 2011a, b; Muñoz et al., 2011; Tolnay and Braak, 2011; Lowe and Kalaria, 2015; Kovacs, 2015; Kovacs and Tauopathies, 2015; Kovacs et al., 2017). Familial tauopathies are linked to mutations in *MAPT* and they are usually manifested neuropathologically as frontotemporal lobar degeneration (FTLD) and clinically as dementia (FTD) with parkinsonism; tau deposits are composed of 4R-, 3R- or 4R + 3R-tau repeats depending on the site of the mutation (Ghetti et al., 2011a, b).

Alzheimer's disease (AD) has a component of neuronal tauopathy but the presence of β-amyloid plaques is mandatory, at present, for its categorization. Primary age-related tauopathy (PART) is a recently named sporadic 4R + 3R-tauopathy which is characterized by the presence of NFTs in the same localtions and with the same Braak stages but without β-amyloid plaques (Crary et al., 2014; Jellinger et al., 2015). Whether PART is part of AD is a matter of academic discussion (Duyckaerts et al., 2015; Giaccone, 2015). Advanced stages of PART may be causative of dementia with only tangles (Jellinger and Bancher, 1998). Aging-related tau astrogliopathy (ARTAG) is another 4R-tauopathy in old age restricted to astrocytes (Kovacs et al., 2016). Globular glial tauopathy will be defined later.

A combination of different tauopathies is not rare in old-aged individuals (Rahimi and Kovacs, 2014; Kovacs et al., 2017).

White matter atrophy, including demyelination and axonal loss, is common in tauopathies (Chin and Goldman, 1996; Dickson et al., 1996). Axonal damage in tauopathies is commonly interpreted as the result of neuronal damage (Kneynsberg et al., 2017). However, glial cells may act as additional pivotal players because of their damage resulting from abnormal tau deposits in astrocytes and oligodendroglia.

Several types of inclusions in oligodendrocytes and oligodendroglial processes are distinguished in tauopathies (Fig. 2). Coiled bodies and threads are found in PiD, PSP, CBD and AGD (Wakabayashi et al., 1994; Feany et al., 1995; Nishimura et al., 1995; Arima et al., 1997; Tolnay et al., 1997; Ikeda et al., 1998; Jellinger, 1998; Komori, 1999; Arai et al., 2001; Oyanagi et al.,

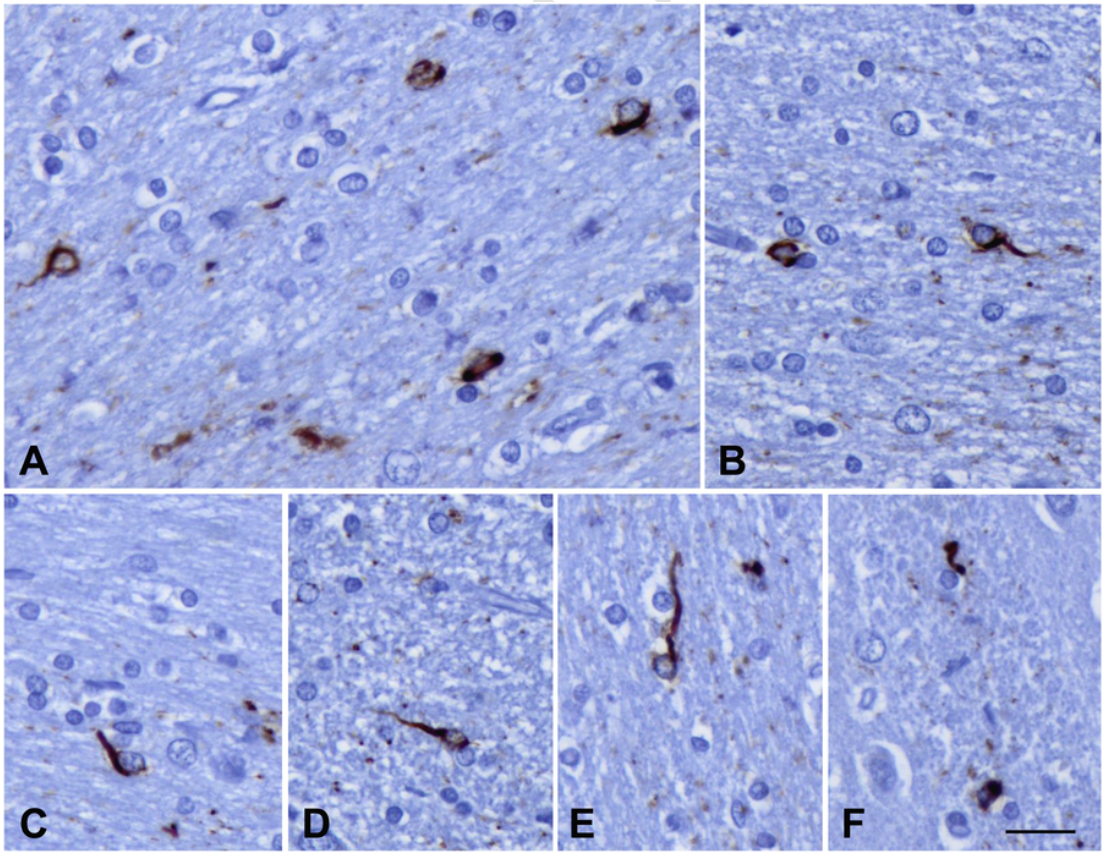

Fig. 2. Tau-immunoreactive oligodendroglial inclusions in tauopathies. A: progressive supranuclear palsy (PSP); B: corticobasal degeneration (CBD); C: argyrophilic grain disease (AGD); D: frontotemporal lobar degeneration FTLD-tau (deln296); E: frontotemporal lobar degeneration FTLD-tau (P301 L); F: Pick's disease (PiD). Paraffin sections, AT8 immunohistochemistry slightlhy counterstained with haematoxylin; bar = 25 μm.

2001; Williams, 2006; Ferrer et al., 2008; Grinberg and Heinsen, 2009; Mimuro et al., 2010; Pham et al., 2011; Kovacs et al., 2018; Komori, 2017). Similar inclusions are noted in the majority of cases with FTLD linked to *MAPT* mutations (FTLD-tau) (Spillantini et al., 1997; Bird et al., 1999; Iseki et al., 2001; Spina et al., 2008; Dickson et al., 2011a, b; Ghetti et al., 2011a, 2011b). Coiled bodies also occur in dementia pugilistica and chronic traumatic encephalopathy (Saing et al., 2012; Ling et al., 2017), inflammatory diseases such as subacute sclerosis panencephalitis (Ikeda et al., 1995a, b), and LBDs (Dugger et al., 2014), among other neurodegenerative disorders (Tacik et al., 2016).

Coiled bodies and interfascicular threads in PSP are composed of abnormal tubules of 13 nm–15 nm in diameter and fuzzy outer contours which are immunolabelled with anti-tau antibodies (Arima et al., 1997). Oligodendroglial inclusions are fine and branching in PSP and thick and comma-like in CBD (Komori, 1999; Arima, 2006; Williams, 2006). Differences in the morphology of abnormal tubules in oligodendroglial inclusions in tauopathies probably reflect differing molecular, including tau, composition between these entities (Arima, 2006). Coiled bodies are stained with antibodies against anti-phosphorylated tau antibodies (Fig. 3), and antibodies against 4R-tau, but 3R-tau-immunoreactive oligodendroglial inclusions are also recognized in PiD (Ferrer et al., 2014).

Tau in coiled bodies is hyperphosphorylated at different sites including Thr181, Ser199, Thr231, Ser262, Ser422, Ser202-Thr205 (antibody AT8), Ser396-Ser404 (antibody PHF1) and Thr212/Ser214 (tau-100), and has altered conformation as revealed by antibodies Alz50 (amino acids 5–15) and MC-1 (amino acids 312–322); however, coiled bodies are not stained with tau-C3 (which recognizes tau truncated at aspartic acid 421) (Ferrer et al., 2014). Oligodendrocytes containing hyperphosphorylated tau inclusions coexpress phosphorylated (active) tau kinases p-38, stress-activated kinase/c-Jun N-terminal kinase (SAPK/JNK), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and glycogen synthase kinase-3 (Ferrer et al., 2002, 2003a, c). PP2 A-like phosphatases probably modulate tau phosphorylation (Goldbaum and Richter-Landsberg, 2002).

In contrast to neurons with tangles in AD and tauopathies, the sequence encoded by exon 3 of the tau protein is under-expressed in oligodendroglial coiled bodies in CBD but not in PSP (Feany et al., 1995; Nishimura et al., 1997). Ubiquitin, apolipoprotein E, alpha1-antichymotrypsin and heparan sulfate are all absent from glial inclusions (Ikeda et al., 1998).

Globular glial tauopathy (GGT) is a rare form of 4R-tauopathy with predominant involvement of the white matter, and characterized by the presence of globular inclusions in oligodendroglia and distinct tau-positive inclusions in astrocytes, in addition to deposition in neurons (Molina et al., 1998; Bigio et al., 2001; Berry et al., 2001; Ferrer et al., 2003b; Powers et al., 2003; Clark et al., 2015; Piao et al., 2005; Josephs et al., 2006; Kovacs et al., 2008; Giaccone et al., 2008; Fu et al., 2010; Ahmed et al., 2011; Graff-Radford et al, 2016) (Fig. 4). Neuropathological consensus has classified GGT into three types: type I is usually manifested as frontotemporal dementia and the principal involvement corresponds to the frontal and temporal lobes; type II is commonly manifested by motor involvement and parkinsonism, and affects the corticospinal tracts; and type III presents with frontotemporal dementia, parkinsonism and motor neuron disease, which implies a more generalized distribution of the tauopathy (Ahmed et al., 2013b). This schematic classification has some affect on clinical practice (Burrell et al., 2016).

GGT is mostly sporadic but certain taoupathies linked to *MAPT* mutations show variable amounts of globular inclusions in oligodendrocytes and bizarre astrocytic inclusions resembling sporadic GGT (Tacik et al., 2015; Zarranz et al., 2005, see also Ferrer et al., 2014; Borrego-Écija et al., 2017). Tau phosphorylation sites and conformational modifications described in coiled bodies also occur in globular inclusions in oligodendrocytes; in addition, globular inclusions contain truncated forms of tau at the carboxy-terminal and are ubiquitinated (Ferrer et al., 2014). Therefore, a major difference between coiled bodies and globular glial inclusions is the stage of pre-tangle in the former and the stage of tangle in the latter. Decreased nuclear TPPP/p25α parallels microglial activation, myelin loss and association with tau inclusions in GGT (Rohan et al., 2016).

Small globular oligodendroglial inclusions (called small Pick bodies) are seen in the white matter in PiD (Kovacs, 2015). Rare globular inclusions have been reported in a single case of familial AD (Gelpi et al., 2013).

Protein aggregation in glial cells compromises stress responses and protein degradation pathways. αB-crystallin and other small HSPs are expressed in oligodendroglia (and astrocytes) in tauopathies. However, they do not necessarily co-localize with tau inclusions, thus suggesting generalized stress rather than restricted response in glial cells with abnormal protein aggregates (López-González et al., 2014). It may be posited that stress responses are directed to correcting protein misfolding, and that, to a certain extent, they succeed, and aggregates are not formed in many glial cells.

Ubiquitin-immunoreactivity is found in a minority of coiled bodies but it is almost a constant in globular inclusions in GGT (Ferrer et al., 2014). This might indicate variable involvement of the ubiquitin-proteasome system in the development of oligodendroglial inclusions. Additional information comes from cellular models in which proteasomal inhibition in cultured oligodendrocytes leads to protein aggregate formation (Leik et al., 2013). Histone deacetylase HDAC6 is expressed in oligodendrocytes and its inhibition results in microtubule alteration, and acetylation and phosphorylation of tau (Noack et al., 2014). Tau acetylation inhibits its degradation and contributes to tau aggregation (Min et al., 2010; Cohen et al., 2011). Accordingly, HDAC6 inhibition induces tau acetylation, the formation of protein aggregates, the alteration of stress responses and the impairment of autophagy (Leyk et al., 2015).

A few glial cells colocalize with HSP and ubiquitin thus pinpointing the combined reaction of stress responses and impaired function of the ubiquitin-protesome system (Richter-Landsberg and Bauer, 2004). Further insights linking HDAC6, tau acetylation, tau phosphorylation, stress responses, proteasome and autophagy are exemplified in oligodendroglia cell culture paradigms (Richter-Landsberg, 2016).

Whether the constructs in cell cultures occur in *all* human tauopathies deserves further research. Tau is acetylated in oligodendroglial inclusions in FTLD-tau (Irwin et al., 2013) but apparently not in AGD including grains and coiled bodies (Grinberg et al., 2013). In this way, factors coming into play in individual oligodendrocytes probably have multiple facets in the different tauopathies.

Hyperphosphorylated tau intracytoplasmic filamentous inclusions are commonly seen in transgenic mouse models of tauopathies both in animals overexpressing human tau and those bearing different tau mutations which are causative of familial FTLD-tau.

Tau pathology in glial cells has been generated in transgenic mice overexpressing human tau in neurons and glial cells. In these animals, tau pathology resembling astrocytic plaques and coiled bodies in oligodendrocytes is observed in old mice; these changes

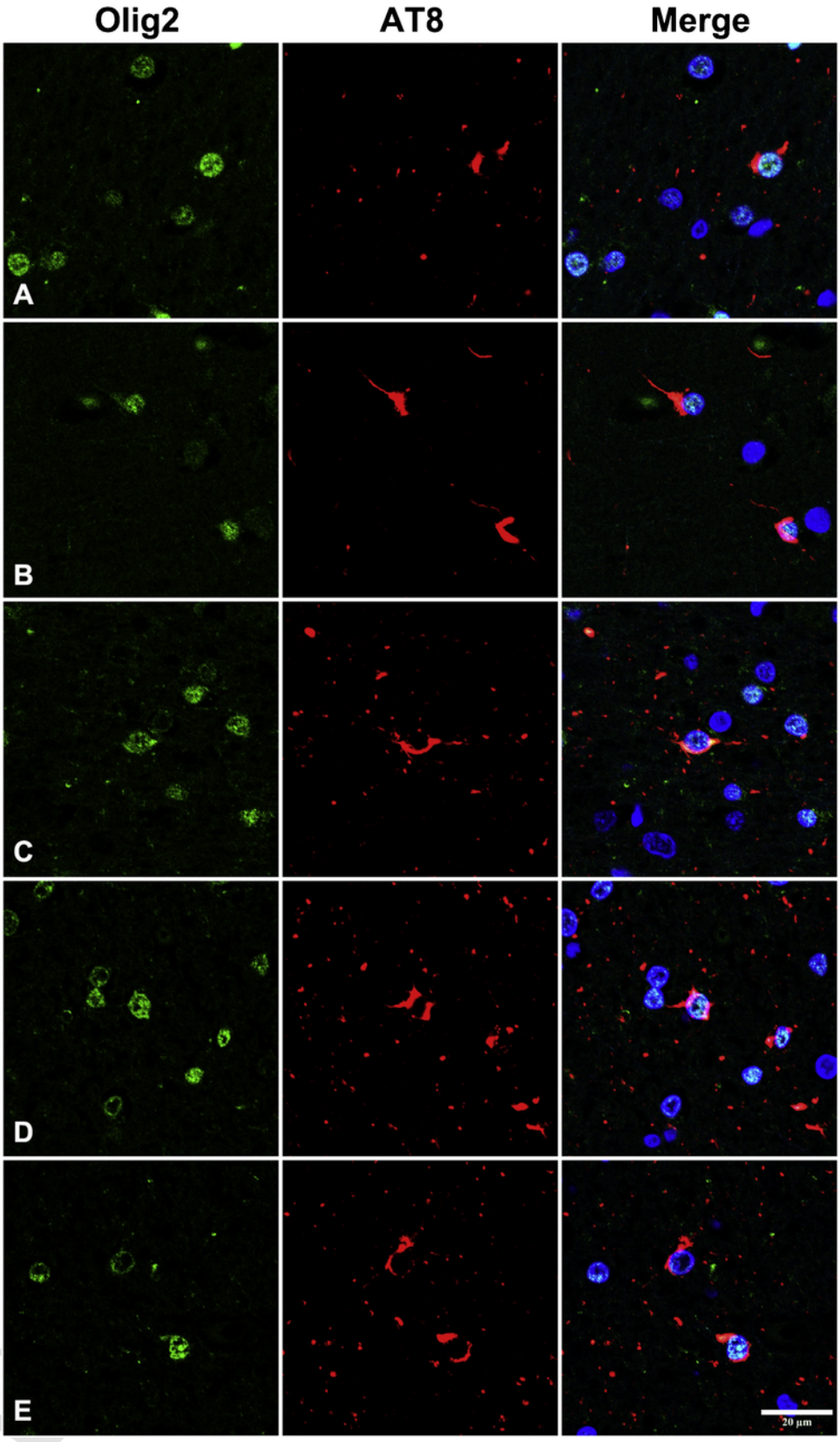

Fig. 3. Double-labelling immunofluorescence and confocal microscopy to Olig2 (green) and AT8 (red) in several tauopathies: A: corticobasal degeneration (CBD); B, C: progressive supranuclear palsy (PSP); D, E: argyrophilic grain disease (AGD). Paraffin sections, nuclei stained with DRAQ5™(blue), bar = 20 µm.

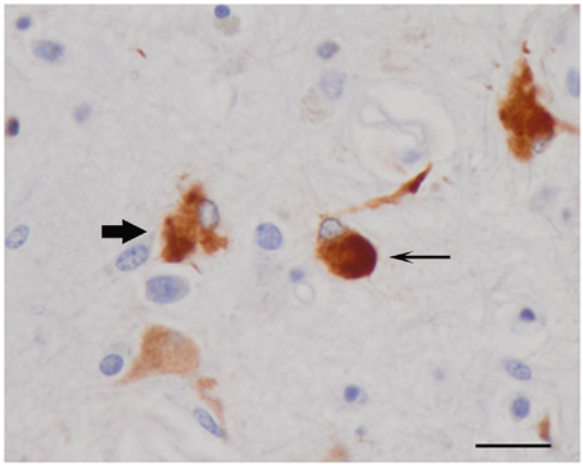

Fig. 4. Tau-immunoreactive oligodendroglial inclusion (thin arrow) in globular glial tauopathy (GGT). An astrocyte with hyper-phosphorylated tau deposits is labelled with a thick arrow. Paraffin sections, AT8 immunohistochemistry slightlhy counterstained with haematoxylin; bar = 25 μm.

are associated with glial and axonal degeneration (Higuchi et al., 2002).

Transgenic mice expressing G272 V tau accumulate abnormal filaments in oligodendrocytes; these filaments are either straight or have a twisted structure with a periodicity of 75 nm, and they are composed of abnormal tau hyperphosphorylated at different sites. Fibrillar oligodendroglial and neuronal inclusions are also seen in the spinal cord (Götz et al., 2001). Transgenic mice bearing P301 L tau develop cytoplasmic neuronal inclusions, and oligodendroglial and astrocytic filamentous inclusions composed of abnormal hyperphosphorylated tau aggregates (Lin et al., 2003). Oligodendroglial inclusions are also seen in transgenic mice bearing the P301S mutation (Fig. 5). Selective overexpression of mutant tau in oligodendrocytes using CNP promoter in mice produces filamentous inclusions in oligodendrocytes and progressive impairment of axonal transport followed by myelin and axonal disruption; these changes precede the appearance of thioflavin-S-positive tau inclusions in oligodendrocytes (Higuchi et al., 2005). Interstingly, endogenous mouse tau is deposited in oligodendrocytes in mice expressing transgenic human tau, in a way that makes evident that mouse tau has the capacity to be recruited and aggregated in oligodendrocytes (Ren et al., 2014).

These models reveal that tau accumulation in oligodendroglial cells is accompanied by axon degeneration and demyelination. White matter damage is further demonstrated in the spinal cord of transgenic mice bearing the P301 L tau mutation (Zher et al., 2004; Lin et al., 2005a, b). Lesions are consistent with vacuolar myelopathy and dying-back axonopathy; myelin debris is engulfed by macrophages whereas oligodendocytes in damaged regions have membrane-bound cytoplasmic inclusions (Lin et al., 2005a, 2005b). Other studies stress the occurrence of active caspase-3-immunoreactive, TUNEL-positive oligodendrocytes in affected white matter, arguing that axonal degeneration is accompanied by apoptosis of oligodendrocytes (Zher et al., 2004). Deleterious effects of abnormal tau in oligodendrocytes are further proven in cultured oligodendrocytes in which the expression of human tau and FTDP-tau mutant tau causes cell death (Richter-Landsberg, 2008).

Defective microtubule network and altered myelination in tau transgenic mice is associated with reduced expression of kinesin which modulates intracellular trafficking; abnormal tau may interfere with kinesin-dependent MBP translocation thus favoring altered myelination in these mice (Carson et al., 1997; Higuchi et al., 2002; Richter-Landsberg, 2008).

Curiously, neuronal expression of P301S tau accelerates OPC differentiation and myelin formation following focal white matter demyelination (Ossola et al., 2016). Whether these changes move in favor of regeneration is not known.

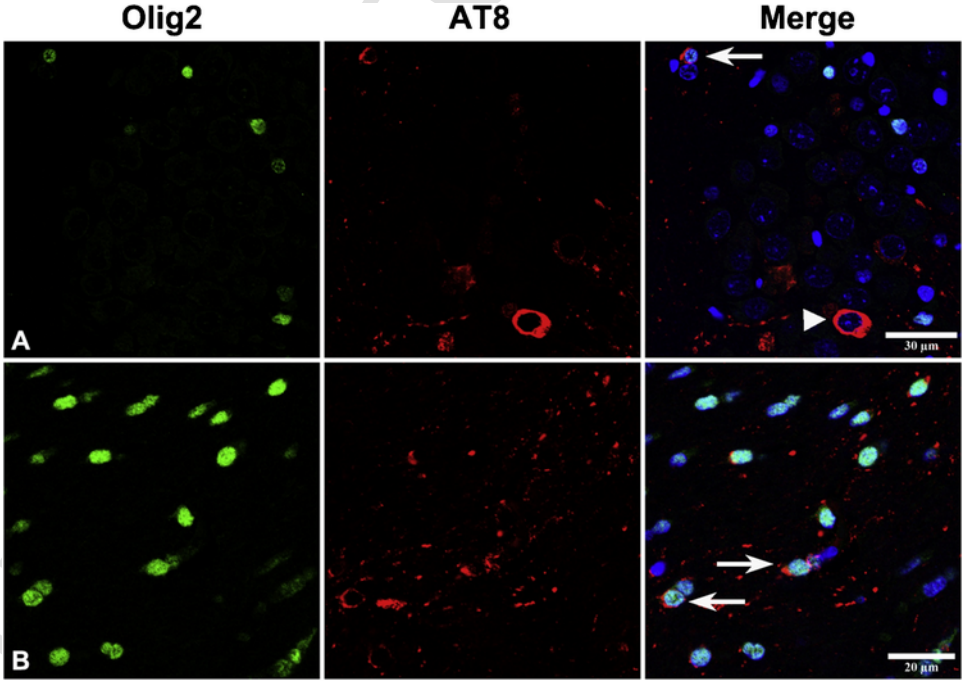

Fig. 5. Hyperphosphorylated tau accumulation in oligodendrocytes in P301S mice aged 8 months (thin arrows). A: hippocampus (one neuron containing tau is labelled with a thick arrow); B: white matter of the somatosensory cortex. Double-labelling immunofluorescence and confocal microscopy to Olig2 (green) and AT8 (red); the figure on the right of the panel is merge of the other two. Paraffin sections, nuclei are visualized with DRAQ5™(blue); A, bar = 30 μm; B, bar = 20 μm.

Tau seeding *in vivo* has been demonstrated in a number of mouse models after inoculation of human brain homogenates (Goedert et al., 2017). Seeding and spreading of abnormal tau occurs after inoculation of brain homogenates from AD and other tauopathies into the brain of transgenic mice overexpressing human tau or mutated tau (Boluda et al., 2015; Clavaguera et al., 2009, 2015; Lewis and Dickson, 2016). The use of transgenic mice is based on the assumption that this substrate facilitates tau seeding and propagation. The characteristics of seeding differ depending on the type of tauopathy, implying that several types of tau species have particular properties (Clavaguera et al., 2013a, b; Boluda et al., 2015; Narasimhan et al., 2017). Seeding of human tau from homogenates of AD and tauopathies with neuronal and glial components is also observed after inoculation into the brain of wild-type mice (Guo et al., 2016; Narasimhan et al., 2017). Tau-immunoreactive oligodendroglial inclusions are observed after inoculation of CBD homogenates but apparently only very rarely or not at all following inoculation of AD homogenates (Boluda et al., 2015). All these experiments have been performed using brain samples with tau pathology only in neurons or in neurons and glial cells. Recent studies have shown that sarkosyl-insoluble fractions of brain homogenates from ARTAG inoculated into the hippocampus of wild-type mice generate intracytoplasmic hyperphosphorylated tau inclusions in astrocytes, oligodendrocytes, fiber tracts and neurons near the site of injection (Ferrer et al., 2018) (Fig. 6). These observations indicate that not only neurons but also astrocytes containing hyperphosphorylated tau have the capability of seeding tau to neurons and glial cells. Moreover, they point to the cardinal role of astrocytopathy in the pathogenesis of neurodegenerative diseases with abnormal protein aggregates, including the participation of oligodendrocyte targets in this process (Ferrer et al., 2018).

9.4. Alzheimer's disease

Alzheimer's disease (AD) is the most frequent cause of cognitive decline and dementia in the elderly. Pathologically, AD is classically defined by the combination of senile plaques composed of different β-amyloid species, and neurons with neurofibrillary tangles (NFTs) containing hyperphosphorylated 3R- and 4R-tau which disturbs microtubule assembly, and results in the formation of paired helical filaments. β-amyloid deposition also occurs in blood vessels, leading to β-amyloid angiopathy, whereas abnormal tau is also accumulated in dystrophic neurites surrounding senile plaques and in neuropil threads (Duyckaerts and Dickson, 2011; Lowe and Kalaria, 2015). NFTs progress from the entorhinal and transentorhinal cortex to the hippocampus, limbic system and cerebral cortex. NFTs also involve in parallel the olfactory bulb, selected nuclei of the brain stem, nuclei of the basal forebrain, amygdala and diencephalon. NFT progression follows a sterotyped pattern which allows the categorization of severity into stages (Braak and Braak, 1991, 1999). β-amyloid deposition and distribution of senile plaques also extends with disease progression but the pattern differs from that of NFTs, at least in sporadic AD (Thal et al., 2002). In addition to these basic alterations, AD exhibits a compendium of biological alterations which modify many molecular pathways and variegated functions (Ferrer, 2012; Braak and Del Tredici, 2015).

Reduced size of the white matter, white matter hyperlucencies and myelin pallor are common abnormalities in AD (Barber et al., 1999; Bartzokis et al., 2003; Gouw et al., 2008; Holland et al., 2008; Radanovic et al., 2013; Amlien and Fjell, 2014; Firbank et al., 2016; Joki et al., 2018). Changes in white matter are parallel but do not correlate with β-amyloid deposition (Roseborough et al., 2017), and, importantly, they are recognized at early stages of the disease (Hoy et al., 2017). The size of the nuclei of oligodendrocytes is reduced in AD (Gagi et al., 2012). In addition, several oligodendroglial nuclei in the white matter show DNA oxidative damage, while other oligodendrocytes exhibit increased expression of p53 as a marker of stress, and a senescent phenotype (Al-Mashhadi et al., 2015; Wharton et al., 2015; Tse and Herrup, 2017).

White matter radiological and neuropathological changes are accompanied by early and progressive reduction in the levels of cholesterol and myelin proteins MBP, PLP and CNP (Vlkolinsky et al., 2001; Roher et al., 2002), and decreased Olig2- and NG2-glia-immunoreactive cells (Behrendt et al., 2013; Nielsen et al., 2013). The mechanisms of oligodendroglial damage are not known, and several factors including inflammation, oxidative stress, apoptosis and tau deposition in neuronal processes have been suggested (Cai and Xiao, 2016). *in vitro* studies show the toxic effect of β-amyloid species on OPCs and oligodendrocytes (Xu et al., 2001; Takao et al., 2004; Desai et al., 2010). Activated microglia induces death of OPCs and limits their function in remaining cells (Pang et al, 2010). Curiously, Bridging interactor 1(BIN1), the second most significant susceptibility locus in late-onset AD, is mainly expressed in mature oligodendrocytes and in white matter tracts (De Rossi et al., 2016). Increased BIN1 expression and BIN1 interaction with tau have been reported (Holler et al., 2014; Sottejeau et al., 2015); BIN1 also interacts with actin (Dräger et al., 2017), together pointing to possible BIN1-linked cytoskeletal alterations in oligodendocytes in AD.

Oligodendroglial cell death and myelin loss occur at early stages in 3xTg-AD mice harbouring the human precursor amyloid protein Swedish mutation, a presenilin knock-in mutation and P301 L tau. Exposure to $A\beta_{1-42}$ increases caspase-3 expression and induces apo-

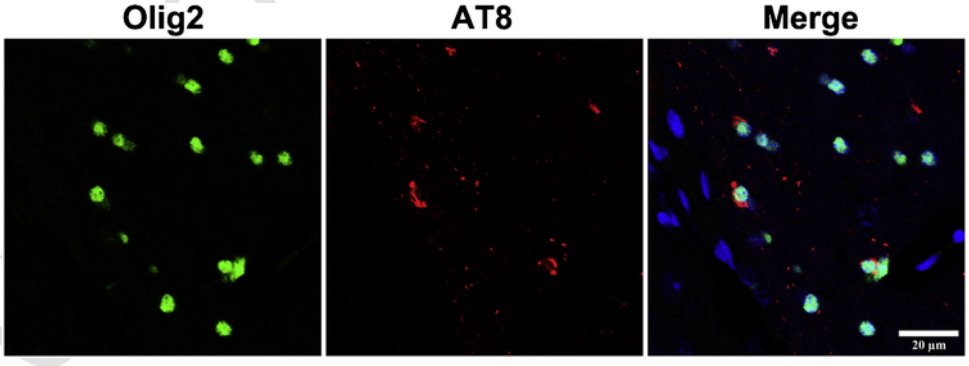

Fig. 6. Hyperphosphorylated tau accumulation in two oligodendrocytes of the corpus callosum of wild-type mice aged ten months following hippocampal inoculation of sarkosyl-insoluble fractions from pure Aging-related tau astrogliopathy (ARTAG) at the age of three months. Double-labelling immunofluorescence and confocal microscopy to Olig2 (green) and AT8 (red); the figure on the right of the panel is merge of the other two. Paraffin sections, nuclei are visualized with DRAQ5™(blue); bar = 20 µm.

tosis of oligodendrocyte precursors *in vitro* that is reversed following viral vector-derived intracellular transport of an antibody against $A\beta_{1-42}$ (Desai et al., 2009, 2010).

These data must be interpreted with caution regarding white matter changes in AD and their relation with altered oligodendrocytes. Vascular pathology, mostly affecting small blood vessels, is practically constant in AD. In addition to β-amyloid angiopathy, atrophy, edema and increased pynocitosis in endothelial cells, atrophy of the muscle cells, thickening and disruption of the basal membrane and increased expression of collagen IV, heparan sulfate, proteoglycans and laminin are detected in capillaries and arterioles. Moreover, aquaporin-4 expression is altered in perivascular astrocytes (Kalaria et al., 1996; Ferrer, 2010). These changes are consistent with chronic hypoperfusion (Kalback et al., 2004).

Tau-immunoreactive inclusions in oligodendrocytes are not characteristic of AD, although coiled bodies can be found in AD combined with other tauopathies such as AGD. However, age-related increase in β-amyloid plaques and β-amyloid angiopathy, tau-positive astrocytes and oligodendrocytes (coiled bodies), and neuritic clusters occurs in housed gorillas (Perez et al., 2013). Curiously, tauopathy but not β-amyloidopathy develops in wild mountain gorillas of similar age (Perez et al., 2016). Intraneuronal and intraoligodendroglial tau accumulation occurs in the temporal cortex in non-human primate cynomolgus monkey before the age of 20 months with poor correlation to the levels of insoluble β-amyloid; AD-related pathology increases at more advanced ages (Oikawa et al., 2010). Tau-immunoreactive oligodendroglial (and neuronal and astrocytic) inclusions composed of straight filaments of 10–14 nm are also found in the brains of aged baboons (Schultz et al., 2000). Available data are consistent with the idea that brain aging in non-human primates is predominantly manifested as a tauopathy with involvement of neurons and glial cells.

9.5. Amyotrophic lateral sclerosis and Frontotemporal lobar degeneration-TDP (ALS/FTLD-TDP)

9.5.1. Amyotrophic lateral sclerosis (ALS)

ALS is a neurodegenerative disease involving the cortical motorneurons, the motorneurons of the spinal cord and selected nuclei of the brain stem, producing spasticity, muscle wasting, difficult swallowing and final respiratory insufficiency. In addition to the motor system, other regions can be affected; the frontal and temporal cortex is damaged in some cases leading to cognitive impairment and dementia of frontotemporal lobe type. Indeed, variable overlap exists between ALS and FTLD (Hortobágyi and Cairns, 2015; Ince et al., 2015).

ALS can be classified as sporadic (sALS) or genetic (gALS), often affecting several members of a family (fALS). The principal gene defects causing adult fALS are mutations in *SOD1* (superoxide dismutase 1), *VAMP* (vesicle associated membrane protein B and C), *CHMP2B* (charged multivesicular body protein 2B), *ANG* (angiogenin), *TARDBP* (transactive response (TAR) DNA binding protein of 43 kD: TDP-43), *FUS* (fused-in-sarcoma), *OPTN* (optineurin), *ATXN2* (ataxin 2), *UBQLN* (ubiquilin 2), *C9Orf72* (chromosome 9 open reading frame 72) and *SQTM1* (sequestosome 1 p62) (Hortobágyi and Cairns, 2015). Of these, *SOD1*, *CHMP2B*, *ANG*, *TARDBP*, *VCP*, *UBQLN*, *C9Orf72*, *FUS* and SQTM1 are also causative of FTLD (Hortobágyi and Cairns, 2015; Ince et al., 2015). The majority of patients suffering from ALS are sporadic with no known mutations; however, hexapeptide repeat expansions in C9Orf72 are recognized in a number of apparently non-genetic ALS.

Loss of large motorneurons (Betz cells) in the motor cortex, degeneration of the pyramidal tracts, loss of motorneurons in selected nuclei of the brain stem and anterior horn of the spinal cord, and myelin pallor of the corresponding optic nerves and anterior roots of the spinal cord are the principal neuropathological characteristics of ALS. Curiously, oculomotor nuclei in the brain stem and Onuf's nuclei in the lower spinal cord are spared in classical forms. Additonal involvement of the Clarke's column, posterior spinocerebellar tracts and posterior tracts occurs in cases bearing SOD1 mutations. As indicated before, other regions of the brain, mainly the frontal and temporal cortex, may be affected in some cases (Hortobágyi and Cairns, 2015; Ince et al., 2015).

In addition to neuron loss, astrogliosis and microgliosis are accompanying reactions in the affected regions. Proximal axonal balloonings filled with neurofilaments are rather common in rapidly progressing cases. Remanining motorneurons show variable alterations including disruption of the Golgi complex and intracytoplasmic inclusions which have the morphology of skein-like inclusions, round inclusions and small granular deposits, all of them containing abnormal TDP-43 (Ince et al., 2015; Hortobágyi and Cairns, 2015). Bunina bodies composed of cystatin C and transferrin are also concurrently observed. fALS due to mutations in fused-sarcoma (FUS) do not contain these types of TDP-43 inclusions but rather round basophilic neuronal inclusions composed of FUS, ubiquitin and p62 (Mackenzie and Neumann, 2017). Therefore fALS-FUS cannot be considered within the spectrum of TDP-43 proteinopathgies.

Staging of TDP-43 pathology in ALS has been proposed in line with similar categorization stages in AD and PD (Brettschneider et al., 2013). In stage 1, abnormal TDP-43 inclusions are restricted to motorneurons of the primary motor cortex, motorneurons of the anterior horn of the spinal cord and certain motor nuclei of the brain stem. In stage 2, abnormal TDP-43 extends to neurons of the reticular formation of the brain stem and deep nuclei of the cerebellum. In stage 3, TDP-43- immunoreactive inclusions are also noted in the prefrontal cortex and basal ganglia. In stage 4, the hippocampal formation and the anteromedial areas of the temporal cortex show TDP-43-immunoreactive inclusions.

In a refinement of this staging proposal, posterior assessment identifies oligodendroglial TDP-43-immunoreactive inclusions as an early pathological event in the spinal cord in ALS, and occasional involvement of the oculomotor nucleus and sometimes the Onuf's nucleus, at advanced stages of the disease, categorized as stage 5 (Brettschneider et al., 2014b)

9.5.2. Frontotemporal lobar degeneration-TDP

Frontotemporal lobar degeneration-TDP defines a subgroup of non-tau FTLD cases with ubiquitin-immunoreactive inclusions whose main component is abnormal TDP-43. About 50% are familial and mainly linked to mutations in granulin (*GRN*), *TARDBP*, valosin (*VAL*) and *C9Orf72*. Clinically, FTLD-TDP is manifested as behavioural variant, progressive non-fluent aphasia or semantic dementia. Pathologically, the frontal and temporal lobes are atrophic, while the cerebral cortex in these regions shows neuron loss and spongiosis in the upper cortical layers, and astrocytic gliosis; the white matter shows variable reduction and myelin pallor. The hallmarks of FTLD-TDP are nuclear TDP-43 mislocalization, neuronal intracytoplasmic and intranuclear inclusions, and aberrant neurites containing abnormal TDP-43. The majority of tau-negative, TDP-43-negative FTLD cases with intracytoplasmic inclusions contain FUS, and they are considered FUS-proteinopathies (Neumann et al., 2009; Urwin et al., 2010).

Four FTLD-TDP neuropathological types have been proposed depending on the amount and distribution of the types of inclusions which roughly match with genetic variants (Mackenzie et al., 2009; Mackenzie and Neumann, 2011; Bigio, 2011a; Cruts et al., 2013; Ash et al, 2013; Hortobágyi and Cairns, 2015). In addition to

the cerebral neocortex and hippocampus, other brain regions are affected, particularly the amygdala, striatum, thalamus, several nuclei of the brain stem and motorneurons of the spinal cord. Characteristic TDP-43-negative, p62- and ubiquitin-positive inclusions are noted in the granular layer of the cerebellum in FTLD-TDP linked to C9Orf72 hexanucleotide repeat expansions (Simón-Sánchez et al., 2012). Further molecular properties point to ALS/FTLD-TDP linked to C9Orf72 repeat expansions as a particular type within TDP-43-proteinopathies (Bigio, 2011b, 2012).

Rather than a stage categorization, as applied in other neurodegenerative diseases, sequential distribution of TDP-43 pathology has been proposed in FTLD-TDP (Brettschneider et al., 2014a). Pattern I (lowest burden of pathology) is characterized by TDP-43 inclusions in the orbital gyri, gyrus rectus and amygdala; pattern II affects the middle frontal and anterior cingulated gyrus, anteromedial temporal lobe areas, superior and medial temporal gyri, striatum, and red nucleus; stage III involves the motor cortex, bulbar somatosensor neurons and the anterior horn of the spinal cord; finally, pattern IV exhibits, in addition, involvement of the visual cortex (Brettschneider et al., 2014a).

9.5.3. Common protein inclusions: common dysfunctions?

As mentioned above, neuronal intracytoplasmic TDP-43-immunoreactive inclusions are neuropathological hallmarks of the majority of cases with ALS and, by definition, of all cases of FTLD-TDP (Arai et al., 2006; Neumann et al., 2006). The presence of TDP-43 inclusions in human and transgenic mice bearing SOD1 mutations is controversial (Cai et al., 2005; MacKenzie et al., 2007; Tan et al., 2007; Turner et al., 2008; Shan et al., 2009; Maekawa et al., 2009; Okamoto et al., 2011).

TDP-43 in ALS/FTLD-TDP is abnormally phosphorylated (P-TDP43), has abnormal solubility, presents truncated, pathogenic forms (Winton et al., 2008; Zhang et al., 2009) and has characteristics of amyloid (Bigio et al., 2013). This abnormal TDP-43 together with normal TDP-43 translocates from the nucleus to the cytoplasm giving rise to intracytoplasmic neuronal inclusions and aberrant neurites which are linked to toxic effects on neurons (Hasegawa et al., 2008; Nishimura et al., 2010; Barmada et al., 2010; Yang et al., 2010). Yet the effects of abnormal TDP-43 are more complex, encompassing gain and loss of function (Halliday et al., 2012). Altered proteasomal function and autophagy play a role in the process of protein aggregation and deposition in affected cells (Urushitani et al., 2010; Wang et al., 2010; van Eersel et al., 2011; Barmada et al., 2014). Direct evidence of this involvement is the immunoreactivity to ubiquitin and p62 of typical inclusions in ALS/FTLD-TDP.

In addition to neuronal and neuritic TDP-43-positive inclusions, oligodendroglial TDP-43-immunoreactive inclusions are found in the anterior horn of the spinal cord in ALS (Brettschneider et al., 2013; Rohan et al., 2014; Hortobágyi and Cairns, 2015) (Fig. 7). P-TDP-43-immunoreactive oligodendroglial inclusions in ALS are also encountered in the motor, sensory and premotor cortex, but not in the corpus callosum, cingulum or lateral tracts of the spinal cord (Fatima et al., 2015).

TDP-43 oligodendroglial pathology in the deep layers of the cerebral cortex and white matter is a characteristic feature in FTLD-TDP (Neumann et al., 2007) (Fig. 8). It is more marked in frontal and temporal lobes but the brainstem and spinal cord are also affected (Neumann et al., 2007).

Cerebral and cerebellar white matter damage when compared with controls is observed in ALS cases bearing C9Orf72 repeat ex-

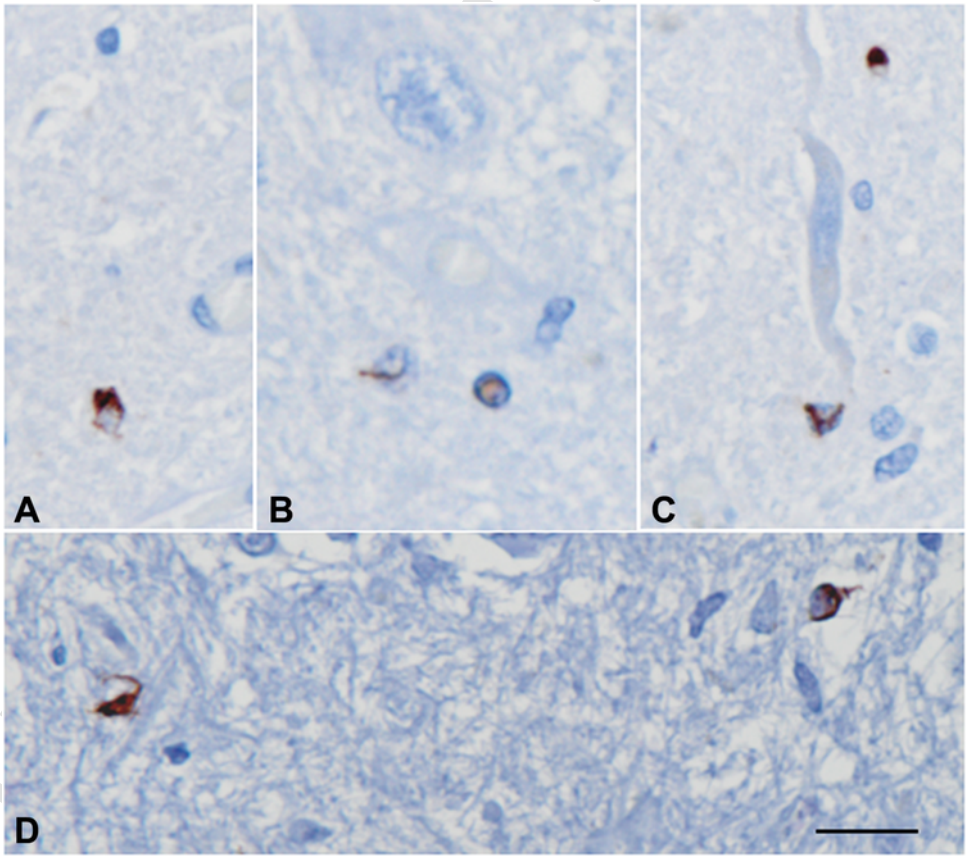

Fig. 7. Phosphorylated TDP-43-immunoreactive oligodendroglial inclusions in the white matter of the lumbar spinal cord in amyotrophic lateral sclerosis (ALS). Paraffin sections; immunohistochemistry with anti-phosphorylated TDP-43 antibody slightly counterstained with hematoxylin; bar = 25 μm.

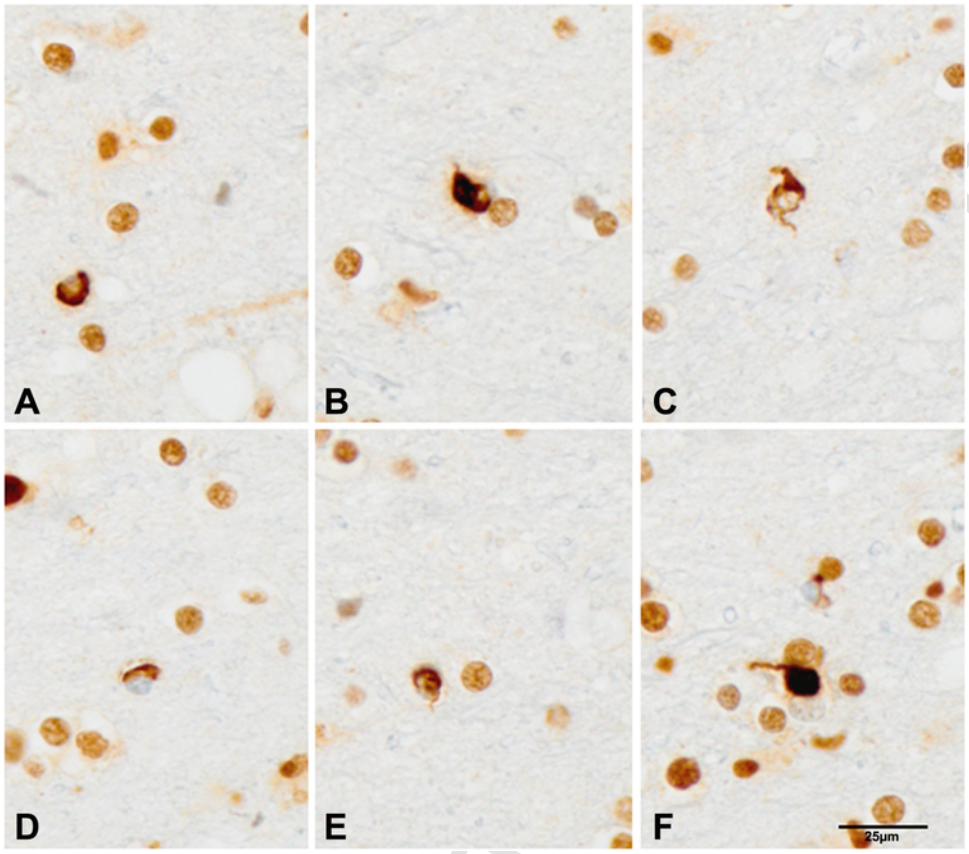

Fig. 8. TDP-43-immunoreactive oligodendroglial inclusions in the white matter in frontotemporal lobar degeneration-TDP43 (FTLD-TDP). A-C: linked to repeat expansions in *C9Orf72*; D-F: sporadic cases with not known mutations. Paraffin sections; immunohistochemistry with anti-TDP-43 antibody, slightly counterstained with hematoxylin; bar = 25 μm.

pansions (Bede et al., 2013; Agosta et al., 2017). White matter involvement is common in FTLD-TDP, and it is more marked in FTLD-TDP in patients bearing *GRN* mutations when compared with patients bearing C9Orf72 repeat expansions (Ameur et al., 2016; Papma et al., 2017; Sudre et al., 2017).

Oligodendroglial cells have been implicated in the pathogenesis of ALS in a cascade of effects which includes ROS production and damage, recruitment of alterations derived from activated microglia and astrocytes, effects of toxic substances produced by damaged neurons and abnormal responses of NG2-glia (Ince et al., 2011; Nonneman et al., 2014). However, most studies of this are based on SOD1 transgenic mice, which are used as a model for a minority of cases with fALS responding to unique pathogenic mechanisms not shared by other forms of familial and sporadic ALS. Oligodendroglial SOD1 toxicity in transgenic mice can barely be translated to sALS (Ferraiuolo et al., 2016). In the mouse model of SOD1 mutation, altered oligodendrocytes appear in the grey matter before disease onset and they increase with disease progression; abnormal oligodendrocytes have reduced MBP and MCT1 expression, thus resulting in altered myelin formation and impaired support to axons (Lee et al., 2012; Philips et al., 2013; Morrison et al., 2013).

MCT1 protein levels in motor cortex and MCT1 mRNA expression in the spinal cord are also reduced in sALS (Lee et al., 2012): This is important information, revealing altered oligodendroglial function in oligodendrocytes in common forms of ALS. Moreover OPCs increase in number in motor cortex, but OPC differentiation is impaired and myelination diminished, in transgenic mice and in human ALS (Kang et al., 2013).

Levels of oligodendrocytic connexin32 and connexin 47 are reduced in the ventral horn of the spinal horn in SOD1-transgenic mice, implying that oligo-astroglial interactions are disturbed in fALS (Cui et al., 2014).

Prion-like spreading has been postulated in ALS (Polymenidou and Cleveland, 2011; Kanouchi et al., 2012; Grad et al., 2015). The description of TDP-43 stages in ALS progression points to the likelihood of abnormal TDP-43 spreading (Brettschneider et al., 2013). *in vitro* studies suggest the possibility of oligodendroglia involvement in the spreading of TDP-43 pathology and subsequent neuronal degeneration in ALS. In favor of this hypothesis is the observation of TDP-43 aggregates in TDP-43-transfected neurons, astrocytes and oligodendrocytes under conditions of proteasome inhibition; aggregates from dying cells are incorporated into neighbouring cells thus facilitating spreading of TDP-43 aggregates *in vitro* (Ishii et al., 2017). However, TDP-43 oligodendroglial inclusions are not found in deep corticospinal and other white matter tracts from the motor cortex, and as a consequence the propagation of pathology between neurons may not involve oligodendrocytes (Fatima et al., 2015).

FTLD-TDP linked to *GRN* mutations has a unique combination of neuronal and glial inclusions. In addition to neuronal and glial TDP-43-immunoreactive aggregates, other abnormal proteins are consistently recognized in the cerebral cortex including 3R- and 4R-tau neuronal pre-tangles and tau-immunoreactive astrocytes and oligodendrocytes, together with α-synuclein-positive oligodendroglial cells (Hosokawa et al., 2017).

TDP-43 neuronal and oligodendroglial inclusions are also found in the brains of AD and DLB but not in PD and tauopathies. TDP-43-immunoreactive neuronal inclusions predominate in the hippocampus and amygdala where they rarely co-localize with neurofibrillary tangles or α-synuclein inclusions. No co-localization of TDP-43,

α-synuclein and tau is seen in oligodendroglial cells (Higashi et al., 2007).

9.6. Creutzfeldt-Jakob's disease (CJD) and other prion diseases

Prion diseases or prionopathies are a group of transmissible encephalopathies linked to the prion protein (PrP^{C}) which is converted into an abnormally conformed protein named prion (PrP^{SC}). PrP^{SC} is pathogenic and aggregates in brain and other tissues. Human prion diseases are sporadic, iatrogenic or genetic Creutzfeld-Jakob's disease (CJD), Gerstmann-Straüsler-Scheinker (GSS) disease, and fatal familial insomnia (FFI) due to mutations in *PRNP* gene. Animal prion diseases are typical and atypical scrapie in sheep and goat, chronic wasting disease in deer, elk, moose and reindeer, and bovine spongiform encephlalopathy in cattle (Prusiner, 2004; Head et al., 2015).

Characteristic neuropathological lesions are neuron loss, spongiform change (vacuolization of the neuropil due to extreme swelling of neuronal processes), neuronal vacuolization and deposition of PrP^{SC} in the neuropil forming synaptic-like inclusions, plaque-like, linear and perineuronal deposits, and neuronal aggregates in some cases. This is accompanied by marked astrogliosis and reactive microgliosis (Gambetti et al., 2011; Budka et al., 2011; Parchi et al., 2011; Ghetti et al., 2011a, b; Head et al., 2015).

PrP^{C} is normally expressed not only in neurons but also in astrocytes and oligodendrocytes. PrP mRNA expression is similar in glial cells and neurons and doubles during post-natal development in hamsters and rats (Moser et al., 1995). Functions of PrP^{C} during development include modulation of the differentiation of human stem cells into neurons, astrocytes and oligodendrocytes; silencing PrP surpresses differentiation of OPCs into neurons, astrocytes and oligodendroglia (Leey and Baskakov, 2014). This observation is in line with previous studies showing that PrP^{C} during development and adulthood controls OPC proliferation and oligodendroglial differentiation; PrP^{C} knock-out mice show increased OPC proliferation, decreased oligodendroglial differentiation and increased numbers of OPCs in adulthood without changes in myelination (Bribián et al., 2012). The effect of PrP upon stem/progenitor cell signaling is through modulation of Notch (Martin-Lannere et al., 2017).

Little is known about the molecular pathology of oligodendrocytes in prion diseases. Yet recent studies have shown preserved expression of *OLIG1*, *OLIG2*, *SOX10, NG2* and genes involved in myelination but *GALC* (coding for galactosylceramidase), *SLC2 A1* (solute carrier family 2 member 1: glucose transporter member 1: GLUT1) and *MCT1* (monocarboxylic acid transporter 1) mRNA expression levels significantly reduced in the frontal cortex in CJD MM1 and CJD VV2 (Andrés-Benito et al., 2018).

Prion diseases are the paradigm of transmissible neurodegenerative disease in which the infectious agent is not a nucleic acid but a protein. Prion protein (PrP^{C}), encoded by *PRNP*, is normal in the brain where it has a number of physiological functions (Wulf et al., 2017). PrP^{SC} has the same amino acid sequence as PRP^{C} (excepting in mutated forms due to mutations in *PRNP*) but with abnormal conformation which confers unique properties to the pathogenic protein, mainly resistance to several physical and chemical agents, toxic effects on neurons, and, importantly, the capacity to transmit the same abnormal conformation to PRP^{C} under physical contact between PrP^{SC} and PrP^{C} (Prusiner, 1982; Prusiner et al., 1998; Prusiner, 2004; Collinge and Clarke, 2007; Aguzzi et al., 2008; Aguzzi and Falsig, 2012; Collinge, 2016). Recent studies have shown that human astrocytes have the capacity to take up and degrade normal and protease-resistant prion protein (Choi et al., 2014) and that they can transfer PrP^{SC} to neurons via nanotubules (Victoria et al., 2016) thereby contributing to prion disease progression.

Oligodendrocytes are apparently resistant to PrP^{SC} infectivity (Prinz et al., 2004). However, axon and myelin damage in human, experimental scrapie and bovine spongiform encephalopathy is well documented by optical and ultrastructural examination (Liberski et al., 1992). Abnormal interactions between oligodendroglia and astrocytes are observed in experimental CJD and scrapie (Liberski et al., 1997), as is engulfment of oligodendrocytes by hypertrophic astrocytes in the white matter in CJD (Shintaku and Yutani, 2004). Moreover, PRP^{SC} is localized as arrays adjacent to myelin fibers in the cerebrum and cerebellum in CJD (El Hachimi et al., 1998). This is borne out by the observation of PrP in the inner mesaxon and paranodal cytoplasm of oligodendroglia in atypical (but not in classical) scrapie, thus supporting the idea that certain prion strains may interfere in trafficking between axons and oligodendroglia (Jeffrey et al., 2017). Altered astrocyte/oligodendrocyte interactions are probably important in the pathogenesis of CJD and other glial prionopathies. The lack of information on this matter invites further inquiry. Rarely, PrPRes can be seen in the nucleus and perinuclear region in oligodendrocytes in CJD (Fernandez-Vega et al., 2018) (Fig. 9).

10. Final comments

There is extensive information about the structure and function of oligodendrocytes, oligodendroglial precursors, diversity of precursors and adult oligodendroglial cells, signaling pathways modulating maturation and development of myelinating cells, interactions of oligodendrocytes and neurons and astrocytes, and participation of oligodendrocytes in energy metabolism, as well as mainte-

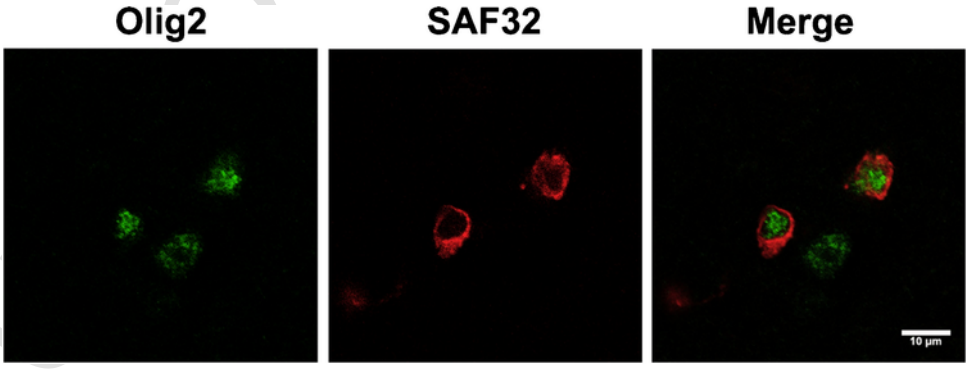

Fig. 9. Double-labelling immunofluorescence and confocal microscopy with antibodies Olig2 (green) and SAF32 (red) in Creutzfeldt-Jakob disease (CJD) type VV2. Perinuclear PrP^{SC} deposition is found in two oligodendrocytes in the subcortical white matter. Paraffin sections, nuclei stained with DRAQ5™(blue), bar = 10 µm.

nance of axon integrity and the normal functioning of the central nervous system. Oligodendrocytes can be damaged following ischemia, trauma, and inflammation of the central nervous system. The term oligodendrogliopathy refers to the role of altered oligodendrocytes in the pathogenesis of aging and certain neurological diseases. Oligodendrogliopathy has been recognized in neurodegenerative diseases with abnormal protein aggregates in which abnormal proteins (i.e. α-synuclein, tau, TDP-43 and PrP) accumulate in the brain, including multiple system atrophy, Lewy body diseases (such as Parkinson's disease and Dementia with Lewy bodies), sporadic and genetic tauopathies, Alzheimer's disease, amyotrophic lateral sclerosis, frontotemporal lobar degeneration linked to TDP43-proteinopathy, and Creutzfeldt-Jakob's disease. In most of these disorders, abnormal protein aggregates accumulate in oligodendrocytes (in addition to neurons and astrocytes). Such deposits are not mere bystanders but rather are associated with functional alterations in oligodendrocytes which impair myelination and energy transfer to neurons and axons, and which disrupt the oligodendrocyte/astrocyte syncytium that maintains homeostasis in the central nervous system. Moreover, functional alterations in oligodendrocytes are also detected in the absence of oligodendroglial inclusions in certain diseases. These aspects are emerging as cardinal factors in the pathogenesis of neurodegenerative diseases with abnormal protein aggregates. Despite recent advances, work is still needed to identify oligodendroglial signaling pathways altered in neurodegenerative diseases with abnormal protein aggregates, the regeneration capacities of oligodendrocyte precursors, and the factors that can contribute to the restoration of oligodendroglial function in these disorders.

Conflict of interests

No relevant data.

Uncited references

Armstrong et al. (2010), Belachew et al. (2003), Cai et al. (2015), Crawford et al. (2014), Davidson et al. (1998), Mobius et al. (2008), Nagaishi et al. (2011), Tawk et al. (2011), Vigano and Dimou (2016) and Zehr et al. (2004).

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