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Review

Autophagy in neuroinflammatory diseases

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ABSTRACT

Autophagy is a metabolically-central process that is crucial in diverse areas of cell physiology. It ensures a fair balance between life and death molecular and cellular flows, and any disruption in this vital intracellular pathway can have consequences leading to major diseases such as cancer, metabolic and neurodegenerative disorders, and cardiovascular and pulmonary diseases. Recent pharmacological studies have shown evidence that small molecules and peptides able to activate or inhibit autophagy might be valuable therapeutic agents by down- or up-regulating excessive or defective autophagy, or to modulate normal autophagy to allow other drugs to repair some cell alteration or destroy some cell subsets (e.g. in the case of cancer concurrent treatments). Here, we provide an overview of neuronal autophagy and of its potential implication in some inflammatory diseases of central and peripheral nervous systems. Based on our own studies centred on a peptide called P140 that targets autophagy, we highlight the validity of autophagy processes, and in particular of chaperone-mediated autophagy, as a particularly pertinent pathway for developing novel selective therapeutic approaches for treating some neuronal diseases. Our findings with the P140 peptide support a direct cross-talk between autophagy and certain central and peripheral neuronal diseases. They also illustrate the fact that autophagy alterations are not evenly distributed across all organs and tissues of the same individual, and can evolve in different stages along the disease course.

Contents

Abbreviations: Aβ, amyloid-β; Ab, antibody; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APC, antigen-presenting cell; APP, amyloid precursor protein; ATG, autophagy-related; ATG1/ULK, unc-51 like autophagy activating kinase-1; ATG6/Beclin-1, Bcl-2 interacting myosin/moesin-like coiled-coil protein-1; ATG18/WIPI, WD-repeat protein interacting with phosphoinositides; BBB, blood brain barrier; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMA, chaperone-mediated autophagy; EAE, experimental autoimmune encephalomyelitis; EAN, experimental autoimmune neuritis; ER, endoplasmic reticulum; HD, Huntington's disease; HSPA8/HSC70, heat shock 70-kDa protein 8; Htt, huntingtin; IL, interleukin; LAMP2A, lysosome-associated membrane protein 2A; lpr, lymphoproliferation; MAP1LC3B/LC3, microtubule-associated protein 1 light chain 3β; MHC, major histocompatibility complex; mHtt, mutated Htt; MRL, Murphy Roths large; mTOR, mammalian target of rapamycin; MS, multiple sclerosis; NMDAR, *N*-methyl-D-aspartate receptor; NP, neuropsychiatric; NPSLE, neuropsychiatric systemic lupus erythematosus; OS, oxidative stress; PD, Parkinson's disease; PE, phosphatidylethanolamine; PINK1/PARK6, phosphatase and tensin homolog (PTEN)-induced putative kinase 1; PI3KC3, phosphatidylinositol triphosphate kinase complex 3; PtdIns3/PI3P, phosphatidylinositol-3-phosphate; SLE, systemic lupus erythematosus; SNCA, α-synuclein; SOD1, superoxide dismutase-1; SQSTM1/p62, sequestosome-1/ubiquitin-binding protein p62; TCR, T cell receptor; TDP-43, transactive response DNA binding protein 43 kDa; TLR, Toll-like receptor; TREM, triggering receptors expressed on myeloid cells; UPS, ubiquitin-proteasome system.

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1. Introduction

1.1. Neuronal autophagy

Autophagy is a vital, finely-regulated and evolutionary-conserved intracellular pathway that continuously degrades, recycles and clears unnecessary or dysfunctional cellular components (e.g. damaged organelles, proteins abnormally folded or produced in excess) [1]. This dynamic, self-recycling process is crucial for adaptation to the environment and to maintain cell homeostasis, especially under stress conditions, such as nutrient deprivation, hypoxia, oxidative stress (OS), changes of intracellular level of Ca^{2+}. Autophagy is thus particularly involved in cellular processes, such as development, lineages differentiation [1,2], as well as in many aspects of lymphocyte development, activation and differentiation [3]. In macroautophagy, the most extensively studied form of autophagy, cellular cargo are sequestered within double-membrane vesicles called autophagosomes (Fig. 1). The latter are formed de novo upon induction of autophagy and initially appear as small membrane structures referred to as isolation membranes or phagophores. The highly conserved machinery leading to the formation of autophagosome is timely coordinated by a "battery" of autophagy-related (*ATG*) genes and regulators (Fig. 2). At an upstream stage, the latter involves mammalian target of rapamycin (mTOR) complex 1, a multiprotein complex that contains different protein partners, namely RAPTOR/KOG1 and SEC13 protein 8, the ATG1/unc-51 like autophagy activating kinase (ULK)-1 complex, the class III phosphatidylinositol triphosphate kinase (PI3KC3) complex 1, ATG9, the ATG18/WIPIs, and the ATG12-ATG5-ATG16 and microtubule-associated protein-1 light chain-3β (MAP1LC3B)/LC3-γ-aminobutyric acid receptor-associated protein conjugation systems, which reside in the isolation membrane at some stages of autophagosome formation. Subsequently, the outer membrane of the autophagosome fuses with the lysosome membrane, giving rise to autolysosomes, and the autophagosome inner membrane and autophagosome cargo are degraded by acidic lysosomal proteases and recycled (Fig. 2).

Two other major forms of autophagy co-exist along with macroautophagy (the latter is often just mentioned as "autophagy", leading sometimes to confusion in the discussions), namely microautophagy, which directly engulfs cytosolic material into lysosomes via the formation of characteristic invaginations of the lysosomal membrane [4], and chaperone-mediated autophagy (CMA; Fig. 1), which involves the recognition of substrate proteins containing a KFERQ-like motif by a HSPA8/HSC70-containing complex [5]. This pentapeptide motif, found in ~30% of cytosolic proteins, is normally buried in native proteins but can become exposed on the surface of misfolded proteins [6]. Targeted proteins recognized by HSPA8 then undergo

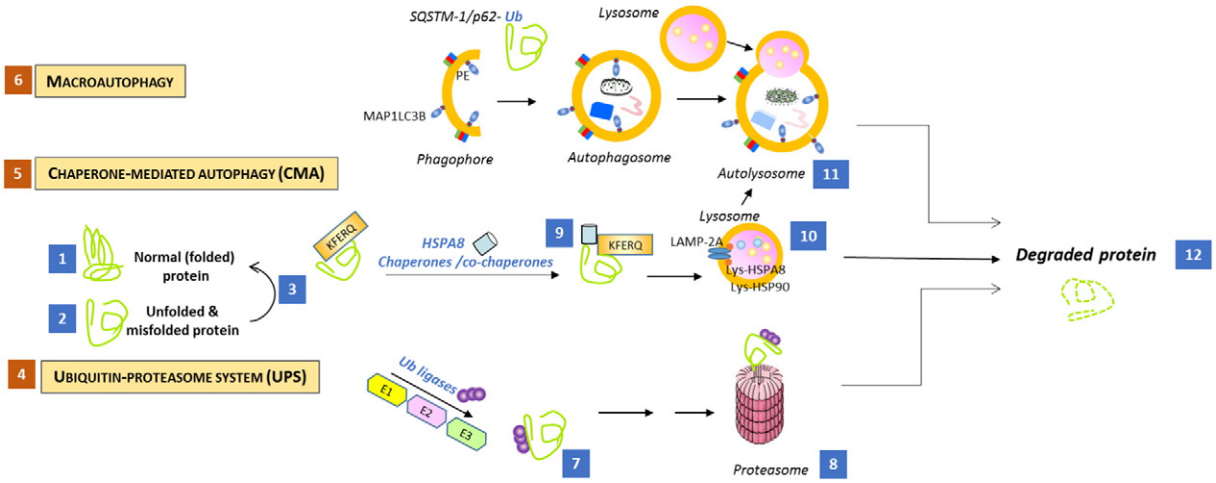


Fig. 1. Degradation of misfolded and unfolded proteins. Cellular proteins (1) can be altered by genetic mutations, aging, and exposure to harmful intracellular or extracellular conditions (e.g. OS, changes in pH, UV radiation), which may induce some changes in their conformation (e.g. unfolding or misfolding) (2). These altered proteins may be repaired and/or refolded and then recover their full bioactivity (3) or may be released by several proteolytic systems, including the ubiquitin-proteasome system (UPS) (4), the chaperone-mediated autophagy (5), and macroautophagy (6). Chaperones are very much involved in these pathways (7, 8, 9). They deliver the substrates to the UPS, CMA and macroautophagy, depending on the nature of misfolding, size and solubility of damaged components. Soluble and monomeric misfolded proteins are essentially degraded by the UPS and CMA process. The UPS is a proteolytic system in which substrates are tagged with ubiquitin (Ub), unfolded into nascent polypeptide chains (7), and degraded by the proteasome (10). In CMA, substrates carrying the KFERQ degradation motif are recognized and bound by HSPA8 in association with co-chaperones (8), and are further delivered to the LAMP2 complex on the lysosomal membrane (11), translocated to the lumen, and degraded into amino acid residues by lysosomal hydrolases. The translocation of unfolded proteins through LAMP2A requires lysosomal chaperone proteins, such as Lys-HSPA8 and Lys-HSP90, present in the lumen. Once proteins are captured by the lysosome, the HSPA8/co-chaperone complexes are released from the lysosomal membrane and again available to bind other cytosolic KFERQ motif-tagged proteins that are structurally altered. Aggregates that escape the surveillance of UPS and CMA can be directed to macroautophagy. In this system, MAP1LC3B that is attached to the phagophore membrane binds to SQSTM1protein, which in turn links damaged substrates that are tagged by ubiquitin (9). The resulting complexes are sequestered into double-membrane vesicles (autophagosomes) that fuse with lysosomes to give autolysosomes where altered substrates are degraded (12). The macroautophagy and CMA pathways are finely coordinated processes. A functionally decisive cross-talk exists between these two processes and also between autophagy and other processes of elimination as apoptosis, for example. Markers of macroautophagy are notably the autophagic adaptor SQSTM1 and the MAP1LC3B proteins, the accumulation of which is measured to evaluate the activity of this process. Abbreviations: HSPA8, heat shock 70-kDa protein 8; LAMP2A: lysosome-associated membrane protein 2A; MAP1LC3B, microtubule-associated protein light chain 3; OS, oxidative stress, PE, phosphatidylethanolamine; SQTM1/p62, sequestosome-1/ubiquitin-binding protein p62; Ub, ubiquitin; UPS, ubiquitin-proteasome system; UV, ultraviolet.

unfolding and cross the lysosomal membrane to reach the lumen where they are taken-up by other proteins associated into a translocation complex at the lumenal side, especially by the receptor monomeric lysosome-associated membrane protein 2A (LAMP2A), which upon association with substrate proteins, will transiently form a multi-protein complex (Fig. 1). Thus, in contrast to macroautophagy, which is largely nonselective with regard to the cargo enclosed in autophagosomes, CMA, on the contrary, is a selective process that removes specific proteins that are abnormal or produced in excess with regard to the cell need [7]. This process makes CMA a selective proteolytic system efficient for the degradation of abnormal proteins that are dysfunctional in metabolically central complexes. CMA represents therefore a system of waste recycling that is vital for cell maintenance. A number of other forms of autophagy have been described such as aggrephagy, mitophagy, and xenophagy, for example. This (young) area of investigation is currently in an extraordinary growing expansion and an unified nomenclature for genes and proteins was rendered necessary by the multiplicity of names given to autophagy-related compounds [8]. In the 1990s, when *ATG* genes were identified, their names were APG, AUT, CVT, GSA, PAG, PAZ, PDD. The unified nomenclature was adopted in 2003 [9] and nowadays, it is universally used.

In pathological conditions, autophagy generally corresponds to an adaptive response to stress that, upon the severity of aggression, either promotes cell survival or induces cell death and morbidity. In 1999, a pioneering report linking autophagy with cancer was published [10]. To date, besides oncogenic processes, which has been extensively studied in terms of autophagy impact and dysfunction, autophagy is claimed to be centrally implicated in many other indications including metabolic, cardiovascular, pulmonary and neurodegenerative diseases [5,6,11–15]. Although increasing evidence support the view that altered autophagy processes exist in these disorders, the results should however be treated with caution as they were often generated in experimental cellular or animal settings that remain objectionable since selective chemical activators and inhibitors of autophagy are still scare and some reagents hardly lack to demonstrate these failures with certainty in vivo.

1.2. Neuronal autophagy – therapeutic targets

Anatomically, neurons possess specialized elements (e.g. soma, dendrites, axon, synapses) for performant intercellular communication and in which the synthesis, transport and degradation are precisely regulated. Knowing in addition that mature neurons are post-mitotic and do not replicate, an efficient protein quality control system is thus required in order to avoid accumulation of pathological proteins, which are thought to be toxic and will not be diluted through cell division.

Autophagy plays crucial role during neurodevelopment and neurogenesis, as well as at the synaptic zone [16]. It is supposed to be implicated in axonal dystrophy following excitotoxic damage and axotomy [17], but also in dysfunctional axons during neurodegenerative diseases such as Huntington (HD), Alzheimer (AD), and Parkinson's (PD) diseases [18–20]. Neuronal autophagy is implicated in the synapse zone where the energy needs are high and where a fine control of proteins and organelles turnover is crucial to ensure activity. This has been notably demonstrated in Drosophila neuromuscular junction [21]. Boosting autophagy (by overexpressing *ATG*1) augments synaptic growth, and minimizing autophagy (by mutating *ATG* genes) diminishes synaptic size. Atg1 may also be implicated in the regulation of synapses by downregulating the activity of the so-called mitogen-activated protein kinase/extracellular signal-regulated kinases pathway [22].

Even if basal neuronal autophagy seems to mostly play a protective role in the central nervous system (CNS), being an effective mechanism involved in the turnover of proteins and removal of damaged proteins through lysosomal degradation [23,24], it can also be implicated in the neuronal death observed in several pathological conditions. In some neurodegenerative diseases, including AD, PD, HD, and amyotrophic

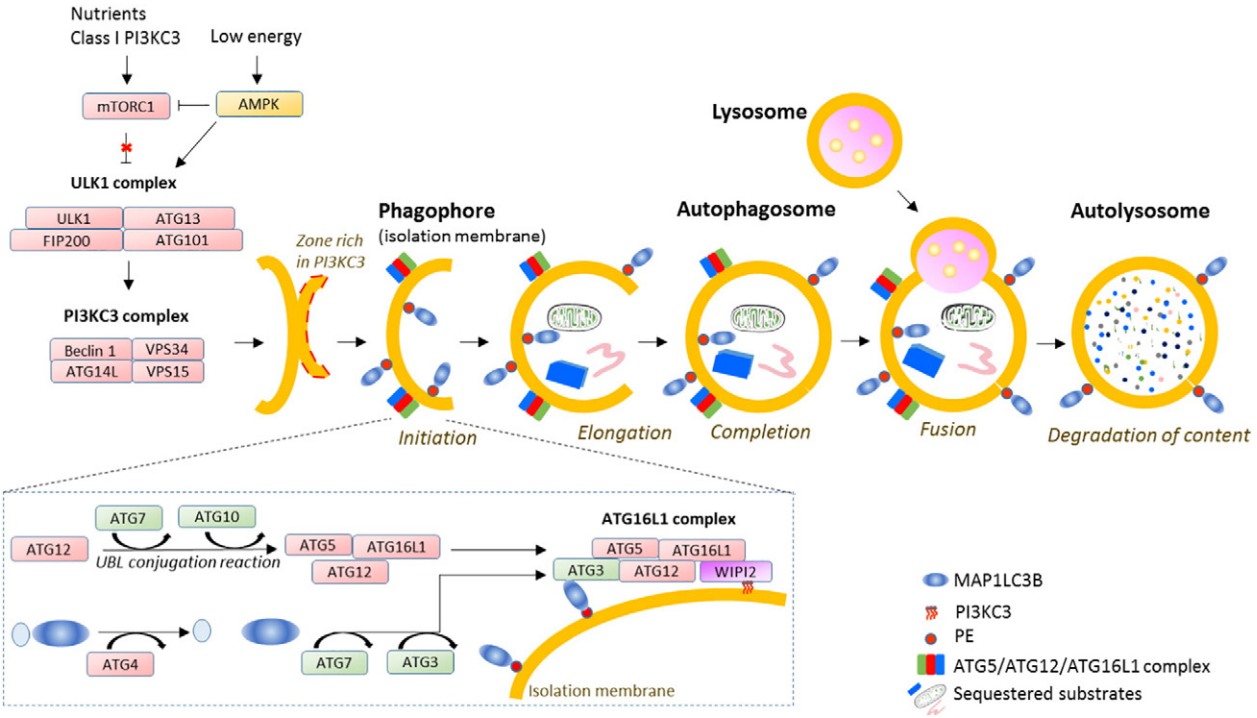


Fig. 2. Schematic autophagy. The generation of autophagosome is mediated by the sequential activities of three key complexes: the ULK1 complex (comprising ULK1, FIP200, ATG13 and ATG101), the phosphoinositide 3-kinase catalytic subunit III (PI3KC3) complex (comprising beclin 1, vacuolar protein sorting 34 (VPS34), VPS15 and ATG14L), and the ATG16L1 complex (comprising ATG16L1, ATG5 and ATG12).The ATG16L1 complex is recruited by WIP12 to the autophagosome precursor structure (that is, the isolation membrane). The ATG16L1 complex is generated through an ubiquitin-like (UBL) conjugation reaction in which ATG12 is conjugated to ATG5 by the sequential action of ATG7 and ATG10. ATG16L1 non-covalently binds the ATG5-ATG12 conjugate to form a multimeric complex. In parallel, another ubiquitin-like molecule, MAP1LC3B, is processed by the ATG4 protease and subjected to as UBL reaction involving ATG7 and ATG3. During the elongation process, the ATG16L1 complex mediates the conjugation of phosphatidylethanolamine (PE) to MAP1LC3B-I, generating MAP1LC3B-II that relocates from the cytosol to the autophagic membrane and is anchored on its surface. The resulting autophagic membrane structures (autophagosomes) are fused with lysosomes to form autolysosomes, wherein sequestrated substrates are degraded by lysosomal hydrolases. Adapted from [248]. Abbreviations: ATG, autophagy related; ATG1/ULK, unc-51 like autophagy activating kinase-1; LC3, Microtubule-associated protein light chain 3; MAP1LC3B, microtubule-associated protein 1 light chain 3β; PE, phosphatidylethanolamine; PI3KC3, phosphoinositide 3-kinase catalytic subunit III; UBL, ubiquitin-like; VPS, vacuolar protein sorting.

lateral sclerosis (ALS), toxic intracellular protein aggregates and damaged organelles commonly accumulate, due in part to down-regulation of ubiquitin-proteosome system (UPS; Fig. 1) [25,26], within specific types of neurons or cerebral areas, inducing neuronal dysfunction and death. Regulating autophagy, and particularly enhancing its activity, may therefore become an efficient therapeutic strategy for this kind of neurodegenerative diseases [27]. The cellular factors underlying homeostasis versus pathological activation of autophagy are not fully understood. Nowadays, it is therefore central to decipher the role of autophagy in neuronal pathological conditions, as it will clarify the design and the development of therapeutic agents [28], such as mTOR inhibitors or substances acting via other pathways (e.g. via the G_i-coupled imidazoline receptors with imidazoline-1 receptor agonists rilmenidine and clonidine, via inositol monophosphatase with lithium, via inhibition of inositol synthesis with carbamazepine, and via inhibition of calpain with calpastatin and calpeptin) [29,30]. Natural compounds have also shown most interests to activate autophagy in neurodegenerative diseases [31]. Several active vegetal compounds have proven effective at regulating autophagy and exerting neuroprotection in HD, AD, PD and ALS (Table 1).

We will focus this article on selected neurodegenerative diseases displaying dramatic issues. Here, AD, PD, HD, ALS and multiple sclerosis (MS) will not be deeply depicted as many reviews, for some very recently published and exhaustive, can provide the reader with updated information dealing with pathophysiology, autophagy processes and therapeutic strategies in these neuronal diseases [32–38]. The scope of our discussion here more particularly includes three neuronal diseases for which we have generated preliminary data with a therapeutic peptide designed in our laboratory. The data we obtained led us to identify some hitherto unknown autophagy alterations and possible new therapeutic routes that could be used by selectively targeting autophagy process regulation in these indications.

2. Regulation of autophagy in neurodegenerative central and peripheral nervous system diseases

2.1. Huntington's disease (HD)

2.1.1. Description

HD is a progressive, autosomal dominant, neurodegenerative movement and cognitive disease that mostly manifests between the ages of 35 and 45 years, and with dramatic repercussions on the daily life of patients and families [39] (Table 2). Death may occur 15–20 years after the onset of neurological events. Earliest modifications in HD are related to executive functions, and are illustrated by abnormal repetitive movements (e.g. mild chorea), dystonia, bradykinesia, slowing of ocular movements, and decline of fine motor coordination. Other behavioural manifestations include irritability, anxiety, moodiness, several negative symptoms (e.g. apathy, disinterest, anhedonia), progressive dementia and psychiatric manifestations [40]. HD has a prevalence of 7–10 cases per 100,000 in Caucasians, and is less frequent in Black and Asian populations. People at risk or who present with signs of HD can benefit from genetic testing in special HD genetic centres. However, according to self-reports, only few people decides to perform the test, presumably due to the lack of effective clinical treatment. Thus, even if genetic

Table 1
Natural compounds and effects on autophagy in selected pathological conditions [31].

Compound	Origin	Pathological conditions	Effects	References
Arctigenin	Asteraceae	AD[a]	↓ Aβ production ↑ autophagy ↓ (Akt)mTOR ↑ AMPK/raptor pathway	[250]
Resveratrol	Grapes		↑ autophagosome formation ↑ autophagy	[251]
Triptolide	Tripterygium		↑ autophagy ↓ Aβ toxicity	[252]
Curcumin	Turmeric		↑ autophagy via PI3K/Akt/mTOR ↓ Aβ production	[253]
Trehalose	Non-mammalian species		↑ autophagy Direct inhibition of Tau aggregation ↓ERK and HSPA8	[87–90]
Isorhynchophylline	Uncaria	PD	↑ autophagy	[254]
Trehalose	Non-mammalian species		↑ autophagy ↑ MAP1LC3B-II	[255]
Resveratrol	Grape		↑ autophagy ↑ HO-1 expression	[256]
Onjisaponin B	Radix Polygalae	HD	↑ autophagy via AMPK/mTOR	[257]
Trehalose	Non-mammalian species		acts as a chaperone ↑ autophagy	[60]
Epigallocatechin gallate	Green tea		↑ autophagy ↓ Htt protein accumulation	[258–262]
Berberine	Isoquinoline alkaloids		↑ autophagy ↓ Htt protein accumulation ↓ SQTM-1 expression	[263]
Trehalose	Non-mammalian species	ALS	↑ autophagy via mTOR-independent pathway ↓ SOD1 and SQTM-1 expression ↑ MAP1LC3B-II ↑ nuclear translocation of FOXO1	[143,264]

[a] Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; AMPK, AMP-activated protein kinase; ERK, extracellular signal-regulated kinase; FOXO1, Forkhead box protein O1; HD, Huntington's disease; HO-1, heme-oxygenase-1; Htt, Huntingtin gene; MAP1LC3B/LC3, microtubule-associated protein-1 light chain 3β; mTOR, mammalian target of rapamycin; SQTM-1/p62, sequestosome-1; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase, SOD1, superoxide dismutase-1.

testing is available, preimplantation to ensure that offsprings are not carrying the abnormal gene, very few parents benefit from this option [41].

2.1.2. Physiopathology

The major pathological modification in HD brains is a selective neuronal loss both in the cortex and the striatum. In HD, the mutant protein results from an aberrant expansion and repeat of the trinucleotide CAG in exon 1 of *huntingtin* (Htt) gene leading to an increase of the length of the polyglutamine domain located at the N-terminus [31] of the mutated Htt (mHtt) protein. An expansion of the CAG repeat over 35 motives is linked with the development of disease, and the length of polyglutamine domain is inversely correlated with the age-onset of HD [42,43]. The accumulation of misfolded mHtt generates the formation of extra-nuclear inclusion bodies in the brain, resulting then to a selective loss of striatal GABAergic neurons. The way by which CAG repeat is linked to HD is still incompletely understood. Authors reported expression of mHtt in numerous neuronal and non-neuronal tissues, but it mainly occurs in neuronal zones such as the medium spiny neurons of the striatum, the *substantia nigra*, the cortex, and Purkinje cells of the cerebellum [44]. Data evidenced that expanded CAG repeat in mHtt favors the cleavage of abnormal protein products, and degraded fragments, most particularly those cleaved by caspase-6, are likely related to their nuclear translocation with toxic repercussions [45]. It has been further demonstrated that the increasing cleavage products of mHtt induce dramatic effects on susceptible neurons (e.g. dysfunctions of mitochondria, nuclear transcription, axonal transport, proteasome, neurotransmitter release) [46–48]. Only caspase 6-mediated cleavage induces toxic outcomes of mHtt. Thus, if this specific cleavage is hindered, transgenic mice displaying the HD phenotype will not develop progressive neurodegenerative failures. In another conditional murine model of HD, blockade of the HD gene in symptomatic mice (i.e. displaying neuronal inclusions, progressive motor dysfunction) led to reversibility of symptoms and complete remission, raising the possibility that HD might be reversible [49].

2.1.3. Autophagy dysfunctions

Autophagy seems to be significantly altered in HD. Thus, accumulation of autophagic vacuoles has been observed in human HD samples and in experimental models [50,51]. The expression of a number of autophagy and ubiquitination pathways genes has also been found to be modified in oligodendrocytes and neurones of HD patients [12,52,53]. Htt, which displays two potential KFERQ-like motifs potentially targeted by HSPA8 for subsequent degradation via the CMA process, is also subject to ubiquitination that is crucial for its degradation via both the UPS and autophagy degradation mechanisms. The alteration of autophagy gene expression (e.g. genes coding for MAP1LC3B, LAMP2, and ULK2) may significantly contribute to the accumulation of damaged and misfolded proteins. Thus a polymorphism in *ATG7* was correlated to the severity of HD [54]. Other mutations, for example in Beclin-1, have also been described [55]. Furthermore, the interaction of mHtt and of Htt-interacting protein Rhes with Beclin-1 complex, by sequestrating Beclin-1, may also directly alter the initiation of autophagy [55,56]. In vitro, activation of autophagy decreased both the number of Htt aggregates, as well as the expression level and toxicity of the mHtt protein [57].

2.1.4. Therapeutic approaches

So far, effective causal therapy delaying the onset of symptoms or stopping the progressive neuronal dysfunction is unavailable in humans (Table 2) and, as a consequence, only palliative treatments exist, essentially relying on behavioural symptoms management. This management is adapted to the gravity of these events. An exhaustive review has been published that dealt with this issue [39]. Generally, having observed the inefficacy of a treatment in family members, most sufferers accept the lack of meaningful therapy. Antidepressants and drugs aimed at

Table 2
Synthetic view of clinical and pathophysiological characteristics of neuronal diseases and their treatment.

	HD[a]	AD	PD	MS	ALS	CIDP	NPSLE
Causes (protein, deposition…)	Huntingtin	Aβ, hyperphosphorilated tau (microtubule-associated protein)	α-synuclein/SNCA	Antigenic peptides derived from myelin-associated proteins (MBP, PLP, MOG)	SOD1, TDP43, FUS	Unknown	AutoAbs, ICs deposition [237,238] [240,241]
Where in the nervous system?	Cortex, Striatum, Substantia nigra, Purkinje cells of the cerebellum	Hippocampus, Cerebral cortex	Substantia nigra, Locus coeruleus	Brain, Spinal cord, Optic nerves	Cerebral cortex, Thalamus, Spinal cord	PNS	Hippocampus, Cerebral cortex, Amygdala, Hypothalamus
Pathological features	Inclusions with mHtt and polyglutamine	Extracellular Aβ plaques, neurofibrillary tangles comprising filaments of intracellular hyperphosphorilated tau	Lewy bodies, Lewy neurites, selective degeneration of dopaminergic neurons, reactive gliosis	CNS demyelination evidenced by RMI, oligoclonal bands and elevated levels of IgG Abs in CSF, disturbed Eps (visual, auditory, sensory)	Selective degeneration of upper and lower motor neurons	Cytoalbuminologic dissociation, interstitial and perivascular endoneurial infiltration by lymphocytes and macrophages, damage to the myelin sheath	Vasculitis, thrombosis, microvascular infarction
Clinical manifestations	Mild chorea, dystonia, bradykinesia, slowing of ocular movements, decline of fine motor coordination. Irritability, anxiety, moodiness, progressive dementia, psychiatric manifestations	Progressive senile dementia, cognitive, memory and behavioural impairments	Movement disorders, bradykinesia, resting tremor, rigidity, postural instability, dementia, depression, anxiety, gastrointestinal disorder	Motor, sensory, and autonomic deficits, fatigue, defects in mood and cognitive function, vision and audition difficulties	Muscle cramps and twitches, progressive muscle weakness, abnormal fatigue of the arms and/or legs, slurred speech	Chronic progressive symmetrical weakness, impaired sensory function (mostly in distal muscles), abnormal sensations, fatigue, areflexia (absence or decreased deep tendon reflexes)	Central (focal and diffuse events) and peripheral manifestations
Therapy	Lack of effective treatment; only palliative treatments relying on behavioural symptoms management	Lack of effective treatment; cholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) and memantine are usually used to treat the cognitive symptoms	Lack of effective treatment; dopamine agonists, levodopa, amantadine, anticholinergics, MAO-B and COMT inhibitors, apomorphine, duodopa, surgical therapy (deep brain stimulation, thalamotomy, pallidotomy), supportive therapy (physiotherapy, occupational therapy, speech and language therapy, diet advice)	Immunomodulating agents (IFNβ, glatiramer acetate, teriflunomide, daclizumab, fingolimod, dimethyl fumarate); novel therapies are natalizumab, alemtuzumab, mitoxantrone, corticoids, therapy alternatives that adapt with the manifestations and involve symptomatic and supportive treatment	Lack of effective therapy; supportive care (nutrition, respiratory support, physical and occupational therapies)	Steroids (prednisone), alone or in combination with immunosuppresssors (rituximab, cyclophosphamide), ciclosporin, plasmapheresis, IVIg, physiotherapy	Lack of effective treatment; corticoids, immunosuppressors, anticoagulants; B cell-depletion, plasmapheresis, intrathecal methotrexate or dexamethasone injection, IVIg, rituximab and haematopoietic stem cell transplan in case of refractory NPSLE; therapy alternatives (NSAIDs, anxiolytics, antidepressants, antipsychotics, cognitive rehabilitation, anti-epileptics); management of any aggravating factors for NP events; drugs acting on autophagy (chloroquine, hydroxychloroquine, P140/Lupuzor™)

[a] Abbreviations: Abs; antibodies; AD, Alzheimer's disease; Aβ, amyloid β; ALS, amyotrophic lateral sclerosis; autoAbs, autoantibodies; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CNS, central nervous system; COMT, catechol-*o*-methyltransferase; Eps, evoked potentials; FUS, fused in sarcoma protein; HD, Huntington's disease; ICs, immune complexes; IFNβ, interferon-β; IVIg, intravenous immunoglobulin; MAO-B, monoamine oxidase-B; MBP, myelin basic protein; mHtt, mutant Huntingtin; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; MS, multiple sclerosis; PD, Parkinson's disease; PNS, peripheral nervous system; NP, neuropsychiatric; NPSLE, neuropsychiatric systemic lupus erythematosus; PLB, proteolipid protein; SOD1, superoxide dismutase 1; SLE, systemic lupus erythematosus; TDP43, TAR DNA-binding protein 43.

stabilizing mood disorders and depression are prescribed if irritability. For more aggressive behaviour, neuroleptics are administered. Due to the cost and the numerous secondary effects generated, antichoreatic medications are only provided to patients when involuntary movements interfere dramatically with routine activity. To date, preliminary evidence for the benefits of pallidal deep brain stimulation for chorea suppression had been however published [58].

Regarding the possibility to target autophagy in this indication, promising data have been obtained in human cells and mouse models of HD with mTOR-independent or -dependent small molecules and

natural compounds (e.g. trehalose, rapamycine, lithium, rilmenidine; Table 1). The data collected so far rather support the potential of inducing autophagy to treat HD [59–64]. Future investigations will tell us however if targeting the autophagy processes is an attractive alternative way for treating HD.

2.2. Alzheimer's disease (AD)

2.2.1. Description

AD, which is the most prominent cause of senile dementia worldwide, is a neurodegenerative irreversible age-related disease clinically characterized by cognitive dysfunction manifesting as memory loss, visuospatial, judgement and decision-making deficits. Pathophysiological features of the disease are massive hippocampal neuronal loss, focal cortical atrophy, altered neuronal connectivity, pathogenic formation of extracellular senile plaques containing the β-amyloid peptide (Aβ, produced by sequential cleavages of amyloid precursor protein, APP), and intracellular neurofibrillary tangles composed of hyperphosphorylated aggregates of the microtubule-associated protein Tau [65] (note that phosphorylation of Tau at threonine residue 205 at the postsynapse has recently been discovered to be protective) [66]. AD is essentially a sporadic disease, with age as principal risk factor; however, autosomal dominant familial forms are also well known. The first mutation causing a familial form of disease has been recognized in the APP encoding-gene in chromosome 21 [67], and subsequently, other mutations have been observed in the presenilin 1 gene on chromosome 14 and presenilin 2 gene on chromosome 1 [68,69].

2.2.2. Pathophysiology

Nowadays, it is well accepted that AD pathogenesis arises from perturbation in the homeostasis (weak clearance) of Aβ, and from accumulation of lysosomes and their hydrolases within neurons. This last process, however, is not restricted to the neuronal zone, but includes interactions with immunological mechanisms in the brain [70]. Neuroinflammation represents a key trigger of the AD pathogenesis, as the binding of Aβ fibrils (which are resistant to enzymatic degradation) and soluble Aβ oligomers to microglia via cell-surface receptors (e.g. CD36, CD14, CD47, α6β1 integrin, SCARA1) and Toll-like receptors (e.g. TLR2, TLR4, TLR6, TLR9) results in production and release of inflammatory mediators [70,71], this mechanism being important part of the inflammation process of AD. To comfort this observation, in vitro studies have shown that a genetic deletion of some of these receptors decreases the Aβ-induced production of cytokines and hampers amyloid accumulation as well as inflammasomes activation [70–72]. Concerning the microglial mechanisms of Aβ clearance described so far in AD, studies showed that microglia interacts with the two forms of Aβ in different manners. After binding to innate immune receptor complex and initiation of intracellular signaling cascades, microglia phagocytes Aβ fibrils, which then penetrate the endolysosomal pathway. This is not the case with soluble Aβ oligomers, which can be degraded extracellularly by several proteases [73]. Inflammatory responses, such as increased cytokine concentrations, influence the activation status of microglia and subsequently regulate their ability to take up, degrade and clear Aβ. Genetic analysis revealed the implication of several genes encoding glial clearance of misfolded proteins in the pathogenesis of sporadic AD [74–76]. Mutation in the extracellular domain of triggering receptors expressed on myeloid cells (TREM2), which is usually highly displayed by microglia [77] and is involved in the phagocytic removal of neuronal fragments [78], augments risk for the disease comparably as what is observed with apoliproprotein E ε4. As well, a single-nucleotide polymorphism in the gene encoding the microglial surface receptor CD33 decreases phagocytosis of Aβ by peripheral macrophages isolated from heterozygous and homozygous mutation carriers. Finally, in a functional dissection of the *CD33* AD susceptibility locus, authors observed an association between the *rs3865444*^{C} risk allele and greater cell surface expression of CD33 in the monocytes, which was also linked with diminished internalization of Aβ 42 peptide, accumulation of neuritic amyloid pathology and fibrillar amyloid on in vivo imaging, and increased numbers of activated human microglia [76].

2.2.3. Autophagy dysfunctions

Autophagy, particularly macroautophagy, is associated with the pathogenesis of AD as many neurites, including synaptic terminals, containing important levels of autophagosomes with Aβ deposits and other prelysosomal autophagic vacuoles are commonly observed in the brain of AD patients [18,79]. Autophagy is also evident in the perikarya of affected neurons, particularly in those with neurofibrillary pathology, where it is associated with a relative depletion of mitochondria and other organelles. The striking accumulation of immature autophagic vacuoles in dystrophic neurites suggest that the transport of autophagic vacuoles and their maturation may be impaired, thereby impeding the suspected neuroprotective functions of autophagy. Several molecular mechanisms linked to autophagy have been shown to be altered in AD. Thus, some defects in the proteolytic properties of lysosomes resulting from a lack of control of luminal pH have been described [80]. Presinilin-1, which is involved in the regulation of lysosome acidification by controlling the maturation of a v-ATPase subunit might be implicated in this defective process [81,82]. In the autophagosomes that accumulate in cellular and animal models of AD, an excess of amyloid precursor protein and of the protease complex that is involved for its cleavage into the pathogenic peptide β1-42 converts these autophagic vesicles into an endogenous reservoir of this pathogenic product [83]. Beclin-1 also represents a major player in autophagy deficiencies in AD [84]. Beclin-1 mRNA and protein levels are decreased in brain regions of AD human and mouse models of AD. Overexpressing Beclin-1 in AD mice was shown to reduce intracellular accumulation of Aβ and extracellular deposition of Aβ plaques. Finally, a consequence of this dysfunction is that late autophagic compartments persist abnormally longer in the cytosol, possibly leading to the release of lysosomal enzymes that can activate cell death [85].

2.2.4. Therapeutic approaches

Currently, there is no cure for AD, but drug and non-drug treatments may help with both cognitive and behavioural symptoms. Two types of medications (e.g. cholinesterase inhibitors such as donepezil, rivastigmine, galantamine, and memantine; Table 2) are usually used to treat the cognitive symptoms of AD. Researches are intensively conducted in order to find new treatments able to slow down the course of the disease and improve the quality of life for people with dementia. In line with the observations related above in relation with autophagy mechanisms, several small molecules targeting those processes were found to exert cellular and clinical protective functions in animal models (Table 1). They are rapamycine, which attenuates cognitive deficits and reduces Aβ levels [59,86] and trehalose, which was shown to reduce the levels of Tau aggregates and improved neuronal survival [87–90], for example. These results suggest that a possible way to hinder the progression of AD might be achieved by using drugs that activate autophagy.

2.3. Parkinson's disease (PD)

2.3.1. Description

PD, that affects 3% of individuals older than 75 years of age, is a common progressive neurodegenerative disorder characterized by bradykinesia, resting tremor, rigidity, postural instability, in which dopaminergic and catecholaminergic neurons are dramatically dying in many cerebral nuclei (e.g. *substantia nigra*, locus coeruleus). Another important characteristic feature of this disease is accumulation of SNCA/α-synuclein protein, further leading to deposition of intracellular inclusions (e.g. Lewy bodies in neuronal somata) and degenerating ubiquitin-positive neuronal processes (e.g. Lewy neurites) in surviving dendrites and axons [91,92] (Table 2). Studies have indicated that the

neuropathological changes observed in PD follow a chronological and regional pattern; non-motor symptoms such as loss of smell, constipation, and sleep disorders are warning signs and help to diagnose PD before beginning of characteristic tremor, bradykinesia, rigidity and postural instability [93]. The characteristic brain pathology and motor symptoms of PD are quite well established, but the details of the disease cause and course are much less depicted. PD is generally sporadic, but numerous PD-related genes have already been described in familial forms of the disease. Mutations in the genes encoding for SNCA, leucine-rich repeat kinase, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase-induced putative kinase 1 (PINK1) and Parkin have thus been identified [16,94,95]. Loss of function of the latter can lead to damaged mitochondrial accumulation and protein aggregates, and then to cellular degeneration. PINK1 is a serine/threonine kinase stabilized at the surface of damaged mitochondria, where it phosphorylates ubiquitin and Parkin, promoting the recruitment of mitophagy receptors [96,97].

2.3.2. Pathophysiology

Aging, mitochondrial dysfunction resulting from complex I defects [98], cellular OS, particularly in dopaminergic neurons in the *substantia nigra* and noradrenergic neurons in the locus coeruleus [99], environmental exposure to heavy metals and pesticides, autophagic alterations and proteins aggregation have been proposed as crucial processes in the pathogenesis of PD [100]. As already noticed, SNCA plays a critical role in the pathogenesis of PD. Environmental toxin, such as rotenone, triggers exocytosis of SNCA from enteric and sympathetic neurons into the extracellular space [101]. Thus, SNCA is endocytosed into neighbouring neurons where it induces aggregation of endogenous SNCA [102]. Such aggregates perturb mitochondrial activity and induces OS in the neurons [99,103]. Studies reported that extracellular SNCA facilitates the release of inflammatory mediators, thus ultimately leading to inflammation [104], and that neuron-derived SNCA induces cell fragmentation and activation of caspase 3, which are signs of apoptosis.

2.3.3. Autophagy dysfunctions

Independent authors demonstrated that SNCA is degraded by macroautophagy and CMA in neuronal cells underlying again the importance of these processes as degradation machinery in the CNS, and that impairment of these systems, notably CMA, lead to accumulation of neurotoxic SNCA aggregates [105–107]. On possible cause of CMA defect is the decline during aging of LAMP2A, which acts as a CMA receptor together with HSPA8 [5]. The levels of two CMA makers LAMP2A and HSPA8 are decreased in SNCA inclusion-forming regions of the amygdala and *substantia nigra* of PD patients. Results obtained in rat models showed that LAMP2A could restore CMA activity and brain neuroprotection [108,109]. Gene transferred Beclin-1 that activates autophagy also ameliorates the synaptic and dendritic pathology and decreases the accumulation of SNCA in the limbic system of PD patients [110]. Mitophagy could also influence a disease like PD since mutations in genes cording for PINK1 and Parkin, which are involved in mitophagy (see above), are responsible for early onset of recessive form of PD [111].

2.3.4. Therapeutic approaches

There is currently no standard treatment capable to block or slow-down neuronal loss. During the early stages of PD, patients may not need any treatment as symptoms are usually mild. However, they may need regular appointments with specialist allowing their condition to be monitored. This means that the treatment for each person is based on his or her symptoms. Treatments include oral medication (e.g. dopamine agonists that either temporarily replenish dopamine or mimic the action of dopamine, levodopa, amantadine, anticholinergics, monoamine oxidase-B and catechol-*o*-methyltransferase inhibitors), non-oral medication (e.g. apomorphine, duodopa), and surgical therapy (e.g. deep brain stimulation, thalamotomy, pallidotomy, subthalamotomy) (Table 2). Surgical treatment is reserved for PD patients who have exhausted medical treatment of PD tremor or who suffer profound motor fluctuations (e.g. wearing off, dyskinesia). Other treatments include supportive therapy (e.g. physiotherapy to relieve muscle stiffness and joint pain through movement and exercise, occupational therapy, speech and language therapy, diet advice) and lifestyle modifications like getting more exercise. These therapies make living with PD easier and help to deal with symptoms on a day-to-day basis. Generally, for people with PD, exercise is more than healthy: it is a vital component to maintaining balance, mobility and the ability to perform activities of daily living. It is also important to threat additional symptoms which include depression and anxiety, problems with sleeping such insomnia, excessive sweating, dysphagia, excessive drooling, urinary incontinence, and dementia.

With regard to autophagy, as in the case of other neurodegenerative diseases described above, the therapeutic use of autophagy up-regulating drugs may be beneficial in PD. A number of small chemical molecules (e.g. rapamycin and tunicamycin, an antibiotic, which inhibits GlcNAc phosphotransferase) and natural compounds (Table 1), as well as gene therapy strategies have been evaluated with success in preclinical models [12]. Before extended clinical studies can be engaged, decisive investigations remain to be done to evaluate whether targeting autophagy with such molecules is safe and devoid of deleterious side effects.

2.4. Multiple sclerosis (MS)

2.4.1. Description and pathophysiology

MS is a chronic, relapsing-remitting CNS inflammatory disease that manifests in several motor, sensory, and autonomic deficits [112]. It is distributed in time, and ends by dramatic disability. Most patients present with an acute episode manifesting as optic neuritis, brain-stem dysfunction or incomplete transverse myelitis [112]. Although neurological symptoms are characteristics of MS, defects in mood, affect and cognitive function can occur as the disease proceeds [113]. As what is observed for the majority of autoimmune diseases, women are more frequently affected by MS.

2.4.2. Pathophysiology

An interaction between several genetic susceptibility (e.g. HLA-DR1501, HLA-DQ0601 alleles) and environmental factors is key determinants of risk [114]. Autoimmune activity may also play important role in the pathogenesis of MS. Animal models, such as experimental autoimmune encephalomyelitis (EAE) that partially mimics MS and is considered as a predominantly (but not exclusively) CD4 T cell-mediated disease, provided evidence that antigenic peptides are derived from myelin-associated proteins; thus, myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein have been extensively studied as potential autoantigens.

2.4.3. Autophagy dysfunctions

As in other cases of neurodegenerative diseases described above, autophagy alterations have been documented in MS and EAE. However, here, the defects seem to be different. *Atg5* expression has been shown to be increased during EAE in mice and in MS patients [115]. SQSTM1 expression was reduced in the spinal cord of naïve and diseased mice at all stages of EAE, whereas levels of MAP1LC3B-II were increased during early EAE and reduced during severe EAE, indicative of an induction of autophagy in spinal cord with progressive autophagy flux during EAE [116]. Loss of *Atg7* in dendritic cells reduced the incidence and onset of EAE by reducing in vivo priming of T cells without affecting $CD8^+$ T cells and NK cells [116].

2.4.4. Therapeutic approaches

Even if we can notice evolution of the treatment over the last years, MS still leads to chronic disability and poor quality of life (Table 2). Usually, patients are provided with immunomodulating agents (e.g.

interferon-β, glatiramer acetate, teriflunomide, dimethyl fumarate). Novel therapies are natalizumab, an humanized anti-alpha4 integrin monoclonal Ab (mAb), alemtuzumab, an humanized mAb targeting CD52, an antigen of unknown function which is found on B and T lymphocytes, and fingolimod or FTY720, an immunomodulator of sphingosine 1-phosphate receptor [117,118]. In animal models, administration of autophagy-lysosomal inhibitor chloroquine, before EAE onset delayed disease progression and when administrated after the onset, reduced disease severity, at least partially [116]. Although a clinical trial in patients with established MS showed that chloroquine given orally could not provide long term benefit over placebo [119], the data obtained so far support the view that specific autophagy inhibitors used in combination with other drugs might ameliorate the clinical status of patients with MS.

2.5. Amyotrophic lateral sclerosis (ALS)

2.5.1. Description

Initially described by Charcot in 1868, ALS is a dramatic neurodegenerative disease selectively affecting motor neurons, generally fatal within a few years of disease onset, and which is increasingly prevalent in last years (about 2–3 per 100,000 individuals). The primary events involve upper and lower motor neurons in the CNS and neuromuscular junction at the periphery. There is secondary muscle wasting and involvement of other brain regions, especially those controlling cognition. The occurrence of ALS is mostly sporadic, but about 5–10% of cases are of familial origin [120]. Recently, authors observed that Gulf War Veterans present a twofold increased risk for developing ALS [119].

2.5.2. Pathophysiology

Despite much research and effort, no clear insights into a pathophysiological mechanism have emerged so far for this disease. Proposed pathogenic pathways leading to motor neuron death include glutamate toxicity, mitochondrial dysfunction, inflammation, OS, glial activation, cytoskeletal abnormality, apoptosis, and protein aggregates [121,122]. An increasing number of genetic factors are recognized. They include a hexanucleotide repeat expansion of the *C9orf72* gene and mutation of superoxide dismutase-1 (*SOD1)* gene (in familial forms of ALS; approximately 10% of cases). Mutations in fused in sarcoma protein (FUS) and transactive response DNA binding protein 43 kDa *(TDP-43)* have already been reported [121,123–130]. The accumulation of proteins, including SOD1, TDP-43 and ubiquitin, and injured mitochondria in the motor neurons are crucial pathological features. Recently, a growing body of evidences provide a new insight on the importance of glia cells and neuroinflammation in relation to the motor neuronal damage via the non-cell autonomous pathway [120,131]. There remains controversy, or lack of knowledge, in explaining how cellular events manifest as the complex human disease, and also as to how well cellular and animal models of disease relate to the human disease.

2.5.3. Autophagy dysfunctions

Controversial information coexists in the literature regarding the nature and extent of possible autophagy defects in ALS [132]. Autophagosomes accumulate in brain tissues from ALS patients [133] supporting a scheme in which autophagy is activated and clearance inhibited. Macroautophagy was also found to be activated in motor neurons of ALS mice at early stage with an accumulation of MAP1LC3B-II and SQSTM, an increase of autophagic vacuoles, aggregated ubiquitin and SOD1 proteins associated to MAP1LC3B-II [134]. However, formation of autophagosomes has also been described as diminished in cells expressing ALS-mutant FUS or with reduced levels of C9orf72 expression [135–137]. Mutations in SQSTM1, valosin-containing protein (VCP), dynactin (a protein complex that activates the dynein motor protein, enabling intracellular transport) and RAB7 (a member of small GTPases that is important in the process of endosomes and autophagosomes maturation) have also been described in ALS [138–141]. These data indicate that diverse mechanisms related to autophagy could occur concomitantly. Abnormalities may be different in distinct neuronal structures, and change with the time of the disease, the evolution and genetic predisposition.

2.5.4. Therapeutic approaches

Currently, there are no effective treatments for ALS related to pathogenesis and stopping progression of the illness (Table 2). Greatest advances to date relate to management of symptoms, often in a multidisciplinary way, and supportive care (i.e. nutrition, respiratory support), in order to improve the daily life of patients and their families [142]. Administration of trehalose was reported to attenuate the motor dysfunction and prolong the survival of a mutant SOD1 murine model. The protective effects of trehalose have been claimed to be associated with autophagy activation [134,143] (Table 1). Other inducers of autophagy (i.e. rapamycin, lithium) have shown either protective or deleterious effects in different models of ALS [144]. The fact that some autophagy key elements can play distinct roles in ALS makes the development of autophagy-regulating molecules rather complex [139,140]. Recent data suggest also that future therapeutic strategy of ALS should be aimed at specific interception of pro-oxidant and pro-death signals in a cell-type specific manner [145,146].

2.6. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

2.6.1. Description

CIDP is an acquired immune-mediated inflammatory disorder of the peripheral nervous system (PNS; Table 2). This neurological disorder is closely related to Guillain-Barre syndrome and is considered the chronic counterpart of that acute disease. CIDP has a relapsing-remitting or chronic progressive course and often presents with a symmetrical weakness and impaired sensory function mostly in distal muscles (e.g. legs, arms), paraesthesia, fatigue, and absent or diminished deep tendon reflexes (areflexia), which evolves slowly over at least 2 months. The disease is caused by damage to the myelin sheath (i.e. the fatty covering that wraps around and protects nerve fibres) of the peripheral nerves. Although it can occur at any age and in both genders, CIDP is more common in young adults, and in men more than in women [147,148]. The disease is a treatable cause of acquired neuropathy and initiation of early treatment to prevent loss of nerve axons is recommended. However, some individuals are left with some residual numbness or weakness.

2.6.2. Physiopathology

The pathogenesis and pathophysiology of CIDP still remain unclear as the target antigens and immunological mechanisms underlying the disease have not yet been identified. However, current knowledge about the pathogenic mechanism involved in CIDP supports an autoimmune origin, in which both cellular and humoral factors are implicated and myelin is presumably the target of the immune attack [149]. Immune cells, including monocytes/macrophages and T lymphocytes, are known to infiltrate the peripheral nerve in patients affected by CIDP [150–153], and several inflammatory genes are upregulated in sural nerve biopsies from patients with this disease [154]. Moreover, patients with CIDP have increased serum levels of pro-inflammatory cytokines [155–157], suggesting T-cell activation. Humoral factors also play a significant role in CIDP as suggested by the beneficial effect of plasma exchange, which removes putative antigenic antibodies (in addition to other inflammatory mediators). Furthermore, passive transfer of serum or IgG from CIDP patients to rats can induce disease and demyelination [158]. Complement-fixing immunoglobulin deposits have been reported on nerves from CIDP patients [159] and antibodies (Abs) to peripheral myelin proteins, like P0, P2 and PMP22 have been found in small numbers of CIDP patients [158,160].

2.6.3. Autophagy dysfunctions

Nowadays, there are no investigations studying autophagy processes in CIDP. The only study on inflammatory demyelinating polyneuropathies was made on experimental autoimmune neuritis (EAN), the animal model mimicking the classical monophasic acute form of Guillain-Barre syndrome. In this recent study based on an EAN rat model induced by the synthetic neuritogenic peptide $P2_{57-81}$, in parallel with the clinical scores that were augmented after immunization, the number of inflammatory cells, the histological scores, and Beclin-1, MAP1LC3B-II expression levels and the ratio MAP1LC3B-II/I were significantly increased, and SQSTM1 expression decreased in sciatic nerves in the EAN model group compared with control rats [161]. Together, these data suggest that autophagy activity is increased in nerve tissue of EAN rats. The macroautophagy inhibitor 3-methyladenine, which acts at the initiation step of autophagy (Fig. 1), partially reversed the pathophysiological signs of the disease in EAN rats (clinical and histological scores, body weight) and ameliorated the neurologic severity of EAN. At this stage, the mechanism of dysfunctional autophagy processes remains to be elucidated in EAN. In line with the findings described above, it could easily be argued that abnormal autophagy also occurs in CIDP.

2.6.4. Therapeutic approaches

Although it is most probably of autoimmune origin the aetiology of CIDP remains largely unclear. Nowadays, first line treatment includes corticosteroids such as prednisone (considered standard therapy because of its long history of use and cost effectiveness), which may be prescribed alone or in combination with immunosuppressant drugs. These latter are often of the cytotoxic class, including rituximab that targets B cells, and cyclophosphamide that reduces the function of the immune system. Cyclosporine that binds to immunocompetent lymphocytes, especially T cells, has also been used in CIDP. Plasmapheresis (plasma exchange) and intravenous immunoglobulin therapy are effective but are very expensive. Some patients are also refractory to these strategies. Non-cytotoxic immunosuppressant drugs include the anti-rejection transplant drugs azathioprine and mycophenolate mofetil. Although chemotherapeutic and immunosuppressant agents have shown to be effective in treating CIDP, significant evidence is lacking, mostly due to the heterogeneous nature of the disease in the patient population in addition to the lack of controlled trials. Physical therapy and occupational therapy may improve mobility, muscle strength and activities of daily living, and minimize the shrinkage of muscles and tendons and distortions of the joints. To the best of our knowledges, autophagy-targeted therapies have not been evaluated in CIDP.

2.7. Neuropsychiatric systemic lupus erythematosus (NPSLE)

2.7.1. Description

Neuropsychiatric (NP) commitment in systemic lupus erythematosus (SLE) is a dramatic complication of the illness with very serious manifestations that profoundly impact disease outcome and patients' quality of life (e.g. poor prognosis, tenfold increase in mortality rate) [162, 163]. It still remains a poorly understood form of SLE disease that can take a variety of aspects [164], affecting the central (CNS; most frequent, around 93%), the peripheral and the autonomous nervous system. The NP symptoms can be mild or severe, focal or diffuse, acute or chronic, active or not active, single or multiple, isolated or with sequential occurrence. Taking all these considerations into account, it appears quite normal that different pathogenic mechanisms drive different clinical NP phenotypes [165]. NPSLE classification evolves for several years [166]. In 1999, the American College of Rheumatology (ACR) published a standard nomenclature for NPSLE with 12 CNS and 7 PNS syndromes, which includes NP manifestations as diverse as mood and anxiety disorders, depression, cognitive dysfunction, acute confusion state, psychosis and seizures [164]. However, although ACR classification can be viewed a milestone in the knowledge of NPSLE, providing definition, diagnostic criteria, exclusion criteria, associations (i.e. consideration of concomitant or pre-existing comorbidities as potential confounding factors), and recommendations to ascertain each NP event, its utility has appeared of limited value in the daily practice [165].

2.7.2. Pathophysiology

No single pathogenic mechanism is likely to explain all the NP manifestations displayed by SLE patients. Rather, multiple pathways, often interrelated, seem to be implicated. Thus, genetic (i.e. non-white people display higher risk for developing SLE), neuroendocrine (i.e. women are more susceptible to the disease, with a peak incidence in childbearing age) and environmental components are engaged in immune dysfunction and emergence of NP symptoms in NPSLE. Polymorphisms in TRPC6 (encoding for the transient receptor potential cation channel, subfamily C, member 6, a sodium/calcium-permeable cation channel expressed in the brain, kidneys and lungs) and TREX1 (encoding for DNAse III) seem to be associated to NPSLE [167–169]. Two mechanisms have mainly been described. The first is of inflammatory/neurotoxic origin and involves activation of the hypothalamic-pituitary-adrenal axis and the vagus nerve, blood–brain barrier (BBB) leakage, upregulation of autoantibodies [particularly to *N*-methyl-D-aspartate receptor (NMDAR)/dsDNA, ribosomal P protein, MAP-2, poly(ADP-ribose) polymerase-1 [117,170,171]] and circulating cytokines, with concomitant penetration in the brain parenchyma. All these dysfunctions contribute to diffuse NP manifestations. The second mechanism, which mostly contributes to focal NP events, and to a lesser extent to diffuse ones, is of vascular/ischaemic/thrombotic origin and involves principally antiphospholipid (e.g. lupus anticoagulant, anti-β2 glycoprotein-1) Abs and immune complexes [172–177].

2.7.3. Autophagy dysfunctions

Nowadays, possible alteration of autophagy processes has not been especially investigated in nervous tissues of CNS and PNS from patients with NPSLE and therefore it is not known if a link exists between autophagy dysfunction and NP involvement in SLE. However, autophagy failures have been detected in immune cells collected from the spleen and peripheral blood in murine and human lupus [30,178]. Thus, the autophagic vacuole load was found to be increased in T cells isolated from two genetically unrelated lupus-prone mouse strains and also from SLE patients [179]. This deregulation was even more obvious when T cells were stimulated by chemical activators of T cell receptor (TCR)-related signaling pathways. It further increased with age, contrary to what was found in control mice. This augmentation in autophagic compartments in SLE T cells was confirmed in three other independent studies [180–182]. Accumulation of MAP1LC3B-II, especially in naive CD4 T cells, was described [180]. Autophagic activity has also been shown to be upregulated in B cells from SLE patients and mouse models for lupus [181, 183]. In B cells from MRL/lpr lupus-prone mice, CMA has also been found to be drastically activated as evidenced by an accumulation of HSPA8 and LAMP2A markers [184,185]. The lumenal pH of lysosomes was also abnormally elevated [184].

Since the discovery of polymorphisms on *ATG5* were identified in lupus [186–188], genetic predisposition in relation to autophagy had been suggested in SLE. Cellular and molecular findings are effectively in agreement with this claim. However, indirect causes could also impair autophagic activity and favor chronic inflammation in this context. Additional investigation have thus to be undertaken to reinforce this assumption especially as some studies failed to identify *ATG5* polymorphisms in certain cohorts of patients [189].

2.7.4. Therapeutic approaches

As no reliable biomarkers do exist, the best management and therapeutic strategy of NPSLE is quite difficult to set up, and remains essentially empirical and based on the clinician's opinion. NPSLE treatment as a whole is not applicable and a multifocal approach has to be considered, which is tailored to cure each NP symptom displayed by NPSLE sufferers. However, a series of recommendations have been published in 2010 by

the *European League Against Rheumatism* [162]; a rapid identification and management of any aggravating factors for NP events, including metabolic dysfunction, infections and predisposing medications (e.g. corticosteroids that present dramatic neuronal toxicity), is imperative [165]. According to the symptoms and their severity (mild versus severe), several treatments can be used. They include anti-coagulants and anti-aggregation drugs if patients present with anti-phospholipid syndrome, vasculitis, ischaemia and/or thrombosis; glucocorticoids and/or immunosuppression (e.g. corticosteroids, azathioprine, cyclophosphamide, hydroxychloroquine, methotrexate, mycophenolate mofetil) if inflammation predominates, and B cell-depletion in case of NPSLE disease that is refractory to classical immunosuppression [174,175,190,191]. In this last case, treatments can also include plasmapheresis, intrathecal methotrexate or dexamethasone injection, intravenous immunoglobulin, rituximab and haematopoietic stem cell transplantation [172]. Therapy alternatives adapt with the manifestations and usually they involve symptomatic or supportive treatment (e.g. NSAIDs for symptomatic relief, antidepressants and anxiolytics if mood and anxiety disorders, antipsychotics if psychosis, cognitive rehabilitation if cognitive dysfunction, anticonvulsants and antiepileptics if seizures, analgesics if headaches, for example). Several drugs that were recognized to act on autophagy have been used for decades to treat patients with SLE. This is the case, for example, of lysomotropic agents as chloroquine and hydroxychloroquine, which raise intralysosomal pH, but have also several other independent targets and important secondary effects [30]. The P140/Lupuzor™ peptide currently evaluated in phase III clinical trials interferes with CMA (see below).

3. Down-regulating CMA hyperactivity by the peptide P140 rescues normal immune functions

3.1. P140 peptide

P140 peptide is a 21-mer fragment of the spliceosomal U1-70K small nuclear ribonucleoprotein that significantly ameliorates clinical and biological manifestations in lupus-prone mice [192,193] and autoimmune patients with SLE [194–196]. In a multicenter, randomized, placebo-controlled phase IIb clinical trial including patients with SLE, P140/Lupuzor™ had no adverse safety signals and met its primary efficacy end points. It is currently evaluated in a phase III clinical trial in the US, Europe and countries of the Indian Ocean.

P140 peptide encompasses residues 131–151 of the U1-70K protein and contains a phosphoserine residue at position 140, hence its name. This chemical modification, which was introduced during its synthesis, was shown later to specifically occur at an early stage of apoptosis, before the cleavage of the C-terminal part of the cognate protein by caspase-3 and the dephosphorylation of other serine residues by a PP1 phosphatase-mediated mechanism [197]. This post-translational modification at Ser140 is thus a natural and normal modification of the protein. This peptide, the sequence of which is highly conserved throughout evolution, is remarkably stable in different media ([184] and showed no immunogenicity in mice and patients when administered in saline [198,199]. Our first experimental in vivo and in vitro data led us to build a functional scheme in which P140 acted as an altered peptide ligand (or partial agonist), which modulates autoreactive T cell intracellular signaling induced upon autoreactive TCR engagement [192,200–202]. This attractive model fit well with our experimental data but could not explain the large diversity of autoantibodies and immune cells specificity that were regulated by P140 peptide. Our mechanistic views changed when we discovered that P140 selectively interacts with the constitutive heat-shock protein HSPA8 [198].

This discovery led us to examine more closely the effects of P140 on autophagy processes in which this chaperone protein is central [203,204] (Fig. 1). In fact, as described above, autophagy cellular aspects were not well known to the scientific community studying autoimmune diseases such as SLE, rheumatoid arthritis, Sjögren's syndrome or MS. It is only relatively recently that abnormalities in the macroautophagy pathway have been identified both in T and B cells of lupus patients [30,179–182]. Thus, in T cells, autophagic vacuoles were found to be

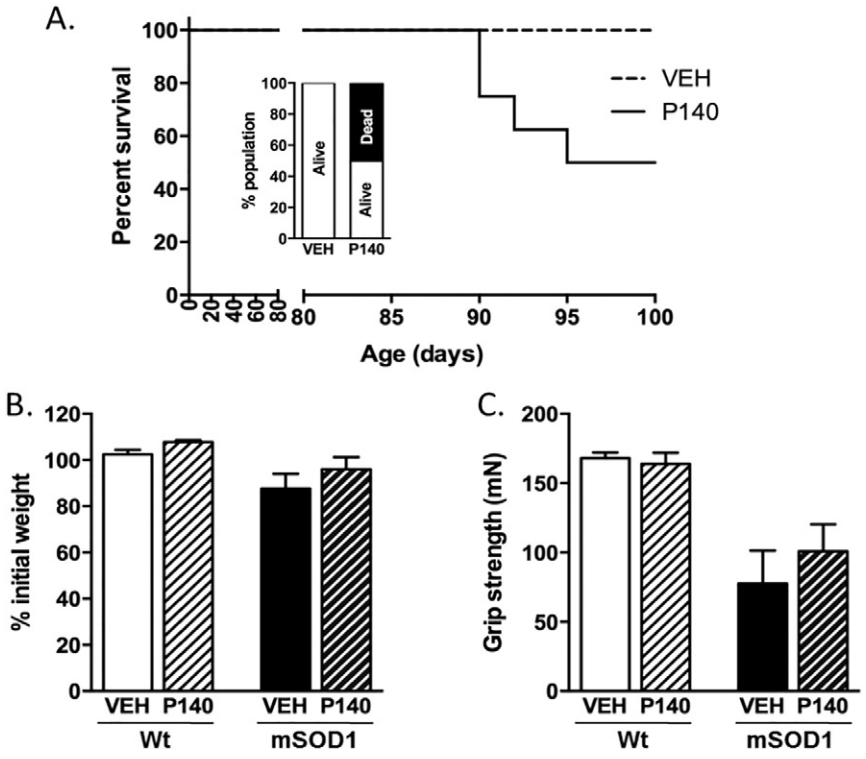


Fig. 3. P140 treatment shortens life expectancy of SOD1^{G86R} ALS mouse model. Male SOD1^{G86R} mice (mSOD1) or their wild type (Wt) littermates received either P140 peptide (4 mg/kg, 100 μL, intraperitoneal route; $n = 8$) or the vehicle alone (VEH, 0.9% NaCl, $n = 5$). (A) Kaplan-Meier survival curve of mSOD1 mice. After 20 days of treatment, 50% of P140-treated mice were dead as compared to VEH-treated mSOD1 mice. In the Wt group, P140 did not have any effect on survival (not shown). (B, C) Weight and grip strength were measured as described previously [249]. P140 did not modify these two mSOD1 mice. Abbreviations: ALS, amyotrophic lateral sclerosis; mSOD1, SOD1^{G86R} mice; VEH, vehicle; Wt, wild type.

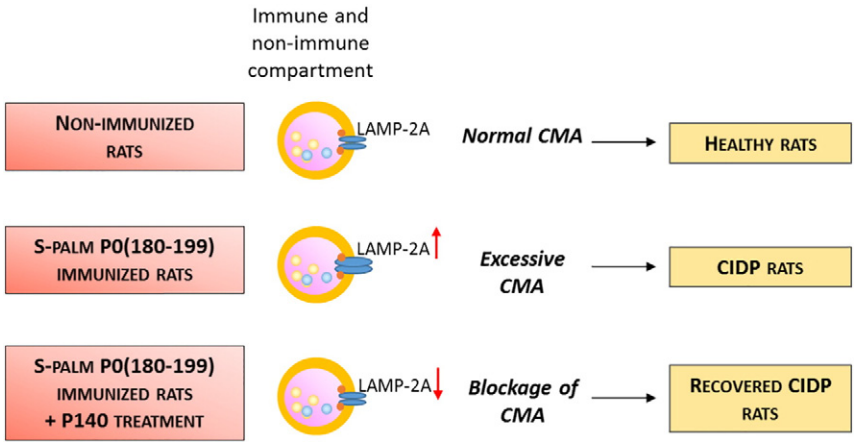


Fig. 4. Hypothetical autophagy processes in CIDP rats. Macroautophagy and particularly CMA, are altered in lymphatic system immune cells and non-neuronal cells of the peripheral nervous system in CIDP rats (also named chronic-EAN, S-palm P0(180-199) immunized rats) when compared to healthy rats (non-immunized rats). Treatment with the CMA-targeting P140 peptide considerably ameliorates the clinical and biological course of the disease in CIDP rats by restoring CMA processes. Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMA, chaperone-mediated autophagy; EAN, chronic experimental autoimmune neuritis.

more abundant and autophagosome-associated MAP1LC3-II isoform over-expressed (particularly in naïve $CD4^+$ T cells isolated from SLE patients), indicating that macroautophagy is hyperactivated. Macroautophagy appears particularly activated in naïve B cell subsets, and when autophagy inhibitors 3-methyladenine, bafilomycin A1 and chloroquine were used, plasmablast differentiation and survival hardly occurred. Recently we also showed that CMA is upregulated in lupus-prone MRL/lpr mice and that a number of abnormalities exist with respect to lysosomes in this strain [184]. The recent findings we accumulated in MRL/lpr mice strongly suggest that P140 peptide especially targets CMA in lupus mice and likely also in patients with SLE (unpublished information).

We effectively observed that after treatment of MRL/lpr mice with P140 peptide, autophagy markers SQSTM1 and MAP1LC3 accumulate in B cells, consistent with a down-regulation of (excessive) autophagic flux [183]. We also found that expression of HSPA8 and the LAMP2A markers of the CMA pathway, which is increased in MRL/lpr B cells, was down-regulated after P140 treatment [183,184,198]. In vitro experiments demonstrated that P140 directly inhibited CMA and that in this process, the phosphorylation of serine residue at position 140 was decisive [184]. Immunocytochemical analyses performed after intravenous administration of P140 showed that the peptide enters MRL/lpr B lymphocytes via a clathrin-dependent *endo*-lysosomal pathway and accumulates at the lysosomal lumen [184]. Our in vitro studies suggest a mechanism in which once P140 homes into lysosomes, it might act both by directly hampering HSPA8 chaperoning functions and, as a result of loss of HSP90AA1 function, by destabilizing LAMP2A in the lysosomal lumen. This dual effect may therefore interfere with the endogenous (auto)antigen processing and loading to major histocompatibility complex (MHC)II molecules, which take place in the so called late endosomal MHC class II compartment or MIIC [205–210]. As a downstream consequence activation of autoreactive by T cells would hardly occur.

The basic assumption we currently put forward is that by altering abnormally activated CMA, P140 induces a slowing down and/or a qualitative change of cellular autoantigen processing and peptide loading to MHCII molecules leading to the destabilization and weak expression of the latter (as was demonstrated) [183]. The whole sequence of immune cell activation signaling would be affected, beginning with a weak or no priming of autoreactive $CD4^+$ T (helper) cells (as was demonstrated earlier) [202]. This remarkable process has advantageous downstream outcome in the case of the lupus disease since if autoreactive $CD4^+$ T cells are no longer activated, they cannot in turn activate autoreactive B lymphocytes, and their proliferation and differentiation are extinguished or significantly weakened. This mechanism explains how downstream a significant reduction of autoantibodies to dsDNA and an amelioration of the disease clinical signs occur (as was demonstrated earlier both in mice and patients with lupus) [192,195].

Based on these findings in lupus disease, the therapeutic potential of P140 in other pathological indications in which autophagy failures may occur has thus been investigated with the double ultimate objective to identify possible dysfunctions of autophagy in these settings and to determine whether P140 can advantageously modulate these defects.

3.2. Amyotrophic lateral sclerosis

ALS, in addition to its well documented neuronal lesions (e.g. neurodegenerative loss of upper and lower motor neurons), also presents with more systemic aspects such as hypermetabolism [211] and autophagy modifications [144]. It is now admitted that, in contrast to other neurodegenerative diseases (e.g. PD and AD) models, food restriction in ALS mice accelerates disease progression and shortens life expectancy [212–214]. These observations have conducted to clinical trial of food supply and indeed, increased food/caloric intake shows a positive effect in patients [215]. Also for autophagy modifications, which are documented in both ALS patients and ALS mouse models, it is not clear whether autophagy, which might result from this particular relation to food supply, is a cellular lesion or a protective reaction.

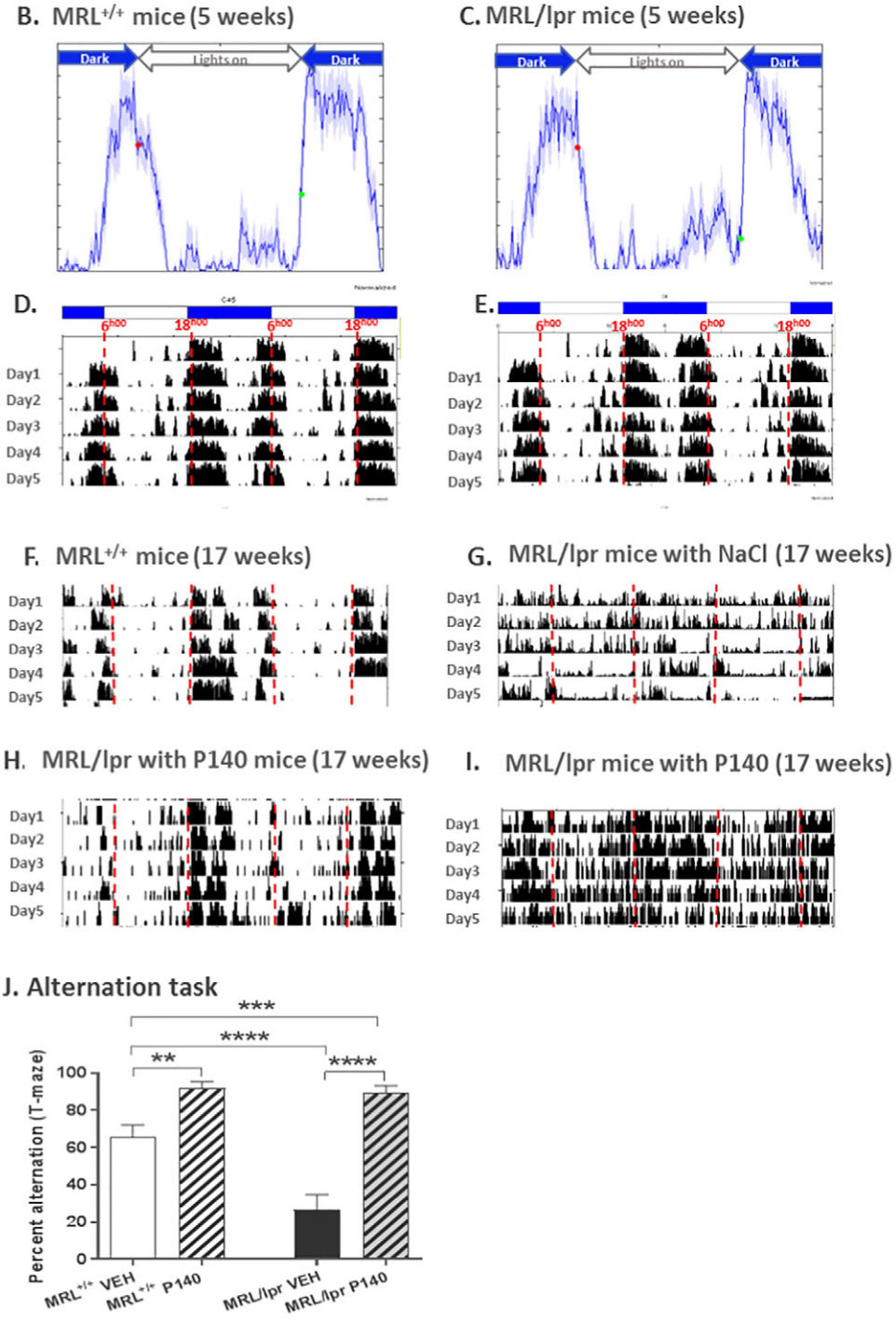
To obtain a preliminary answer to this open question, we used a well-documented ALS model ($SOD1^{G86R}$) to test the contribution of CMA to this disease. Wild type (Wt) littermates and $SOD1^{G86R}$ mice were treated from 80 days of age to 100 days. As seen on Fig. 3, P140 peptide given intraperitoneally at a dose of 4 mg/kg, 3 times/week, had no effect in Wt mice but dramatically shortens the life expectancy of ALS mice. Interestingly, no effect was observed on both weight and grip strength loss in $SOD1^{G86R}$ mice. These observations led us to conclude that CMA is involved in disease progression but represents rather a protective mechanism. It appears that its inhibition through P140 treatment does not represent a therapeutic option for ALS patients.

3.3. Chronic inflammatory demyelinating polyradiculoneuropathy

Since the research studying autophagy processes in CIDP are limited or absent, we have analysed some autophagic and CMA markers in a newly-developed rat model mimicking human CIDP, the chronic experimental autoimmune neuritis (chronic-EAN). This new animal model

A. Design of the study

AGE (weeks)	4	5	6	7	8	9	10	11	12	13	14	15	16
BEHAVIOR			SLEEP-WAKE CYCLE			MOTOR COORDINATION		ANXIETY-BEHAVIOR		COGNITION		SLEEP-WAKE CYCLE	
BEHAVIORAL TESTS			Actimetry			String agility test	Pole test	Plus-maze	Dark/light preference test	Y-maze	T-maze	Actimetry	
INJECTIONS (P140 & NaCl)		↑		↑		↑							
ANIMAL CARE	Arrival – Toe-tattoo – Acclimatation Body Weight and Proteinurea monitored weekly												



was developed in the Lewis rat by active immunization using the immune-dominant P0(180-199) neuritogenic peptide, but this time thiopalmitoylated, the S-palm P0(180-199) [216,217]. In fact, a few years ago, we worked with the EAE model and demonstrated that thiopalmitoylation (i.e. the covalent attachment of a palmitic acid via a thioester linkage to cysteine residues in the polypeptide backbone) of immunogenic myelin proteolipoprotein antigens could amplify the disease and turn it into a chronic condition [218,219].

We attempted to apply this same strategy to the previously known EAN model in order to develop chronic-EAN with symptoms mimicking a chronic or relapsing- remitting disease exhibiting the electrophysiological criteria for demyelination (slow sensory nerve conduction velocity, prolonged motor nerve latency and partial motor nerve conduction blocks) with axonal degeneration [217]. These findings were confirmed by immunohistopathological studies and appear to closely mimic human CIDP [220]. Finally, T lymphocyte, macrophage and IL-17$^+$ cell infiltrates have been found in sciatic nerves and *cauda equina* of chronic-EAN, results that are quite in line with another study who suggested that macrophages participate in the demyelination process [151], although the precise pathophysiological mechanisms operating in CIDP remain unknown.

Interestingly enough, we have identified unknown molecular alterations of autophagy, particularly the CMA, occurring in different immune and non-immune compartments in this newly-developed rat model mimicking human CIDP (Fig. 4). Remarkably, prophylactic and therapeutic treatment of chronic-EAN rats with the CMA-targeting P140 peptide considerably ameliorates the clinical and biological course of the disease in chronic-EAN rats (Brun et al., manuscript in preparation). Preliminary results have been very promising, leading us to evaluate the Lupuzor™ strategy in patients with CIDP.

3.4. Neuropsychiatric systemic lupus erythematosus

In our recent studies dealing with NPSLE, we used the MRL/lpr mouse model that is known to display behavioural deficits that mimic some of those reported in NPSLE patients. This murine model allowed us to investigate circadian activity, motor and sensorimotor coordination, anxiety behaviour, and cognition, in comparison to MRL$^{+/+}$ mice, which have no mutation in the *Fas* gene, develop delayed and mild symptoms and are therefore considered as an adequate control for MRL/lpr mice [221,222]. We already reported, in parallel with the progression of the disease, a desynchronization of the circadian activity and diurnal hyperactivity in diseased MRL/lpr mice as compared to MRL$^{+/+}$ control counterpart [223]. A similar hyperactivity is often reported in lupus patients [224]. Concerning cognition, administration of P140 totally compensated the clear-cut deficit of spontaneous alternation reported in 17-week-old MRL/lpr mice (Fig. 5) but also ameliorated the clinical status (proteinuria scores) of MRL/lpr mice. The alternation task is classically described in the literature as particularly sensitive to hippocampal damage, and could reflect cerebral atrophy. This had already been reported by our group [223]. Again, this observation resemble some findings reported in NPSLE patients where imaging (e.g. magnetic resonance imaging and spectroscopy, magnetization transfer imaging, diffusion tensor imaging, positron emission tomography) studies detected structural anomalies in the brain [225–236].

Research dealing with autophagy mechanisms in SLE is currently very active, but nowadays, nothing is known in NPSLE. We cannot conclude without tackle the point of neuroinflammation and leakage of the BBB in our animal model [237–239]. Many studies conducted in the field of neurodegenerative diseases show clear implication and neuroimmune regulation of microglial cells, which are considered as sentinel cells and act centrally as macrophages [240–243]. Moreover, as those latter, they are able to adopt either a M1-like phenotype (pro-inflammatory) or a M2-like phenotype (anti-inflammatory) according to the cerebral environment and presence of particular cytokines. In other words, they are able to promote neuroprotective or neurotoxic microenvironments, thus controlling neuronal fate. Acquisition of different microglial functions is regulated by intercellular interactions with neurons, astrocytes, the BBB (when this one is becoming permeable, as is the case in lupus disease), and CD4$^+$ T-cells infiltrating the CNS. It would be most interesting at this stage to depict if the beneficial action of the therapeutic P140 peptide in our NPSLE animal model is related to anti-inflammatory actions on the microglial cells, favoring adoption of M2 phenotype [244].

Concluding remarks

The few examples described above highlight if necessary that analysing autophagic dysfunction in neuroinflammation and neurodegeneration is complex and requires a fine evaluation of defects before engaging possible therapeutic strategies [245]. Both failure and hyperactivation of distinct forms of autophagy can co-exist in different neuronal organs or areas, both in the CNS and PNS (and also in other non-neuronal tissues), and examining autophagy globally would be reductive and truncated. Overall, existing data and information reveal, however, that macroautophagy and CMA are rather activated in neuronal diseases (but see ALS as a counter-example). These findings, which have to be completed by far more thorough studies, suggest that therapeutic options that moderate some abnormally activated autophagic pathways might be beneficial [246]. As indicated above, since there are many forms of autophagy pathways, canonical or not, functioning in tandem or in crosstalk with other pathways of death/life equilibrium (e.g. apoptosis) [247,248], attention should be payed when establishing therapeutic protocols. In line, an aspect that is crucial and has largely hampered the development of autophagy-based therapeutic strategies is that until now, very few molecules, if any, have proved to be strictly selective to one autophagy pathway and one target. In general, molecules such as rapamycin, hydroxychloroquine, trehalose, perifosine (an inhibitor of protein kinase B or AKT), or metformin (an activator of 5′ AMP-activated protein kinase), just to quote a few, interact with several targets and receptors. This favors unwanted secondary effects and therefore limits their use as drugs. Nowadays, intense research is focused at identifying specific small molecules and peptides (such as the P140 peptide in the case of excessive CMA), able to specifically up- or down-regulate autophagy processes that are pathologically defective, without interfering with others.

Fig. 5. Behavioural deficits in MRL/lpr mice as compared to MRL$^{+/+}$ mice used as control, and effect of P140 peptide. (A) Timeline and experimental design of the study. (B–E) Circadian activity profiles of 5 week-old MRL$^{+/+}$ (B and D) and MRL/lpr (C and E) mice. All mice displayed a marked nocturnal hyperactivity (as usual in rodents). (F) Circadian activity profile of 17-week-old MRL$^{+/+}$ mice (nocturnal hyperactivity is conserved). (G–I) Circadian activity profile of 17-week-old MRL/lpr mice injected or not with P140. In animals that received the vehicle alone (VEH, 0.9% NaCl), we observed a disruption of nocturnal activity and apparition of a diurnal hyperactivity (G). This abnormality was no longer observed in some mice that were treated with P140 peptide (100 μg/mouse/100 μL, intraperitoneal route) (H). (J) Concerning alternation task, as compared to age-matched counterparts, 17 week-old MRL/lpr mice injected with VEH displayed significant T-maze alternation deficit ($p < 0.0001$), which was totally compensated by administration of P140 peptide ($p < 0.0001$). Statistics: Alternation scores were analysed with ANOVA with Bonferroni post-hoc tests. Significance was defined as $p < 0.05$: $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. Errors bars are mean standard deviation. Ethical statement: The experimental protocol and animal care were carried out in strict accordance with EU regulations (European Community Council Directive 2013–118 of February 1, 2013) and with the recommendations of the French national chart for ethics of animal experiments (articles R 214–87 to 126 of the "Code rural et de la pêche maritime"; authorization no. 04436.02). The protocol was also approved by the local committee on the ethics of animal experiments (CEEA 35). All efforts were made to minimize animal suffering and to respect the concept of the 3Rs (Reduce, Refine, Replace). Abbreviations: lpr, lymphoproliferation; MRL, Murphy Roths large; VEH, vehicle.

Take-home messages

- Autophagy is a vital metabolically-central process whose any disruption can have consequences leading to major pathologies such as inflammatory neuronal degenerative diseases.
- Many forms of autophagy pathways, canonical or not, exist, which function in tandem or in crosstalk with other mechanisms of death/life equilibrium.
- Both failure and hyperactivation of distinct forms of autophagy can co-exist in different neuronal areas, both in the central and the peripheral nervous systems.
- Small molecules and peptides able to activate or inhibit autophagy might be valuable specific therapeutics, capable of correcting autophagy dysfunctions and their immune consequences.
- Our findings with the therapeutic P140 peptide already used in lupus support the view that down-regulating excessive autophagy could improve patient outcomes by reducing neuronal inflammation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could construed as a potential conflict of interest.

Author contribution

All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication.

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