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REVIEW

Autophagy in white matter disorders of the CNS: mechanisms and therapeutic opportunities

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Abstract

Autophagy is a constitutive process that degrades, recycles and clears damaged proteins or organelles, yet, despite activation of this pathway, abnormal proteins accumulate in neurons in neurodegenerative diseases and in oligodendrocytes in white matter disorders. Here, we discuss the role of autophagy in white matter disorders, including neurotropic infections, inflammatory diseases such as multiple sclerosis, and in hereditary metabolic disorders and acquired toxic-metabolic disorders. Once triggered due to cell stress, autophagy can enhance cell survival or cell death that may contribute to oligodendrocyte damage and myelin loss in white matter diseases. For some disorders, the mechanisms leading to myelin loss are clear, whereas the aetiological agent and pathological mechanisms are unknown for other myelin disorders, although emerging studies indicate that a common mechanism underlying these disorders is dysregulation of autophagic pathways. In this review we discuss the alterations in the autophagic process in white matter disorders and the potential use of autophagy-modulating agents as therapeutic approaches in these pathological conditions.

Keywords: white matter disorders; autophagy; demyelination; multiple sclerosis; therapy; demyelinating disease; leukodystrophy

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Introduction

Neurological diseases pose a major public health challenge due to the increasing ageing community. A common pathological feature of many neurological diseases is myelin damage that occurs as a primary event or arises secondarily to neuronal, axonal damage and infections. Here, we focus on white matter disorders (WMDs) that primarily affect the myelin in the CNS [1] and are acquired as a result of infection or due to autoimmunity, or occur as a consequence of genetic mutations. Many of these diseases show increased cell death and have limited therapeutic options available (Table 1).

A prominent CNS demyelinating disease in young adults is multiple sclerosis (MS), which affects one in 1000 people in the UK and the Netherlands, and an estimated 2.3 million cases worldwide. Myelin damage, inflammation and neurodegeneration are key pathological hallmarks in MS. Although MS has been described for many years, the pathogenic processes are still largely enigmatic, and the disease is still inadequately controlled. A similar disease to MS is acute disseminated encephalomyelitis (ADEM), an immune-mediated demyelinating CNS disorder with a predilection to early childhood. Children with ADEM often present with acute neurological deficits following infections. Although the outcome after treatment is generally favourable, therapies are not absolute (Table 1).

More severe yet less common are genetic WMDs or leukoencephalopathies that cause devastating CNS damage in children but are also observed in adults. Leukodystrophies arise as a result of genetic mutations in myelin sheath formation and maintenance, some of which include abnormalities in autophagy pathways that lead to insufficient clearance of accumulated proteins. In these disorders, demyelination, axonal damage and neurodegeneration leads to a spectrum of severe clinical disabilities and early death [14,20]. There is no effective therapy for these diseases, which include, for example, vanishing white matter (VWM), Alexander's disease and X-linked adrenoleukodystrophy (X-ALD).

WMDs also arise following neurotropic infections. These include progressive multifocal leukoencephalopathy (PML), measles, mumps, rubella and Lyme's disease. Although the aetiological agents in these diseases are known, the exact pathological mechanisms leading to myelin damage are unclear, except for PML, in which polyomavirus JC virus lyses the oligodendrocyte.

Table 1. CNS WMDs, cell death mechanisms and therapies.

Type	Disease example	Clinical symptoms	Pathology	Causative factor	Cell death mechanism	Therapy	Reference
Acquired disorders							
Inflammatory	MS	Sensory loss, motor deficits, cognitive changes	Inflammation, demyelination, axonal loss and gliosis	Not known	Viral infection Pathogenic T- and B-cells	Targeting immune response	[2]
	NMO	Vision and spinal cord function loss	Lesions in optic nerve and spinal cord. Loss of AQP4 expression	Antibodies against AQP4	Antibody mediated	Targeting immune response	[3]
	ADEM	Motor and neurocognitive deficits	Widespread CNS inflammation and demyelination	Infection	Autoimmune	Immune therapy	[4]
	AHL	Rapid onset fever, neck stiffness, fatigue, headache, nausea, vomiting, seizures, coma	Inflammatory haemorrhagic demyelination of the white matter	Follows viral and bacterial infections and vaccinations	Autoimmune reaction to viral antigens	Steroids and plasma exchange	[5]
Infectious	PML	Progressive weakness, motor deficits, cognitive changes	Focal areas of demyelination	Polyomavirus JC virus replication	Viral cytotoxicity	No effective therapy	[6]
	SSPE	Progressive neurological and psychological deterioration. Seizures, ataxia, photosensitivity, spasticity, coma	Viral inclusion bodies in neurons, neuronal damage and loss	Abnormal viral replication in neurons	Persistent infection with MeV	No effective therapy. Anti-convulsive therapy for palliative care	[7]
	Congenital cytomegalovirus	Hearing loss, vision impairment, learning disability	Encephalitis, microglial activation	Virus inhibits NSPC proliferation and differentiation. Neuronal cell loss	Neuronal apoptosis, autophagy	Ganciclovir or valganciclovir	[8]
Toxic-metabolic	Paraneoplastic syndrome	Depends on tumour, e.g. NMO		Tumour expressing CNS antigens	Not reported	IVIG	[9]
Hypoxic–ischaemic	Binswanger disease	Vascular cognitive impairment and dementia	Chronic microvascular leukoencephalopathy, white matter lesions, axonal damage, BBB damage	Endothelia cell dysfunction	Not reported	No effective therapy	[10]
	Cerebral hypoxia and ischaemia in newborns	Cerebral palsy, visual, auditory, motor and behavioural problems. Epilepsy, developmental delay, autism	Diffuse white matter damage, gliosis, decreased oligodendrocytes	Damage to neural stem cells and oligodendrocyte progenitors in the SVZ	Increased glutamate, free radicals, apoptosis autophagy	Hypothermia	[11]
Traumatic	Diffuse axonal injury, chronic traumatic encephalopathy	Dependent on location of injury - motor, memory, neuropsychological changes	Axonal damage, tau accumulation, secondary white matter damage, astrogliosis	White matter loss associated with astrogliosis and microglia activation	Glutamate excitotoxicity, intracellular Ca^{2+} accumulation, ROS production	Anti-CD11d, progesterone, valganciclovir tacrolimus, moderate hypothermia (32–33 °C 1 h)	[12]

(Continues)

Table 1. Continued

Type	Disease example	Clinical symptoms	Pathology	Causative factor	Cell death mechanism	Therapy	Reference
Genetic disorders							
Lysosomal storage	Metachromatic leukodystrophy	Gait abnormalities, spasticity, ataxia, polyneuropathy psychosis, cognitive decline	Demyelination, sparing of U fibres. Eosinophilic granules in macrophages, metachromasia	Decrease in arylsulfatase A1. Sulphated glycolipid accumulation in myelin	Sulphatide accumulation induces apoptosis *in vitro*	HSCT, enzyme replacement therapy, gene therapy	[13]
Peroxisomal	X-ALD	Ataxia, dementia, behavioural changes, hyperactivity	Increased saturated VLCFA in serum. Progressive demyelination	Mutations in *ABCD1* gene	VLCFA accumulation in CNS	Allogeneic HSCT	[14]
Mitochondrial dysfunction with leukoencephalopathy	Leber's hereditary optic neuropathy	Acute/subacute painless central visual loss	Loss of retinal ganglion cells. Optic nerve degeneration	Mitochondrial DNA mutations	Proposed to be apoptotic	Antioxidants, experimental gene therapy	[15]
Nuclear DNA repair defects	Cockayne syndrome	Growth and development failure, accelerated, aging	Patchy myelin loss, white matter atrophy, neuronal loss, astrocytic gliosis, microglia nodules	Mutations in *CSA* or *CSB* genes. Lack of repair of damaged nuclear and mitochondrial DNA	Apoptotic cell death	Diet restriction or high fat diet, vitamin D. Otherwise no cure	[16]
Defects in genes encoding myelin proteins	Pelizaeus–Merzbacher disease	Dystonia, ataxia, nystagmus, spasticity, mild cognitive decline	Splitting and decompaction of myelin sheaths, axonal spheroids	Mutations in *PLP1* and accumulation of aberrant protein, or *GJC2* mutation	UPR-induced apoptotic pathway	Experimental neural stem cell and glial progenitor cell transplantation	[17]
Amino acid and organic acid metabolism disorders	Canavan disease	Macrocephaly, loss of head control, developmental delay, hypotonia and spasticity	Diffuse spongiform white matter degeneration, dysmyelination and intramyelinic oedema	Mutation in *ASPA* encoding aspartoacylase and accumulation of NAA	Not reported	No effective therapy	[18]
Miscellaneous	Alexander disease	Macrocephaly, dementia, spasticity, developmental delay	Myelin damage. Elevated GFAP in cerebrospinal fluid. Rosenthal fibres	*GFAP* mutation	Reduced GLT-1, increased autophagy in astrocytes	No effective therapy	[19]
	VWM	Spasticity, loss motor function, epilepsy, ataxia	Progressive demyelination	Mutations in *EIF2B1–EIF2B5*	Increased cellular stress	No effective therapy	[20]
	CADASIL	Migraines, TIAs, dementia, apathy, depression	Diffuse white matter lesions, subcortical infarcts. Granular osmiophilic material in small vessels	*NOTCH3* mutation	Protein misfolding and receptor aggregation	No effective therapy	[15]

BBB, blood–brain barrier; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; GFAP, glial fibrillary acidic protein; HSCT, haematopoietic stem cell therapy; IVIG, intravenous immunoglobulins; NMO, neuromyelitis optica; NSPC, neural stem/progenitor cells; SSPE, subacute sclerosing panencephalitis; SVZ, subventricular zone; TIA, transient ischaemic attack.

For most WMDs there is an urgent unmet clinical need for therapy, as these diseases are currently inadequately controlled (Table 1). A common pathological feature observed in many WMDs is increased cellular stress [21–24], a process that activates the unfolded protein response (UPR). When this response is impaired, apoptotic pathways are activated to remove damaged cells [23] and in many cases increased stress also activates autophagic pathways. Autophagy is a fundamental and conserved lysosomal degradation pathway activated in response to stress. It is important for cell health and growth by maintaining a balance between synthesis and degradation of proteins and organelles [25]. The process acts as a garbage collector to recycle damaged proteins and organelles, a critical event during development, homeostasis and differentiation of cells in mammals. Autophagy can be distinguished into three different categories based on the route of action: chaperone-mediated autophagy, microautophagy and macroautophagy. As macroautophagy has been the most extensively studied and understood, this review will focus on macroautophagy (hereafter termed autophagy) in WMDs. When autophagy is impaired, there is no capacity to degrade damaged organelles, misfolded proteins or invading microorganisms, leading to long-term negative consequences and cell death. The impact of autophagy depends on the disease. Autophagy has been proposed to play a pathogenic role in neurodegenerative diseases including Parkinson's disease [26], Alzheimer's disease [27] and amyotrophic lateral sclerosis [28]. For other diseases, such as MS, X-ALD, VWM or post-infectious WMDs, little is known about the role of autophagy.

Autophagy can have a dual function based on the circumstances. On one hand the autophagic process can be protective; on the other it can be destructive for cells. Autophagy can act as a survival mechanism to prevent oxidative stress and genomic instability by constitutively eliminating defective proteins and organelles, generating nutrients and providing energy for the cell. In this way, autophagy plays a neuroprotective role, promotes cell survival and protects from neurodegeneration. In contrast, under certain conditions, for example excessive upregulation of autophagy or long-term exposure to autophagy, cell death can be triggered. The mechanism by which autophagy induces cell death is not clearly understood. Autophagy-induced cell death might be apoptosis related as autophagy and apoptosis share regulators such as Bcl-2, Beclin-1, ATG5, etc. Based on the consequences of autophagy in WMDs, it might be possible to either inhibit or stimulate autophagy for therapeutic purposes. Autophagy modulation is currently used for cancer therapy and several clinical trials are underway to examine autophagy-modulating compounds.

Here, we review the role of autophagic processes in WMDs of the CNS taking into account the Janus face of autophagy that on one hand it may lead to oligodendrocyte and neuronal death, and on the other hand the pro-survival function of autophagy may aid survival of pathogenic immune cells. We also review how autophagy pathways are modulated experimentally and how these therapeutic approaches can be applied in WMDs.

Autophagy pathways and regulators

Autophagy is regulated by autophagy-related genes (ATGs) that are the core of the autophagic processes. More than 30 ATGs have been identified [29], some of which are involved in several pathophysiological conditions such as neurodegeneration [26–28] and neural infection [30]. Although autophagy is constitutively active at a basal level, several factors influence the rate of the process, including nutrient deprivation, growth factor withdrawal [31], ER stress [32,33], ROS production, hypoxia and mitochondrial dysfunction. During inflammation, which is a key feature of many WMDs, several immune pathways are known to influence autophagy, including the quality and extent of inflammatory signals (e.g. IFN-γ, IL-1β) and activation of TLR and other pathogen recognition receptors [34].

Autophagy is characterised by the formation of an autophagosome and occurs in six stages: initiation, nucleation, elongation, closure, maturation and degradation (Figure 1). During initiation and nucleation, a double membrane phagophore is formed, and this process continues to form a spherical autophagosome. Subsequently, the autophagosome fuses with the lysosome to generate a single membrane autolysosome in which the autophagic cargo will be degraded by lytic hydrolases [35]. Initiation of autophagy is dependent on the Unc-51-like kinase 1 and 2 (ULK1/2) complex and the class III PI3K complex (Figure 1). The ULK1/2 complex, which consists of ULK1/2, ATG13, FIP200 and ATG101 [35], is responsible for controlling levels of autophagy and is highly upregulated during stress. Under nutrient-rich conditions, the mammalian target of rapamycin (mTOR) interacts, phosphorylates and inactivates the ULK1/2 complex. When mTOR is inhibited, ULK1 and ULK2 activate and phosphorylate ATG13 and FIP200. The ULK1/2 complex consequently localises to the phagophore. ATG101 serves a stabilising role for ATG13 in the ULK1/2 complex and is essential for mammalian autophagy [36]. Additionally, AMP kinase (AMPK), a cellular metabolism regulator and energy sensor, phosphorylates ULK1 to induce autophagy. AMPK-dependent and -independent processes activate ULK1 kinase in situations of glucose starvation and amino acid starvation, respectively [37]. Another common pathway that negatively impacts on autophagy is the RAS/cAMP protein kinase A (PKA) pathway that plays a role in sensing the availability of glucose, and is thus activated during nutrient deprivation [38]. When nutrients are readily available, Ras1 and Ras2 induce cAMP generation by adenylyl cyclase. This induces an inhibitory effect on PKA, which then downregulates the autophagy machinery (Figure 1).

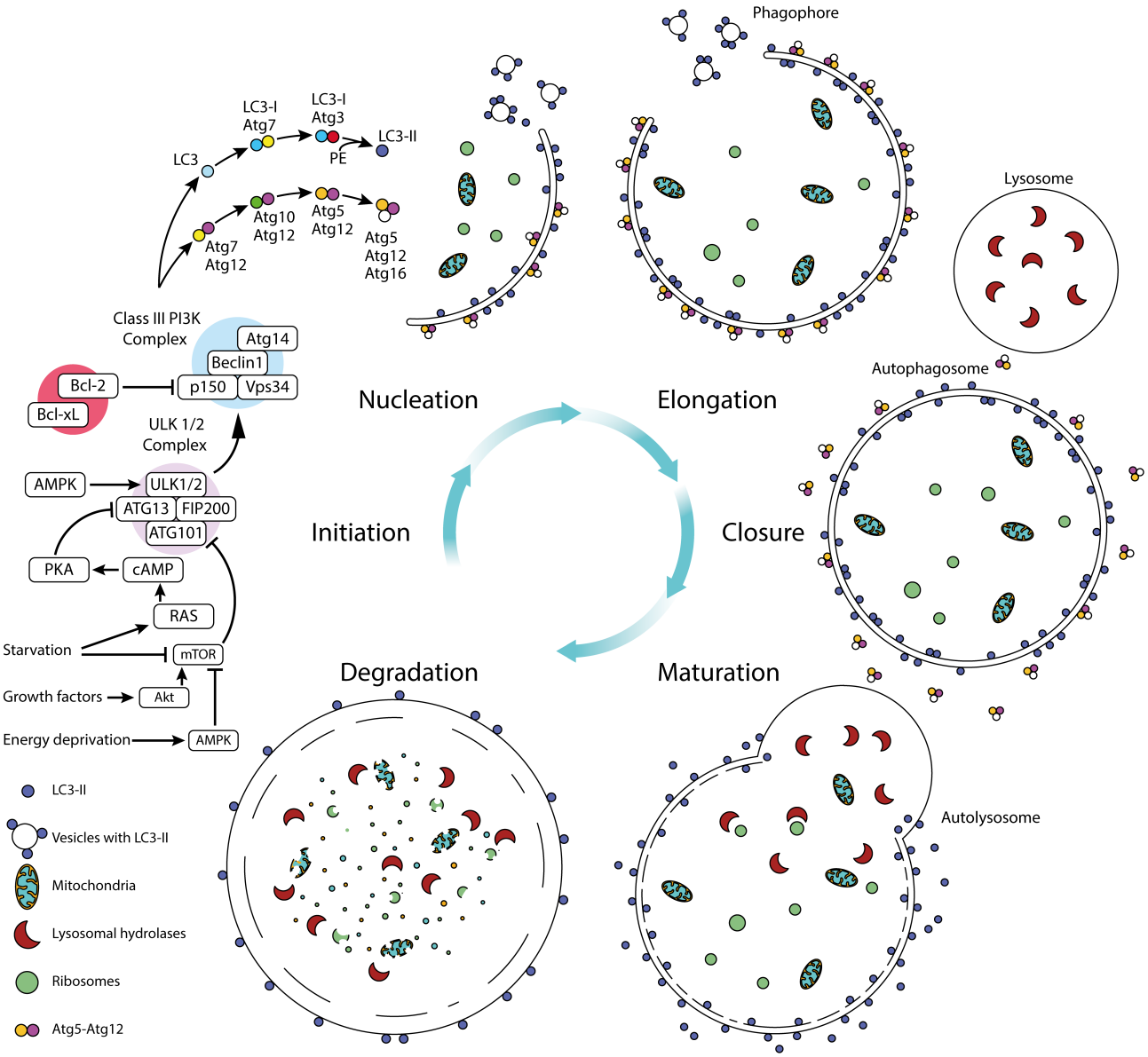

Figure 1. Macroautophagy machinery. Autophagy is regulated in six distinctive stages. Peripheral signals (e.g. starvation, growth factors) stimulate mTOR to activate the ULK1/2 complex, which in turn induces the class III PI3K complex. Nucleation is then initiated by a class III PI3K complex that induces a cascade of conjugations of AGSs, which lead to the formation of the dimeric ATG5–ATG12 complex and the production of LC3-II, which aids in elongation of the now forming phagophore. Once the expanding phagophore is large enough it closes and an autophagosome is formed. The outer ATG5–ATG12 and LC3-II are then cleaved from the membrane, after which it is ready to fuse with a lysosome, which is filled with lysosomal hydrolases. Fusion between the autophagosome and the lysosome creates an autolysosome, termed maturation. After fusion, the cargo (e.g. mitochondria or ribosomes) is degraded by lysosomal hydrolases and the end products are ready for reuse after export to the cytoplasm.

Phagophore assembly is regulated by the class III PI3K complex consisting of Beclin-1, vacuolar protein sorting 34 (Vps34), p150 and ATG14 [35,38]. Beclin-1 is inhibited by Bcl-2, which dissociates from Beclin-1 during nutrient starvation. The class III PI3K complex then scouts for two ubiquitination-like conjugation systems, ATG5–ATG12 and microtubule-associated protein 1 light chain 3 (LC3). The ATG5–ATG12 complex is formed with the help of ATG7 and ATG10 and subsequently interacts with ATG16 followed by association with the phagophores. Furthermore, LC3-I interacts with ATG7 and ATG3, after which it conjugates to phosphatidyl-ethanolamine to form LC3-II. LC3-II localises on the forming autophagosome, where it serves as a recognition site for autophagosome synthesis to ensure elongation and expansion of the membrane [39]. LC3-II levels are strongly correlated with the extent of autophagosome formation and LC3-II is therefore often used to measure autophagic activity [40]. Lastly, ATG9 functions as a carrier by trafficking membranes from the *trans*-Golgi network to the late endosomes, which are labelled with LC3-II [41]. Once the phagophore transitions into the autophagosome it docks and fuses with a lysosome in the presence of LAMP-2 and Rab7 proteins. After fusion of the autophagosome and lysosome into the autolysosome is complete, the content is degraded by lysosomal

proteases (cathepsins B, D and L) and the lipids are exported to the cytosol for reuse.

Emerging evidence suggests a dual role of autophagy in cancer [42] but also in neurodegenerative diseases [43]. Autophagy can act as a survival mechanism by generating nutrients and energy during nutritional scarcity and increasing cell longevity and viability, and conversely contributing to cell damage when autophagy is dysregulated.

Autophagy in WMDs

Autophagy is a multistep process that has been suggested to dysfunction in neurodegenerative diseases [26–28]. In health, autophagy has been demonstrated to downregulate neuroinflammatory processes to minimise damage from pro-inflammatory factors. However, the exact contribution of autophagy in acquired and genetic WMDs of the CNS has not been well characterised. Uncovering the role of autophagy in WMDs may help to understand the pathological processes, as well as allowing approaches to modulate autophagy pathways to treat these diseases.

Multiple sclerosis

MS is widely considered to be an autoimmune disorder of the CNS characterised by neurological damage, chronic inflammation and demyelination. Although the aetiology is unclear, the clinical episodes of disease are associated with the entry of pathogenic myelin-reactive auto-aggressive T- and B-cells into the CNS. Although autophagy has been associated with neuroinflammation in MS, whether autophagy actively contributes to cell damage in MS (e.g. by prolonging the survival of autoreactive T-cells) or acts as a rescue mechanism to counteract glial cell activation (e.g. dampening the neuroinflammatory response), is not yet known [44]. For example, peripheral T-cells in people with active relapsing–remitting MS express increased ATG5, suggesting that autophagy may prolong the survival of autoreactive pathogenic T-cells. However, although an association in gene variants for *ATG5* was found in the optic tract in neuromyelitis optica, an autoimmune disease closely related to MS, this was not observed in MS [45]. Decreased levels of ATG16L2 in the serum of people with MS are related to the abnormal activation of T-cells [46]. Furthermore, the pathogen receptor and inducer of autophagy CD46 was reported to impair regulatory functioning in T-cells of people with MS upon pathogen recognition [34,47]. To investigate the role of autophagy in MS, several studies have utilised experimental autoimmune encephalomyelitis (EAE), the autoimmune animal model of MS that is induced by immunising susceptible animals with myelin proteins or peptides administered in strong adjuvants. Such immunisation triggers myelin-reactive pathogenic T-cells that enter the CNS, inducing neuroinflammation and myelin damage [48]. Similar to MS, a role for autophagy has been proposed in EAE as circulating T-cells have increased expression of Atg5 [49], whereas a reduction in LC3-II/LC3-I ratio [50] and reduced Beclin-1 [51] resulting in reduced autophagy correlate with disease severity. Thus, the balance between reduced and increased markers of autophagy probably represent differential expression in activated immune cells versus damage to CNS cells. Autophagy is also implicated in CNS repair, reflected by the finding that rapamycin, an mTOR inhibitor, enhances remyelination in experimental peripheral neuropathy and tuberous sclerosis in mice [52,53]. Additionally, increased levels of LC3-II and p62, a protein that interacts with autophagosomes and ubiquitinated proteins that are ready for degradation, were observed in oligodendrocytes in myelin mutant Long-Evans rats. After intermittent fasting, p62 levels in the rats were reduced, indicating an upregulation of autophagy that was associated with increased thickness in myelin sheaths [54], supporting the idea that autophagy pathways are able to aid in repair mechanisms in the CNS. Furthermore, inducing mTOR signalling with oestrogen receptor β ligand diarylpropionitrile in oligodendrocytes improved remyelination during EAE in mice [55]. These studies underscore a key role for the mTOR signalling pathway in oligodendrocyte survival and axon myelination. The chronic inflammation in MS is associated with increased levels of cytokines, including IL-17 in T-cells [56] that is reported to suppress autophagy by activating TAK-binding proteins 2 and 3 and inducing MAPK [57]. Thus, increased IL-17 exacerbated the effects of increased ATG5, and reduced LC3-II in pathogenic T-cells (Table 2).

A possible mechanism of autophagy-induced oligodendrocyte damage in the CNS in MS is shown in Figure 2. Increased levels of ATG5 may influence apoptosis as ATG5 is also involved in apoptotic pathways [65]. Atg5 can be cleaved by calpains and the resulting truncated version of ATG5 then interacts with Bcl-xL and translocates from the cytosol to mitochondria where it may trigger apoptosis [66]. Another mechanism in which increased Atg5 can result in apoptosis is by interacting with Fas-associated protein with death domain (FADD), which induces apoptosis through a cascade of interactions (for a review see [67]). Thus, the overexpression of ATG5 in MS, together with a decrease in ATG16L2 and LC3-II/LC3-I ratio, could trigger excessive activation of apoptotic pathways by increased binding to FADD or Bcl-xL. Consequently, apoptotic signalling may induce cell death and white matter damage characteristic for MS.

In summary, pathogenic survival mechanisms facilitated by increased autophagy are present in T-cells contributing to CNS damage. On the other hand, there are pro-survival mechanisms that need an increase in autophagy in the CNS that contribute to remyelination. Targeting remyelination through autophagy in the CNS will be beneficial for slowing down the disease progression of MS.

VWM disease

VWM disease is an autosomal recessive leukoencephalopathy leading to progressive ataxia, spasticity and

Table 2. Autophagy pathways in CNS WMDs.

Type	Disease	Autophagy pathways associated with disease	Impact on autophagy	Reference
Inflammatory	MS	Increased ATG5 in T-cells in relapsing–remitting MS	Supports (autoimmune) T-cell survival	[49]
		Reduced LC3-II/LC3-I ratio	↓	[50]
		Increased IL-17	↓	[56,57]
		Decreased ATG16L2	↓	[46]
	NMO	*ATG5* variants		[45]
	ADEM	Unknown		
	AHL	Unknown		
Infectious	PML	Reduced Bag3	↓	[58]
	MeV	Increased LC3-II	↑	[47]
	Rubella virus	Reduced LC3-II	↓	[59]
		Reduced Atg5	↓	[59]
		Reduced Atg12	↓	[59]
Peroxisomal	X-ALD	Increased p62	↓	[60]
		Reduced LC3-II	↓	[61]
		Increased mTOR signalling	↓	[62]
Miscellaneous	VWM	Decreased ATG3 and ATG7 in EIF2B3 oligodendrocytes and reduced LC3-II	Depressed autophagy flux	[63,64]

NMO, neuromyelitis optica.

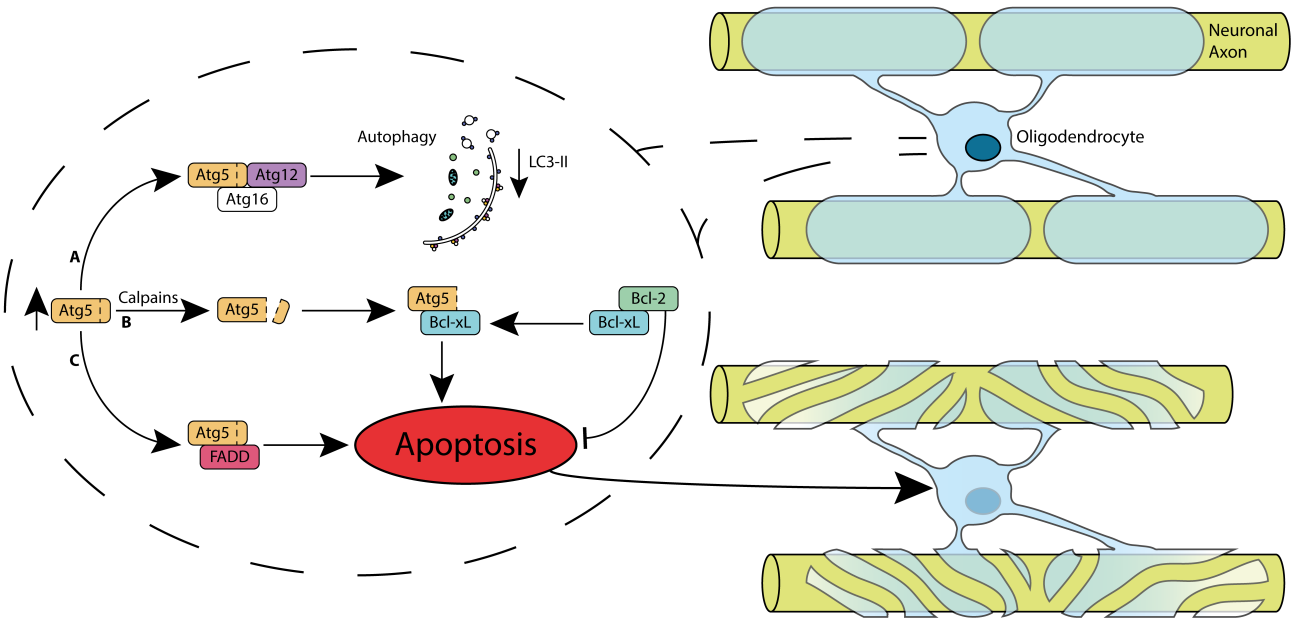

Figure 2. A mechanism of autophagy-induced oligodendrocyte death in MS. ATG5 is involved in both autophagic and apoptotic pathways. (A) Atg5 regulates autophagy by interacting with ATG12 and ATG16 to initiate the nucleation process of autophagy and to form an autophagophore. (B) ATG5 is cleaved by calpains, leading to binding of truncated ATG5 with Bcl-xL, which will dissociate from Bcl-2 resulting in the initiation of apoptotic pathways. (C) ATG5 interacts with FADD, which results in the initiation of apoptotic pathways. Both apoptotic pathways can result in the death of oligodendrocytes in MS.

seizures. Mutations in eukaryotic factor 2B (eIF2B) are present in VWM [20] and, although eIF2B is ubiquitously expressed, the pathology is almost exclusively in astrocytes and oligodendrocytes. eIF2B is essential for protein synthesis and the cellular response to stress, indicating that mutations in eIF2B may impair protein synthesis and the adaptability to cellular stress. Furthermore, ER stress [68] and upregulation of the UPR [63,69], reported to trigger autophagy, may play a role in oligodendrocyte damage in VWM. *In vitro*, human oligodendrocytes expressing mutant eIF2B have reduced tolerance to ER stress [63,70] and decreased levels of LC3-II, indicating a decreased autophagy response [63]. In support of this, mutant eIF2B oligodendrocytes pre-treated with autophagy inducers rapamycin and ridaforolimus showed normal levels of autophagy *in vitro*, resulting in higher tolerance to ER stress and cell survival [70].

Adrenoleukodystrophy

The pathology of X-ALD arises due to the dysfunction of the peroxisomal ABCD1 transporter [62] that is critical for transporting very long chain fatty acids (VLCFAs).

Such dysfunctions lead to an accumulation of VLCFAs as they cannot be transported into peroxisomes for degradation. VLCFA accumulation triggers oxidative stress and mitochondrial toxicity that may alter autophagy, although this has not been extensively investigated in human tissues. *In vitro*, VLCFAs activate autophagy pathways and induce lysosomal membrane destabilisation in rat oligodendrocytes [71], indicating that this may also be the cause of cell damage in X-ALD. Indeed, impaired autophagy has been reported in human brain samples from X-ALD cases, as well as in *Abcd1*$^{-}$ and *Abcd1*$^{-}$/*Abcd2*$^{-/-}$ mouse models of X-ALD [60]. During progressive neurological disease, people with X-ALD, as well as *Abcd1*$^{-}$ mice, have decreased LC3-II and increased p62 levels in the CNS, indicative of impaired autophagy [60]. Thus, the pathology of X-ALD might arise due to aberrant activation of the mTOR pathway as VLCFAs accumulate in the cell, or a gradual increase in mTOR levels that inhibit autophagic processes leading to axonal degeneration.

Systemic lupus erythematosus

Although systemic lupus erythematosus (SLE) is not a classical WMD, it is pertinent to discuss the CNS manifestations, as transverse myelitis is a rare myelopathy complication that may arise early in SLE and is associated with a poor recovery rate and high mortality [72,73]. SLE has been associated with autophagy genes in numerous genome-wide association studies, many of them implicating a role for *ATG5* [74–79]. Another autophagy-related gene is leucine-rich repeat kinase 2 (LRRK2). Several studies have shown the critical role of LRRK2 in regulating autophagy [80,81]. In SLE, LRRK2 is upregulated in primary B-cells and correlates with disease severity [82]. Furthermore, sera from people with SLE induced autophagy in neuroblastoma cells *in vitro* [83], suggesting a role in the neurological symptoms in people with SLE. Recently, it has also been suggested that mTOR signalling might be affected in SLE [84]. Activation of mTOR signalling leads to aberrant activation of lymphocytes and reduces regulatory T-cell expansion, which is characteristic for SLE [85,86]. Increased type 1 IFNs, for example IFN-α, play a crucial role in SLE pathogenesis [87,88]. Inhibition of the mTOR pathway has also been reported to supress stimulator of IFN genes (STING), an ATG5-dependent autophagy pathway, effectively reducing IFN-α expression in SLE monocytes [89,90]. In summary, mutations in the *ATG5* gene in SLE impact on autophagy and disease, and a genetic association between the autophagy-related LRRK2 gene and SLE susceptibility indicates a strong association with a dysfunctional autophagy pathway in this disease.

Infectious WMDs

PML is a rare and generally fatal viral disease observed in people with severe immunodeficiency. PML arises due to human polyomavirus JC virus replication in the CNS leading to severe demyelination. In healthy individuals, the virus establishes a latent infection; however, viral reactivation and replication in glial cells leads to PML [91]. Overexpression of Bag3, a modulator of the cellular response to stress, induced autophagic degradation of viral proteins by activation of LC3-II [92]. However, Bag3 is downregulated in cells infected with JC virus [58], possibly contributing to increased viral load.

Other pathogens have also developed strategies to utilise the autophagy machinery to their own advantage. Measles virus (MeV) is highly contagious and infectious and leads to the severe and often fatal disease subacute sclerosing panencephalitis, in which neurons and oligodendrocytes in the CNS are destroyed [93]. An important hallmark of the route of action of MeV is autophagic induction by the MeV receptor CD46 that contributes and sustains viral particle formation in infected cells [34,47,94]. After CD46-dependent induction of autophagy, a second wave of autophagy induction may follow, resulting in a significant increase of viral transcripts [94]. This later wave of autophagy is reported to be dependent on interaction between the MeV C-protein and the human immunity-related GTPase family M [95]. Significantly increased LC3-II was found in MeV-infected host cells [47]. In contrast, rubella virus infection of oligodendrocytes utilises the autophagy machinery by reducing LC3-II, ATG12 and ATG5 levels *in vitro* [59]. Rubella virus infection also inhibits autophagic flux and reduces the number and size of autophagosomes in the SIRC cell line, which may be beneficial for viral replication [59]. These viruses exemplify the intricate strategies that they have evolved to exploit autophagic pathways for self-replication.

ADEM is a rare WMD that arises following a viral or bacterial infection and in rare cases by vaccination [96,97]. ADEM causes an acute widespread inflammation of the CNS with severe demyelination and white matter destruction. Although symptoms resemble those of MS, ADEM follows a monophasic course, with full recovery rates from 50 to 70% [96]. Studies of the impact of autophagy in the pathogenesis of ADEM are lacking. However, as ADEM is closely related to other post-infectious demyelinating diseases, the involvement of autophagy requires further exploration. Likewise, acute haemorrhagic leukoencephalitis (AHL), a fulminant and aggressive form of ADEM with a high mortality rate, is characterised by perivenular demyelination and inflammation. Case reports reveal that aggressive immunosuppressant therapy fails to halt the course of the disease [98]. The similarities with MS and infectious WMDs suggest that autophagy modulation in combination with immunosuppressive therapy might be more effective in controlling the disease and offer a more favourable outcome for ADEM and AHL.

Autophagy as a therapeutic target

Strong evidence indicates that autophagy plays an important role in the pathogenesis of WMDs and may

thus be a target for therapeutic strategies. Emerging reports reveal that targeting the autophagy pathways in neurodegenerative diseases may reduce toxic accumulation of proteins (e.g. in Parkinson's disease, Alzheimer's disease, Huntington's disease) (for a recent review see [99]). Such approaches, as discussed below, may therefore also be beneficial in WMDs in which neuronal and axonal damage occur.

Autophagy inducers

A well-known class of autophagy inducers are drugs that target mTOR signalling, indicating that these might prove useful to support oligodendrocytes and myelin repair in MS. Rapamycin functions as an immunosuppressive agent as well as increasing autophagy by inhibiting mTOR during nutrient-rich conditions [100]. mTOR serves a central role in the regulation of various housekeeping functions, including autophagy. Although rapamycin has been studied in MS, those studies focussed on its impact as an immunomodulatory agent and not on the effects on autophagy [101]. Rapamycin reduced EAE severity and decreases of LC3-II, p62 and Beclin-1 (Table 3) [102]. Similarly, rapamycin also showed significant anti-inflammatory actions in EAE and MS, in which disease progression was slowed [148–151]. Thus, rapamycin may control aberrant autophagy in addition to its immunomodulatory functions. The rapamycin ester temsirolimus has been shown to be effective in an X-ALD mouse model, restoring autophagy and reducing the axonal degenerative processes [60], indicating that these drugs may also be useful in other neurodegenerative disease and WMDs. Other drugs that act through a similar working mechanism and that may have similar effects are PP242 and Torin 1 [104,105]. Resveratrol acts by directly binding to the ATP binding pocket of mTOR, thereby competing with ATP and inducing autophagy [106].

Although lithium was the first drug found to induce autophagy in an mTOR-independent manner by lowering inositol synthesis [133], other FDA-approved drugs may also regulate autophagy in mTOR-independent manners [124]. Two of these, carbamazepine and sodium valproate, act similarly to lithium, whereas xestospongin B decreased intracellular IP3 levels [152]. The compounds rilmenidine and clonidine reduce cAMP levels by inhibiting G-protein signalling pathways that in turn inhibit adenylyl cyclase, after which autophagy is initiated [124]. Rilmenidine is known for its positive characteristics and safe long-term use in chronic diseases and has been tested in neuronal cell cultures [125]. The cannabinoid receptor 2 (CB2R) inhibits adenylyl cyclase directly, which reduces cAMP levels similarly to the working mechanism of rilmenidine, clonidine and H89 [124,126]. Activation of CB2R with HU-308 alleviated clinical signs of EAE through activation of autophagy and restoring the reduced LC3-II/LC3-I ratio [127]. Cannabis, which targets CB2R, is used to treat MS and has been reported to reduce disease progression via autophagic-related pathways [153]. Additionally, cAMP-dependent PKA inhibitor H89 was found to induce autophagy through downstream modulation of Akt [126].

Another class of autophagy inducers targets the initiation process by increasing the activity of ULK1 or Beclin-1. Corynoxine and BH3 mimetics were found to induce autophagy in a Beclin-1-dependent manner [64,128]. Glycyrrhizic acid was found to not only induce Beclin-1 production but also has antiviral properties that could prove useful in post-infectious demyelinating diseases [129]. Similarly, cucurbitacin B increased Beclin-1 and ULK1 levels, although its working mechanism is probably mediated by increased ROS production [132].

Recently, gefitinib and erlotinib [113], RY10-4 [114], berberine [115], concanavalin A [116], curcumin [154], tunicamycin [117], piperlongumine [118], baicalein [119], plumbagin [120], emodin [121] and ivermectin [122] have all been found to induce autophagy through modulation of the Akt–mTOR pathway. Pinosylvin and chebulagic acid were found to induce autophagy through AMPK activation reducing necrotic progress and pathological symptoms of Parkinson's disease, respectively [107,108]. Another AMPK activator is the anti-diabetic drug metformin, which also induces autophagy [155]. Additionally, autophagy might be regulated by indirect targeting through microRNAs (miRNA-18, miRNA-21) [130,131], nitric oxide synthase inhibitors such as L-NAME that reduce cell stress [124] or disaccharides that may act as chaperones to induce autophagy [156].

Autophagy inhibitors

On the other end of the spectrum are autophagy modulators that reduce autophagy-associated pathways and may be useful to salvage neuronal and oligodendrocyte death in WMDs. For example, Pollen typhae and bafilomycin A1 were shown to reduce autophagy by acting on the Akt/mTOR pathway [137,139]. That this pathway is essential for myelination suggests that this approach may aid remyelination in WMDs [157]. U0126, an ERK kinase inhibitor, was found to reduce Beclin-1 and LC3 levels, which indicates a suppressive effect on autophagy [142]. Similarly, gastrodin, normally used as an anti-convulsant, prevents lipopolysaccharide-induced autophagy by reducing LC3-II, p62 and Beclin-1 levels [138]. Spautin-1 indirectly targets Beclin-1 through degradation of ubiquitin-specific peptidases USP10 and USP13 [158]. 3-MA blocks class III PI3K to prevent autophagosome formation, which shows neuroprotective effects [159] similar to Wortmannin [138]. Angiotensin (1–7) targets autophagy by reducing oxidative stress in the cell [144]. Matrine was found to have a similar mechanism of action by reducing stress in oligodendrocytes and ameliorating EAE [143]. One drug commonly used in clinical oncology trials to block autophagy is chloroquine, an anti-malaria drug. Recently, chloroquine was used to block autophagy in a model for myelin mutants [54]. Similarly, chloroquine

Table 3. Therapies targeting autophagy pathways in CNS WMDs.

	Compound	Mode of action	Effects in WMDs	Reference
Autophagy inducers				
Targets of mTOR	Rapamycin	Inhibits mTOR	Ameliorates EAE by blocking immune cell activation. May be effective in PND. Improves viability of M03.13/EIF2B3 cells	[51,102,103]
	Ridaforolimus	Inhibitor of mTOR complexes	Improves viability of M03.13/EIF2B3 cells	[70]
	Temsirolimus	Rapamycin analogue	Prevents protein accumulation, energetic failure and proteasome malfunctioning in *Abcd1*$^{-}$ mice	[60]
	Pp242	Inhibits the active site of mTOR	Blocks Akt phosphorylation	[104]
	Torin 1	mTOR inhibitor	Unknown	[105]
mTOR ATP competition	Resveratrol	Inhibits mTOR–ULK1 pathway	Unknown	[106]
AMPK activation	Pinosylvin	Induces conversion of LC3-I to LC3-II, and activates AMPK	Unknown	[107]
	Chebulagic acid	Increases phosphorylated AMPK	Protects against cytotoxicity in SH-SY5Y cells	[108]
	Metformin	Activates AMPK by increasing cytosolic AMP	Reduces lesions in cuprizone model Rejuvenates OPC ageing Reduced lesion load in MS	[109–112]
Akt–mTOR modulation	Gefitinib	Inhibits PI3K/Akt/mTOR pathways	Unknown	[113]
	RY10-4	Inhibits phosphorylation of Akt and mTOR	Unknown	[114]
	Berberine	Inhibits upstream mTOR signalling and MAPK phosphorylation	Unknown	[115]
	Concanavalin A	Inhibits PI3K/Akt/mTOR pathways	Unknown	[116]
	Curcumin	Inhibits PI3K/Akt/mTOR pathways	Ameliorates EAE progression and delays onset	[51]
	Tunicamycin	Induces ER stress	Unknown	[117]
	Erlotinib	Inhibits PI3K/Akt/mTOR pathways	Unknown	[113]
	Piperlongumine	Inhibits PI3K/Akt/mTOR pathways	Unknown	[118]
	Baicalein	Decreases expression of Akt/ULK1 and 4EBP1	Unknown	[119]
	Plumbagin	Inhibits PI3K/AKT/mTOR pathways	Unknown	[120]
	Emodin	Increases LC3-II	Unknown	[121]
	Ivermectin	Promotes degradation of PAK1	Unknown	[122]
	Corynoxine	Inhibits PI3K/AKT/mTOR pathways	Unknown	[64]
NOS inhibitor	L-NAME	Inhibits NOS activity	Unknown	[123]
Reducing cAMP	Rilmenidine	Binds to imidazoline-1 receptor to reduce cAMP	Unknown	[124,125]
	Clonidine	Binds to imidazoline-1 receptor to reduce cAMP	Unknown	[124]
	H89	Inhibits cAMP-dependent protein kinase	Unknown	[126]
	HU-308	Activates CB2R	Ameliorates EAE progression	[127]
Targeting ULK1/2 or class III PI3K complexes	BH3 mimetics	Inhibits Beclin-1 interaction with Bcl-2	Unknown	[128]
	Glycyrrhizic acid	Induces Beclin-1 production	Unknown	[129]
MicroRNAs	miRNA-18	Inhibits mTOR signalling pathway	Unknown	[130]
	miRNA-21	Upregulates Bcl-2 expression	Unknown	[131]
Enhanced ROS production	Cucurbitacin B	Increases expression of Beclin-1, ULK1, reduces expression of mTOR	Unknown	[132]
Lowering inositol synthesis	Lithium	Inhibits inositol monophosphate	Reduces aggregates of GFAP in a mouse model of Alexander disease	[133,134]
	Carbamazepine	Inhibits inositol monophosphate	Unknown	[135,136]
	Sodium valproate	Inhibits inositol monophosphate	Unknown	[135,136]

(Continues)

Table 3. Continued

	Compound	Mode of action	Effects in WMDs	Reference
Autophagy inhibitors				
Akt–mTOR modulation	Pollen typhae	Increases LC-3 and Beclin-1	Unknown	[137]
	Gastrodin	Decreases LC3-II, p62 and Beclin-1	Protects astrocytes *in vitro* from LPS-induced cell death	[138]
	Bafilomycin A1	Blocks lysosome fusion with autophagosomes	Unknown	[139]
	Spautin-1	Promotes degradation of Vps34 by inhibiting ubiquitin-specific peptidases	Unknown	[140]
	Chloroquine	Blocks lysosome fusion with autophagosomes	Ameliorates EAE disease severity	[141]
ERK kinase inhibitor	U0126	Inhibits ERK	Unknown	[142]
PI3K inhibitor	3-methyladenine	Blocks class III PI3K	Increased severity of EAE and inflammation	[102]
	Wortmannin	Blocks autophagosome formation	Unknown	[138]
	Matrine	Blocks autophagosome formation	Reduces stress in oligodendrocytes in EAE	[143]
Other	Angiotensin (1–7)	Reduces oxidative stress	Unknown	[144]
MicroRNAs	miRNA-30a	Suppresses expression of TP53INP1	Unknown	[145]
	miRNA-205	Suppresses expression of TP53INP1	Unknown	[145]
	miRNA-101	Suppresses RAB5A	Unknown	[146]
	miRNA-223	Targets ATG16L1	Unknown	[147]

GFAP, glial fibrillary acidic protein; LPS, lipopolysaccharide; OPC, oligodendrocyte precursor cell; PND, paraneoplastic neurological disorder.

was found to reduce EAE symptoms [160]. However, the precise working mechanism is not known. Several miRNAs (miRNA-30a, miRNA-205, miRNA-101 and miRNA-223) also inhibit autophagy [145–147]. Although research in this field is scarce, recent evidence in other diseases shows that these strategies might also be beneficial for WMDs given the role of autophagy in these diseases.

Conclusion

Emerging evidence supports the role of autophagy in WMDs. An increased understanding of the mechanisms driving autophagy has resulted in increased insight into the pathogenic processes that are affected in disease. A pressing problem is the heterogeneity between WMDs, which is also apparent in neurodegenerative disorders [161]. Indeed, in a disease such as MS there is evidence that some aspects of autophagy are upregulated whereas others are downregulated. This heterogeneity emphasises the need for thorough investigative research focusing on autophagy in WMDs to better understand the progression of autophagy malfunctioning during the disease and whether this is a causal aspect or a consequence of other facets of WMDs.

The development of pharmacological agents that modulate autophagy has been very successful. However, there are important obstacles to highlight. Most WMD cases are sporadic, but treatment early in the disease relies on the identification of the disease prior to symptomatic onset. Therefore, drugs that target autophagy will probably not rescue cells that have already undergone permanent damage. Furthermore, some autophagy modulators might have non-specific targets that thus carry risks associated with unwanted side-effects. Although there are obstacles to overcome, the recent surge in modulatory compounds for autophagy shows that there is no lack of treatment possibilities. If we can better understand the underlying pathological processes in autophagy for WMDs there is a great potential in finding new treatment strategies.

Author contributions statement

EN performed the literature search, generated figures, wrote and edited the review. EN, MCM, SA and SC critically reviewed and edited the final submitted version.

Abbreviations

ADEM, acute disseminated encephalomyelitis; AHL, acute haemorrhagic leukoencephalitis; AMPK, AMP kinase; CB2R, cannabinoid receptor 2; EAE, experimental autoimmune encephalomyelitis; eIF2B, eukaryotic factor 2B; FADD, Fas-associated protein with death domain; LC3, light chain 3; LRRK2, leucine-rich repeat kinase 2; MeV, measles virus; MS, multiple sclerosis; mTOR, mammalian target of rapamycin; PKA, protein kinase A; PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus; ULK, Unc-51-like kinase; UPR, unfolded protein response; VLCFA, very long chain fatty acid; Vps34, vacuolar protein sorting 34; VWM, vanishing white matter; WMDs, white matter disorders; X-ALD, X-linked adrenoleukodystrophy.

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