Autophagy in Astrocytes and its Implications in Neurodegeneration

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Abstract

Autophagy is a major degradation pathway where double-membrane vesicles called autophagosomes deliver cytoplasmic content to the lysosome. Increasing evidence suggests that autophagy dysfunction contributes to the pathogenesis of neurodegenerative diseases. In addition, misfolded proteins that accumulate in these diseases and constitute a common pathological hallmark are substrates for autophagic degradation. Astrocytes, a major type of glial cells, are emerging as a critical component in most neurodegenerative diseases. This review will summarize the recent efforts to investigate the role that autophagy plays in astrocytes in the context of neurodegenerative diseases. While the field has mostly focused on the implications of autophagy in neurons, autophagy may also be involved in the clearance of disease-related proteins in astrocytes as well as in maintaining astrocyte function, which could impact the cell autonomous and non-cell autonomous contribution of astrocytes to neurodegeneration.

Introduction

Autophagy, a self-degradation mechanism that delivers unwanted and damaged cellular content to the lysosome for degradation, is essential for maintaining cellular protein homeostasis. Autophagy has proven important for physiological conditions such as development or the immune response, as well as in diseases including cancer and neurodegeneration [1]. In the brain, where accumulation of aggregate-prone proteins is a general hallmark in almost all neurodegenerative diseases [2], autophagy dysfunction may contribute to the abnormal accumulation of these disease-related proteins and to the progression of neurodegenerative diseases. For this reason, over the last few years, autophagy induction has been studied as a therapeutic strategy to promote the clearance of disease-related proteins and to counteract autophagy deficiencies in neurodegeneration. Thus, the search for safe and efficient pathways to upregulate autophagy for therapeutic use has become an intense field of research [3].

Neurons are postmitotic cells that maintain active synaptic transmission and electrical potentials for an entire human lifetime. An age-related decline in proteostasis mechanisms, together with the inability of neurons to dissipate protein aggregates by cell division, has explained why protein aggregation in the brain has been mostly observed and studied in neurons. Only recently the contribution of glial cells to neurodegenerative diseases has started to be studied in-depth, and understanding how protein homeostasis in glial cells is maintained and its consequences in neurodegeneration represents an underexplored field. Glial cells are critical for brain development and function. Microglia, the brain immune surveyors, are myeloid cells of embryonic hematopoietic origin that migrate to the brain during the early days of development [4], while astrocytes and oligodendrocytes share a common neuronal progenitor with neurons in the developing brain [5]. The role of oligodendrocytes and microglia in the synthesis and repair of the myelin sheath and in brain immune surveillance, respectively, is well established. Meanwhile, the multiple functions of astrocytes in providing not only metabolic and structural support to neurons but also in having an active role in neurogenesis and synaptic

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homeostasis and functioning are only now starting to be unraveled.

In this article, we will first summarize some of the emerging roles attributed to astrocytes in the progression of neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS) and Huntington disease (HD) and other polyglutamine diseases. Given the important role that autophagy plays in both innate and adaptive immunity where autophagy eliminates pathogens, regulates inflammatory signaling and secretion of immune modulators and modifies antigen presentation [6–8], several studies have highlighted in recent years the importance of autophagy in microglia functions. These aspects have recently been reviewed in detail [9,10] and will not be addressed here. We will focus on the current literature investigating the role of autophagy in astrocytes and its potential implications in the aforementioned neurodegenerative diseases. We will comment on recent findings that have underlined how autophagy is important as a clearance mechanism not only in neurons but also in astrocytes, and how astrocyte autophagy may also play a critical role in disease development. Importantly, we will discuss the potential role of astrocytes as non-cell autonomous regulators of neuronal autophagy.

Emerging Roles of Astrocytes in Neurodegeneration

Glial cells constitute about 50% of total cells in the human brain, exhibiting great variability across brain regions [11,12]. Approximately 20% of these glial cells are astrocytes [13]. Astrocytes have generally been accepted as "housekeeping cells", promoting neuronal health and survival. This role includes the surveillance and maintenance of the extracellular area by control of the ion and water composition and uptake of neurotransmitters, the regulation of blood flow and circulation in response to neuronal activity, the maintenance of the blood–brain barrier, and the development and upkeep of synaptic function [14,15]. The vast array of functions with which astrocytes are involved could be due, in part, to the physiological diversity of these glial cells [16,17].

Astrocytes respond to injury through their own morphological and functional reaction, becoming reactive astrocytes. Reactive astrocytes play a complex role under different pathological situations, changing their morphology, gene expression and function depending on the form and severity of the insult [18]. The effect that these changes elicit in their activity and to what extent reactive astrocytes are protective or damaging during disease progression, due to the potential loss or gain of function, is not well understood. Adding to this complexity, it is difficult to distinguish the contribution of reactive astrocytes and microglia, the main players of the immune responses in the brain [19]. Communication between the two types of glial cells occurs through release of molecular signals from astrocytes to microglia and vice versa, and activation of both reactive astrocytes and microglia is a central feature in neurodegeneration [20].

Alzheimer disease

Alzheimer disease (AD) is the most common form of dementia, characterized by cognitive deficits, including memory loss and learning impairment [21]. The classic hallmarks of AD are the accumulation of intracellular neurofibrillary tangles of hyperphosphorylated tau and extracellular plaques of amyloid β (Aβ) in the brain of patients [22], while in recent years neuroinflammation has also been regarded as an essential component of the disease [23,24].

In AD, reactive astrocytes are often surrounding Aβ plaques [26,27] and the accumulation of reactive astrocytes in AD brain, together with tau phosphorylation, correlates with disease progression and cognitive decline [28,29]. Astrocytes mediate the clearance of Aβ through the uptake and degradation of Aβ, as well as the secretion of Aβ-degrading proteases directly into the media [30]. In addition, astrocytes are the main source of *APOE*, involved in Aβ uptake and degradation by astrocytes [31,32]. The E4 allele of *APOE*, which confers the strongest genetic risk factor in late-onset AD [33–35], reduced the ability of astrocytes to clear Aβ 42 from the media compared to *APOE3* [32].

On the other hand, transcriptomic studies have shown that astrocytes in AD mice develop a proinflammatory phenotype and reduce expression of genes involved in neuronal support [36]. This is in line with a recently suggested "A1" subtype of reactive astrocytes, attributed to astrocytes in AD and other neurodegenerative diseases, which lose the ability to promote neuronal and synaptic protection [37], and with the literature reporting that astrocytes mediate the Aβ-dependent neuronal cell death [38–41]. More recently, it was shown that lowering astrocyte reactivity through inhibition of the STAT3 pathway in mice reduced amyloid deposition, restored synaptic deficits and improved spatial learning, supporting a model where reactive astrocytes have a deleterious role in AD [42].

Parkinson disease

Parkinson disease (PD) is the second most prevalent neurodegenerative disorder after AD that

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mainly affects the motor system. It is characterized by a significant loss of dopaminergic neurons in the substantia nigra, a disruption in dopaminergic neurotransmission and a buildup of cytoplasmic inclusions known as Lewy bodies [43].

Alpha(α)-synuclein, the main component of Lewy body inclusions, accumulates in astrocytes, which correlates with the extent of neuronal loss [44,45]. Furthermore, α-synuclein released from neurons is taken up by astrocytes [46–48]. This may constitute a protective clearance mechanism [49,50], but could also have a detrimental role by participating in the spreading of the pathology [51]. When exposed to α-synuclein, astrocytes in culture release pro- and anti-inflammatory molecules [46,52], exhibit mitochondrial dysfunction and lead to glial and neuronal toxicity [47,48,53,54]. Similarly, a mouse model selectively expressing the PD-related A53T mutant α-synuclein in astrocytes displayed microglia and astrocyte activation accompanied by a loss of dopaminergic neurons, early onset paralysis and shortened life span [53].

Besides α-synuclein, some of the genes identified as causative factors in PD are expressed in astrocytes at similar or even higher levels than in neurons. These include *PARK2*, *PARK7*, *GBA*, *LRRK2*, *PINK1*, *ATP13A2* and *PLA2G6* [55]. These genes have been linked to functions that are crucial for astrocyte biology such as inflammation and lipid metabolism, as well as more general cellular pathways, including mitochondria and lysosome function. Therefore, mutations in these PD-associated genes may result in compromised astrocyte homeostasis [55].

Huntington disease and polyglutamine diseases

The expansion of a polyglutamine tract is responsible for nine autosomal dominant neurodegenerative conditions, including several spinocerebellar ataxias and Huntington disease (HD) [56]. HD is a fatal neurodegenerative disorder caused by the unstable expansion of the trinucleotide repeat (CAG) within the gene coding for the protein huntingtin (HTT). Toxicity in HD arises from a gain of function of the mutant protein that leads to a selective loss of medium-sized striatal spiny neurons in the caudate nucleus, resulting in progressive motor, psychiatric and cognitive dysfunction [57].

In HD brain, disease progression correlates with an increase in reactive astrocytes, where the HTT protein also accumulates [58,59]. Loss of the glutamate transporter GLT1, which is mainly expressed in astrocytes, is a common characteristic found in HD human brain and in animal models [58,60,61] pointing to a contribution of astrocytes in HD pathology. In line with this, mouse models selectively expressing mutant HTT in astrocytes showed age-dependent motor deficits and shortened life span [62]. When expressed both in astrocytes and neurons, it exacerbated neurological symptoms seen in the mice expressing mutant HTT only in neurons [63]. This seems to be predominantly mediated by a reduction in the levels of the glutamate transporter and glutamate uptake by astrocytes [58,61,62], together with other mechanisms such as an imbalance in astrocyte-mediated potassium homeostasis via Kir4.1 ion channels [64] or a reduced secretion of BDNF [65].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common form of adult motor neuron disease, defined by progressive degeneration of the upper and lower motor neurons. The majority of ALS cases are sporadic while about 5% are familial and linked to mutations in more than 20 genes, including *C9ORF72*, Cu/Zn superoxide dismutase (*SOD1*), TAR DNA binding protein-43 (*TDP-43*) and fused in sarcoma (*FUS*). Many of these genes converge on pathways related to RNA metabolism and protein homeostasis [66,67].

Astrocytes and other glial cells have received much attention in ALS, where non-cell autonomous mechanisms have been proposed as important contributors to the disease. Most of these studies have been performed in experimental rodent models of ALS expressing mutant *SOD1*. Initial studies showed that restricted expression of *SOD1* mutants to neurons [68,69] or to astrocytes [70] failed to develop neurodegeneration. However, when mutant *SOD1* was expressed simultaneously in neurons and glial cells, mice developed an ALS phenotype [71,72], and specific deletion of the *SOD1* transgene in astrocytes slowed disease progression and extended life span in these mice [73,74]. Astrocyte transplantation in the spinal cord of rodents also supported a key role of these cells in ALS. While wildtype astrocytes slowed disease progression and extended survival when transplanted into mutant *SOD1* rats [75], astrocytes expressing mutant *SOD1* led to local motor neuron degeneration and motor dysfunction in wildtype mice [76].

Non-cell autonomous toxicity may arise from an active secretion of neurotoxic factors [77,78], such as proinflammatory cytokines [79,80], or from a loss of astrocytic function. Dysfunction of astrocytes has been reported in ALS, including the loss of the glutamate transporter GLT1 and increased excitotoxicity [81,82], increased oxidative stress leading to neuronal toxicity [83,84], and defects in RNA trafficking in astrocytes, which disrupt translation of critical mRNAs required for astrocyte function [85].

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Autophagy as a Protective Mechanism in Neurodegeneration

Autophagy machinery

Autophagy is a ubiquitous catabolic process that mediates the constitutive turnover of intracellular components. In macroautophagy, most commonly known as autophagy, cytoplasmic content is engulfed in double membrane vesicles called autophagosomes, which then fuse with the lysosomes where the cargo is degraded. This should be differentiated from two other forms of autophagy, which will not be reviewed here, chaperone-mediated autophagy (CMA) and microautophagy, in which the cytoplasmic cargo is directly translocated into the lysosomes [86].

The core autophagy machinery is regulated by a series of autophagy-related (ATG) proteins that promote autophagosome precursor formation, elongation of the autophagosome, and autophagosome maturation by fusion with the lysosome [87] (Fig. 1). Autophagy is activated in response to different stimuli, including low energy levels and nutrient depletion, which are sensed by AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) kinase, respectively. These pathways converge on the uncoordinated-51-like kinase (ULK) complex. mTOR-dependent phosphorylation of ULK1/2 inhibits the ULK1/2-ATG13-ATG101-FIP200 complex, while AMPK positively regulates this complex and induces the early stages of autophagosome formation [88,89]. The ULK complex controls the initiation of autophagosome formation by recruiting the class III phosphoinositide 3-kinase Vps34 to the phagophore initiation site, where it forms a complex with beclin 1, VPS15 and ATG4L [90]. For the elongation of the autophagosome membrane, two ubiquitinlike conjugation systems are required. Firstly, ATG12 is conjugated to ATG5 thanks to ATG7 and ATG10, which act as E1-like and E2-like enzymes and mediate their binding to ATG16L1. The ATG12-ATG5-ATG16L1 complex is necessary for the recruitment of microtubule-associated protein light chain (LC3) to the preautophagosome membrane. Firstly, LC3 is cleaved by the cysteine protease ATG4 into the LC3-I form, and then conjugated to phosphatidylethanolamine (PE) to form LC3-II by a second ubiquitinlike conjugation system consisting of ATGT7, ATG3 and ATG12-ATG5-ATG16L1 (for a comprehensive review on the machinery and mechanisms regulating autophagy, read Bento et al., 2016 [91]).

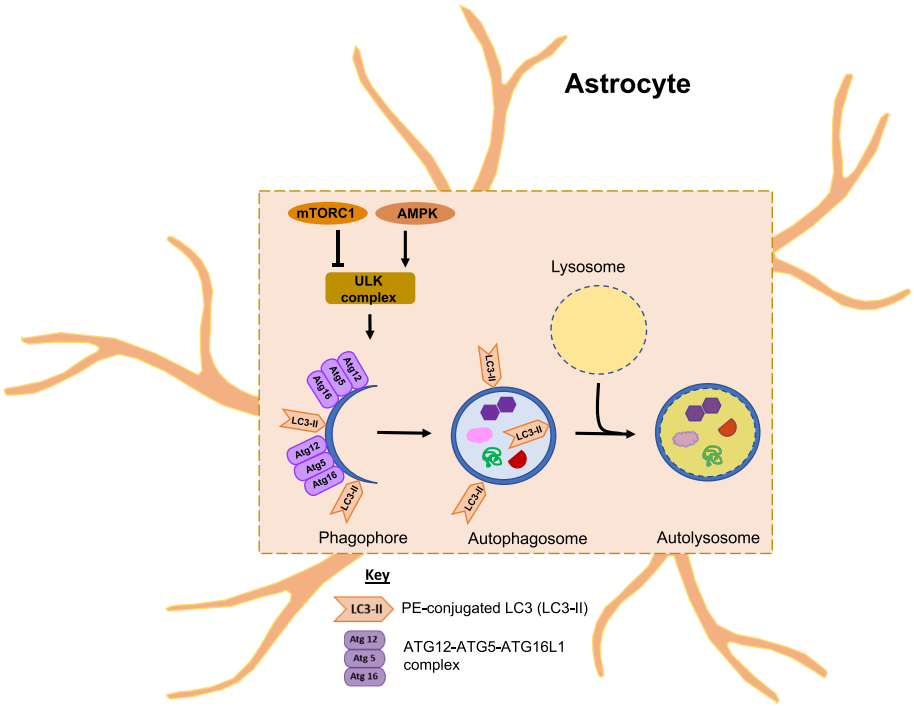

Fig. 1. Overview of the autophagy pathway. mTOR and AMPK regulate the ULK1 complex, which induces the formation of autophagosomes. Autophagy involves the formation of phagophores, its elongation to form an autophagosome, and fusion with lysosomes to form autolysosomes, where cargoes are degraded. The ATG12-ATG5-ATG16 complex is necessary for the initial steps of autophagosome formation and to recruit phosphatidylethanolamine (PE)-conjugated LC3-II.

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What was initially considered as a solely bulk degradation process is now known to also mediate selective degradation of specific cargo. Selective autophagy requires the binding of autophagy substrates to receptors that are then recognized by LC3 to be recruited to autophagosomes in a selective manner, including aggregate-prone proteins, damaged mitochondria, invading pathogens and peroxisomes [92].

Autophagy in neurodegenerative diseases

Protein misfolding is a common pathological hallmark in most neurodegenerative diseases. Importantly, most aggregate-prone proteins associated with neurodegenerative disorders have been shown to be subject to autophagic degradation, including polyglutamine containing proteins such as mutant huntingtin (HTT) [93–96], tau [97–99] and Aβ [100–102] in AD and other tauopathies, α-synuclein in PD [103–105] and TDP43 in ALS [106–108]. Since the accumulation of soluble oligomers and insoluble protein aggregates correlates with toxic gain of function mechanisms, increased autophagic degradation of these disease-related proteins is an attractive therapeutic target for most neurodegenerative diseases. Besides its potential therapeutic use, compromised autophagy has also been related to the pathogenesis of neurodegenerative diseases, as outlined below.

Autophagy and Alzheimer disease

The first evidence suggesting autophagy dysfunction in AD came from the observation that autophagic vacuoles accumulate in human AD brain [109] and in AD transgenic mice [110] and that levels of beclin 1 are decreased in patient brain [111]. However, the link between autophagy and AD has not been straightforward. The effect of autophagy on Aβ levels is complex, as it has been implicated both in the degradation [100–102] as well as in the formation and secretion of A [110,112,113]. Genomewide association studies have implicated additional genes with increased risk of AD. One of these genes codes for phosphatidylinositol-binding clathrin assembly protein (PICALM) [114,115], a protein involved in clathrin-mediated endocytosis, which is involved in autophagy at multiple steps of the autophagosome-lysosome pathway [116] and modulates clearance of tau [116] as well as the amyloid precursor protein C-terminal fragment (APP-CTF) [117].

Accumulation of autophagic vesicles was also observed in a mutant tau (P301L) mouse model of tauopathy [118], and autophagy markers are accumulated in human post-mortem brain from corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and familial AD [119], suggesting a link between tau pathology and autophagy impairment. Furthermore, phosphorylated tau accumulated in ATG7-deficient mature neurons, which may partly mediate the neuronal loss associated with ATG7 deficiency [120].

Autophagy and Parkinson disease

Dysfunctional autophagy, and more specifically mitophagy or selective degradation of mitochondria by autophagy [121], has been closely linked to PD. Autosomal recessive forms of early-onset PD are associated with mutations in the E3 ubiquitin-protein ligase Parkin [122] and the PTEN-induced kinase 1 (*PINK1*) [123], which lead to deficits in mitophagy [124,125].

Several other genes linked to familial forms of PD and inherited syndromes related to PD also converge on the autophagy-lysosomal degradation pathway. These include SNCA, ATP13A2, VPS35, GBA and LRRK2 [126,127]. Mutations in leucine-rich repeat serine/threonine-protein kinase 2 (LRRK2), the most commonly mutated protein in both familial and sporadic PD, can impair autophagy by several suggested mechanisms, including the modulation of the endolysosomal system [128,129]. A PD autosomal dominant mutation in VPS35, a component of the retromer complex, has been related to autophagy impairment through mislocalization of the autophagy protein ATG9A [130] or the chaperone-mediated autophagy component LAMP2A [131]. GBA (glucocerebrosidase), a lysosomal enzyme necessary for the integrity and function of lysosomes, and ATP13A2, a lysosomal ATPase, both converge in the autophagy-lysosome pathway. Homozygous GBA mutations leading to the lysosomal storage disorder Gaucher disease are the greatest risk factor in PD, impairing lysosomal function and potentially compromising autophagy [132]. Mutations in ATP13A2 impair the activity of lysosomal proteases and result in the accumulation of autophagosomes unable to fuse with lysosomes [133]. α-Synuclein inclusions also affect autophagosome maturation and fusion with the lysosome [134,135] and increased α-synuclein levels disrupt autophagy [136].

Autophagy and amyotrophic lateral sclerosis

In recent years, genetic studies have reported more than 20 genes linked to ALS. Many of these are shared with frontotemporal dementia (FTD) and a number of them are associated with deficits in autophagy, including *SQSTM1*, *CHMP2B*, *TBK1*, *OPTN*, *ubiquilin2,* and *C9ORF72* [137].

SQSTM1/P62, *OPTN*, *TBK1*, and *ubiquilin2* are associated with selective autophagy and mediate

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cargo loading [137]. Expansions of hexanucleotide repeats within the non-coding region of the *C9ORF72* gene are the most frequent cause of familial ALS. While loss of function is only one of the potential disease mechanisms of *C9ORF72*, together with RNA and dipeptide repeat protein gain of function, it has been linked to autophagy. Loss of *C9ORF72* in cell lines and primary neurons inhibits autophagosome initiation through the regulation of ULK1 [138,139], via its proposed guanine exchange factor (GEF) role involved in the regulation of RAB GTPases. Other roles of *C9ORF72* modulation in lysosome function have also been reported [140–142], including a negative role in autophagy through upregulation of TFEB [143], a master transcriptional regulator of lysosomal and autophagy genes [144].

Autophagy and Huntington disease and polyglutamine diseases

Recently, a common mechanism for autophagy disruption by polyglutamine expansions has been suggested. The polyglutamine tract in the wildtype deubiquitinase ataxin 3 interacts with beclin 1, a positive regulator of autophagy, and prevents its proteasomal degradation. When pathologic expansions of polyglutamine tracts compete with ataxin 3 for binding to beclin 1, it results in an increase in beclin 1 ubiquitination and thus its degradation, abolishing autophagy activation [145].

Other mechanisms also contribute to autophagy impairment in these diseases. The mutated androgen receptor, responsible for spinal and bulbar muscular atrophy (SBMA), interacts with and inhibits TFEB [146]. In addition, mutant HTT impairs cargo degradation by impairing cargo loading into autophagosomes [147], and it has been associated with a decrease in autophagosome transport and degradation [148].

Protein Aggregation and Proteostasis Mechanisms in Neurons and Astrocytes

As described above, protein aggregation is a common hallmark in most neurodegenerative diseases. While the disease-associated proteins that are most commonly found in these protein aggregates, such as Aβ, tau, TDP-43, α-synuclein or expanded polyglutamine containing proteins do not share obvious similarities, neither structurally nor functionally, in the disease brain they all undergo protein misfolding, oligomerization and accumulation into protein aggregates [149]. Although it was initially proposed that these protein aggregates were the neurotoxic species, more recent evidence supports the view that soluble intermediate oligomeric species constitute the most toxic disease forms. These soluble oligomers expose hydrophobic residues on their surface, facilitating their interaction with other proteins and membranes and resulting in cellular dysfunction. While inclusions may still deplete key cellular components, they also constitute a source of harmful oligomeric species through fragmentation or secondary nucleation [150].

Cell type–specific accumulation of disease-associated proteins

Although disease-related proteins are generally expressed in all brain cell types, accumulation of these proteins has been mostly characterized in neurons or in cancerous neuron-like cells. In HD, HTT protein accumulates not only in neurons, but also in association with reactive astrocytes in post-mortem HD patients [58,59]. However, the proportions and sizes of these inclusions are higher in neurons both in patient brain [151] and in animal models of the disease [152].

α-Synuclein intraneuronal inclusions, known as Lewy bodies, are common to α-synucleopathies. These include PD and Dementia with Lewy Bodies (DLB), where α-synuclein accumulates in neurons, and multiple system atrophy (MSA), where inclusions are primarily found in oligodendrocytes [153]. Astrocytic inclusions of α-synuclein are also common to PD and DLB [44,45] and less frequent in MSA [154]. While α-synuclein is mostly expressed in neurons and at lower levels in astrocytes [155,156], the presence of α-synuclein in astrocytes has been explained by the astrocytic uptake of released neuronal α-synuclein [46–48].

In the brain, tau is predominantly expressed in neurons, whereas in glial cells, expression of tau is variable and only found at trace levels in astrocytes [157,158]. Although tau pathology is only observed in neurons in AD, accumulation of tau in glial cells is a common feature in other tauopathies, where it is presented in the form of thorn-shaped astrocytes in PSP, argyrophilic grain disease (AGD), and Pick disease (PiD); astrocytic plaques in CBD; or tufted astrocytes in PSP [159].

Inclusions of TDP-43 are a hallmark of ALS and are present both in glial and neuronal cells in ALS and frontotemporal lobar degeneration (FTLD) brains [160,161]. Although astrocytes show TDP-43 inclusions in ALS and FTD, they are more commonly observed in oligodendrocytes, where TDP-43 is the main component of glial cytoplasmic inclusions (GCI) [162–164].

Differences in the accumulation of aggregate prone proteins in different cell types in the brain highlight that mechanisms controlling the synthesis, folding and degradation of these proteins might be differentially regulated in different cells and under

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different disease conditions. In addition, it has been suggested that neurons are not only more likely to accumulate misfolded proteins but also to have a higher sensitivity to toxic stimuli than glial cells. Neurons show preferential cell degeneration, since they are more vulnerable to the toxicity exerted by misfolded proteins [165] and have lower capacity to combat oxidative stress [166,167].

Is autophagy differentially regulated in neurons and astrocytes?

In 2006, two papers provided the first genetic evidence that basal autophagy is essential for maintaining the constant turnover of intracellular proteins and to prevent neurodegeneration [169,170]. Notably, this was observed even in the absence of any disease-associated mutant protein. Hara et al. and Komatsu et al. generated autophagy-deficient mice where ATG5 and ATG7, respectively, were specifically depleted in all brain cells of neuronal origin. These animals developed symptoms of neurodegeneration, including motor and behavioral deficits and neuronal cell death, which were accompanied by the accumulation of ubiquitinated inclusions. Interestingly, while in these mouse models all brain cells including neurons, astrocytes and oligodendrocytes were depleted of ATG5 and ATG7, inclusions were only observed in neurons. These findings suggest that glial cells have additional mechanisms to overcome the aberrant accumulation of detrimental proteins [169,170].

Few studies have investigated differential protein degradation in astrocytes versus neurons. In 2008, Tydlaka et al. reported that the proteasome activity might be lower in neurons compared to astrocytes. Using fluorescent reporters, they showed that in primary cultures the proteasome was less active in neurons than in astrocytes and that, in the mouse brain, an age-dependent decrease in proteasome activity was more prominent in neurons than in glial cells [152]. Using an optical pulse-chase probe, Zhao et al. observed that mutant HTT clearance occurs more rapidly in astrocytes than in neurons both in primary cultures and in mouse brain sections, with degradation in both cell types primarily dependent on the proteasome rather than autophagy [171].

Although autophagy is a ubiquitous process and the components of the autophagy machinery are widely expressed, autophagy regulation can be specific to an organ [172], brain region [173] or neuronal subtype [174]. It is therefore not surprising that autophagy may be differentially regulated in neurons compared to glial cells, as has been suggested in certain conditions such as the ischemic penumbra [175] or in response to sphingosine kinase 1 inducers [176]. These studies compared neuronal and glial cell lines [175] or primary neuronal and glial cultures [176]. In culture, different cells may not retain their physiology to the same extent, which makes comparative experiments difficult. Further studies are needed to investigate in detail how autophagy is differently regulated in astrocytes and neurons and its relevance *in vivo*.

Autophagy in Astrocytes in Neurodegeneration

Autophagy has diverse roles in different cells in neurodegeneration and, only recently, the implication of autophagy in astrocytes has started to be investigated. Firstly, autophagy can be beneficial to clear unwanted or misfolded protein in astrocytes. In addition, it is worth exploring whether impairments in autophagy in astrocytes can have an impact in disease. Finally, the astrocyte-neuron non-cell autonomous roles should be considered when studying protein homeostasis regulation in disease (Fig. 2).

Autophagic clearance of disease-related proteins in astrocytes

Autophagy in primary astrocytes is necessary for the clearance of protein aggregates, for example, those that are accumulated upon treatment with proteasome inhibitors [177]. However, the first evidence for autophagy being necessary for the clearance of disease proteins comes from studies in Alexander disease. This is a rare disease restricted to astrocytes, where pathology results from dominant mutations in the glial fibrillary acidic protein, GFAP, which accumulates in inclusions termed Rosenthal fibers [178]. GFAP is an intermediate filament expressed exclusively in astrocytes and whose levels are highly increased when astrocytes become reactive [179]. Heterozygous mutations in GFAP in astrocytes are sufficient to cause this neurological disease, characterized by seizures, encephalopathy and developmental delay in early onset—patients and bulbar symptoms and movement abnormalities mostly in late onset—patients. The disease normally occurs in infants, leading to death within few years, and shows signs of neurodegeneration [178]. Accumulation of mutated GFAP leads to activation of stress pathways and inhibition of the proteasome [180–182]. Autophagy is also induced in astrocytes in Alexander disease brain and can be recapitulated in cell lines and mice by expressing GFAP mutants. Moreover, GFAP is cleared by autophagy suggesting that autophagy is induced in Alexander disease astrocytes to prevent further GFAP accumulation [181].

In AD, astrocytes together with microglia contribute to reduce extracellular Aβ and prevent its toxicity by aiding its internalization and degradation [31,183–185]. APOE4, which confers the highest

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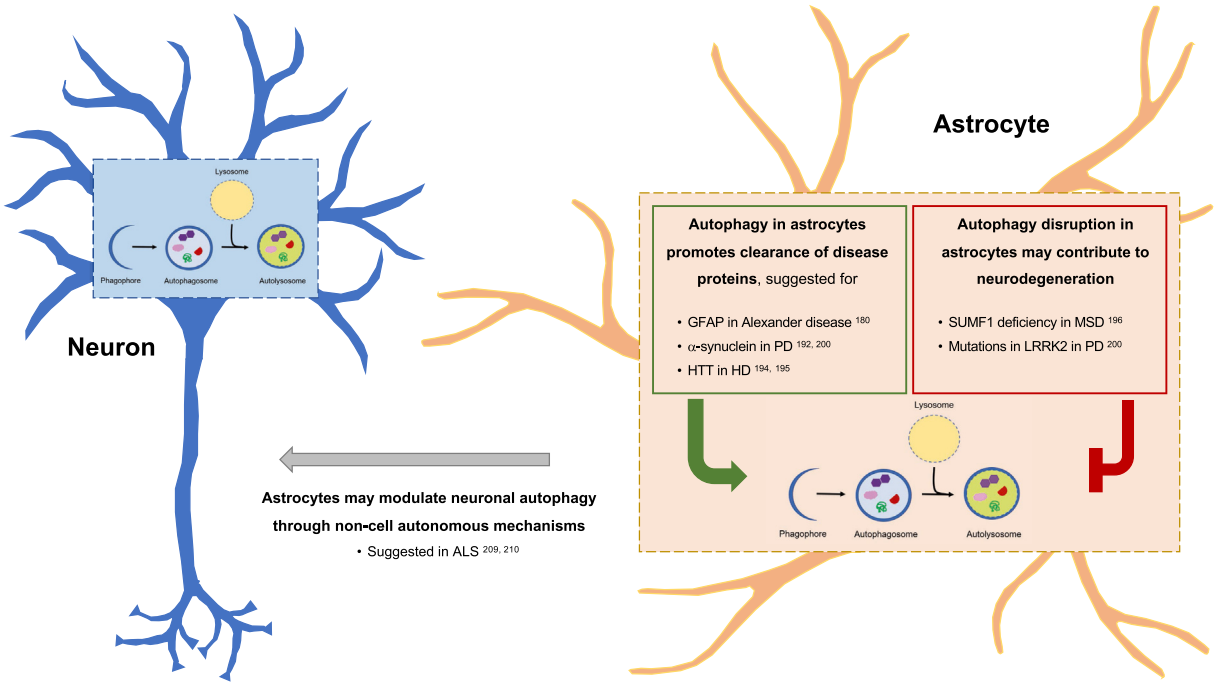

Fig. 2. Overview of the potential implications of astrocytic autophagy in neurodegeneration. Based on the current literature, we propose that autophagy is important for the clearance of disease-related proteins in astrocytes and that autophagy disruption in astrocytes contributes to neurodegeneration. Astrocytes may also be important to regulate neuronal autophagy through noncell autonomous mechanisms.

risk for AD, compromises this ability of astrocytes to clear Aβ [31]. Indeed, in 2016, Simonovitch et al. suggested that autophagy is important for the APOE-dependent Aβ clearance by astrocytes. In this study immortalized mouse astrocyte cell lines derived from APOE4 knock-in mice showed lower levels of autophagy flux compared to APOE3 astrocytes, both in basal conditions and upon autophagy stimulation with starvation or with the mTOR inhibitor, rapamycin. Moreover, using an *in situ* Aβ plaque removal model [183], APOE4 expressing astrocytes were less able to clear the plaques and to internalize Aβ when incubated with brain sections from a 5XFAD mouse model of amyloid pathology. Clearance was enhanced when treated with rapamycin [186].

Interestingly, using viruses to enhance the expression of TFEB selectively in astrocytes in the hippocampus of mice expressing mutant human APP and PSEN1 genes increased lysosomal function and reduced Aβ levels as well as amyloid plaque deposition. Complementary, *in vitro* studies in primary astrocytes showed that expression of exogenous TFEB enhanced uptake, trafficking and degradation of Aβ, indicating a role of the endolysosomal pathway in Aβ clearance by astrocytes [187]. TFEB is known to promote autophagosome-lysosome function by mediating the expression of genes required for autophagosome formation, lysosome biogenesis and lysosome function [188,189]. It is therefore plausible that the function of TFEB on astrocyte Aβ clearance is directly linked to autophagy. In fact, when APOE4 was expressed in a human glioblastoma cell line, it failed to induce the expression of certain autophagy genes in starved conditions in comparison to APOE3 cells, suggesting that APOE4 competes with TFEB for binding to "coordinated lysosomal expression and regulation" (CLEAR) DNA motifs to regulate the expression of genes involved in lysosomal biogenesis and function [190].

A beneficial effect of autophagy inducing drugs such as trehalose or rapamycin in the clearance of tau has been shown *in vivo* in mouse models of tauopathy [191,192], as well as *in vitro* in primary neurons [99]. While the role of autophagy in glial tau has not been investigated, when rapamycin was administered into a P301S tau transgenic mouse, a reduction in tau tangle pathology was accompanied by a reduction in reactive astrocytes, measured by GFAP immunohistochemistry [192]. It remains to be elucidated whether rapamycin has a direct effect on modulating reactive astrocytes or if it is secondary to a reduction in the degeneration of neurons, as well as whether this effect is autophagy dependent.

In post-mortem PD brain, α-synuclein cytoplasmic inclusions are found in astrocytes, as well as in neurons [44,45]. Studies in human glioblastoma cell lines showed that upregulation of BAG3-dependent autophagy by reducing the levels of the small heat

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shock protein CRYAB enhanced the clearance of α-synuclein. In addition, when CRYAB was overexpressed in astrocytes in a mouse model expressing the human α-synuclein A30P mutant, it induced α-synuclein accumulation in the whole brain [193]. This study suggests that autophagy upregulation may modulate levels of α-synuclein in astrocytes [193], which could attenuate the astrocytic and neuronal toxicity exerted by the accumulation of α-synuclein in astrocytes [47,48,53,54].

In relation to ALS, small molecules that induce autophagy and increase clearance of TDP-43 in neurons were also able to reduce mutant TDP-43-associated toxicity when applied to human stem cell–derived astrocytes [106]. While this study did not address whether TDP-43 was cleared by autophagy in astrocytes treated with these small molecules [106], inducing autophagy to clear both neuronal and astrocytic TDP-43 is likely to have a beneficial impact since human astrocytes harboring TDP-43 mutations exhibit cell autonomous toxicity [194].

In HD, expression of mutant HTT in astrocytes leads to a decrease in GLT-1, both in HD mouse brains and in cultured glial cells [58,62]. GLT-1 is a glutamate transporter specifically expressed in astrocytes which, together with another transporter GLAST, clears extracellular excitatory glutamate [81]. Treatment of primary mouse astrocytes with rapamycin reduced the levels of mutant HTT, rescued the decrease in the GLT-1 glutamate transporter levels and reversed the deficiencies in glutamate uptake [195]. A protective role of the autophagy inducer trehalose has also been suggested in primary glia cultures from wildtype and mutant HTT mice by reducing the accumulation of mutant HTT, as well as synuclein observed in these cultures [196]. While these studies point to a beneficial role of autophagy inducers to rescue the harmful phenotypes associated with glial cells in neurodegeneration, they do not exclude the possibility that rapamycin or trehalose exerts these effects independently of autophagy.

Contribution of autophagy disruption in astrocytes to neurodegeneration

As outlined in the introduction, deficiencies at different stages of the autophagy-lysosome pathway have the potential to contribute to neuronal degeneration [3]. One of the first reports documenting dysfunction of autophagy in astrocytes in disease was in relation to multiple sulfatase deficiency (MSD), a severe lysosomal storage disorder caused by mutations in the sulfatase modifying factor (SUMF1) gene [197]. Lysosomal storage disorders comprise several inherited metabolic diseases where lysosomal function is impaired and non-degraded material accumulates. Autophagy impairment in neurons as a result of these lysosomal defects is a central mechanism underlying some lysosomal storage disorders and contributes to the neurodegeneration observed in many of these diseases [198]. Malta et al., 2012, observed that in SUMF1 knockout mice, autophagy is impaired in astrocytes, resulting in the accumulation of autophagosomes and large autolysosomes in these cells. Moreover, primary astrocytes lacking SUMF1 lost their ability to support neuron viability when co-cultured with neurons, and *in vivo* astrocyte deletion of SUMF1 was sufficient to induce degeneration of cortical neurons [197]. It remains to be determined whether this non-cell autonomous lack of support is mediated directly via autophagy dysfunction.

Recently, genes identified as risk factors in PD have been linked to both autophagy and astrocyte biology, including *PARK2*, *PARK7*, *GBA*, *LRRK2*, *PINK1*, or *ATP13A2* [55], suggesting that astrocyte homeostasis is compromised through autophagy dysfunctions. *LRRK2* is associated with both sporadic and familial cases of PD where the most common mutation, G2019S, lies in its kinase domain. While the physiological and pathological role of *LRRK2* is not well understood, research in recent years points to *LRRK2* as a regulator of autophagy and lysosomal pathways in neurons [128,129]. In the human brain, *LRRK2* is also expressed in astrocytes [199]. Primary astrocytes from transgenic mice expressing an *LRRK2* mutant showed enlarged lysosomes, an inhibition of long-lived protein degradation and a reduction of lysosomal pH, although the consequences of this lysosomal dysfunction on astrocyte or neuronal pathology in PD were not explored further [200]. More recently, iPSC-derived astrocytes from patients expressing the G2019S mutation in *LRRK2* showed impairment in autophagy and chaperone-mediated autophagy parallel to a progressive accumulation of α-synuclein in astrocytes. When these were co-cultured with dopaminergic neurons from healthy individuals, a decrease in neuronal survival correlated with an increase in astrocyte-derived α-synuclein in these neurons, suggesting that autophagy impairment in astrocytes in PD may contribute to α-synuclein accumulation and neuronal degeneration [201].

The contribution of autophagy dysfunction in astrocytes to tau and amyloid pathology has not received much attention so far. In a study using human post-mortem brain from CBD, PSP and familial AD, the autophagy markers P62 and LC3 accumulated only in neurons suggesting autophagy disruption in neurons but not in glial cells [119]. On the other hand, in a transgenic model of AD expressing the Swedish and Indiana mutations in the human *APP* gene, astrocytes that were located near the Aβ plaques exhibited enlarged volume and surface areas, as well as increased internal levels of APP-related peptides, which coincided with positive

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staining for LC3, suggesting changes in autophagy in astrocytes located near plaques [202]. In recent years, autophagy has been implicated in secretion through non-conventional pathways [203]. In this context, autophagy-dependent secretion is important for the release of the insulin-degrading enzyme (IDE) by primary mouse astrocytes into the media in response to Aβ [204]. IDE is a protease involved in Aβ degradation in the extracellular space [205]. IDE was detected in the CSF of mice injected with Aβ, while its levels decreased in Atg7 ± mice with reduced autophagy, suggesting that, also *in vivo*, autophagy modulates Aβ-induced secretion of IDE, necessary for the degradation of extracellular Aβ [204].

Neuroinflammation is a crucial component of all neurodegenerative diseases, where microglia and astrocytes mediate an active role by releasing numerous pro- and anti-inflammatory cytokines [19]. Autophagy plays a critical role in the immune response, from regulation of cytokine production and release to inflammasome activation, antigen presentation and phagocytosis of pathogens [6–8]. Autophagy in microglia is important for mediating microglial phagocytosis, as well as for the regulation of microglia inflammatory response including reduction of inflammasome activity and the secretion of proinflammatory mediators [9,10]. In 2013, Motori et al. reported a role of autophagy in modulating mitochondria dynamics in astrocytes during inflammation. In a mouse model of acute injury, astrocytes exhibited changes in the mitochondria network. Proinflammatory stimuli recapitulated this effect *in vitro*, which resulted in increased mitochondria fragmentation and failure of the respiratory chain in reactive astrocytes. Importantly, these mechanisms were dependent on autophagy. ATG7 knockout cultured astrocytes failed to restore mitochondria integrity and showed increased production of reactive oxygen species and cell death, pointing to a key role of autophagy in preserving astrocyte function during inflammation [206]. This protective effect of autophagy in astrocytes may then be extrapolated to the neuroinflammation observed in neurodegeneration. While it has not been studied in much detail so far, autophagy could potentially be involved in astrocyte phagocytosis, as suggested [186], as well as in the secretion of inflammatory mediators by astrocytes.

In the brain, astrocytic end-feet surround the vast majority of blood vessels, constituting the neurovascular unit composed mostly of endothelial cells, pericytes, astrocytes, and neurons [207], and astrocyte dysfunction can contribute to cerebrovascular impairment [208]. Since autophagy is necessary to maintaining vessel function [209], it is therefore possible that astrocytic autophagy may also be important for vascular dysfunction in neurodegeneration.

Modulation of neuronal autophagy by astrocytes in a non-cell autonomous manner

Extracellular signals, in most cases arising from neighboring cells in a paracrine or autocrine fashion, are likely to modulate autophagy. A non-cell autonomous modulation of neuronal autophagy has been attributed to astrocytes in ALS in two independent studies that investigated whether the toxic effects of ALS-astrocytes could be secondary to the inhibition of autophagy in neurons [210,211]. Madill et al. (2017) showed that conditioned media from astrocytes derived from ALS patient iPSCs reduced autophagy levels in a HEK293T cell line, which was concomitant with an increase in endogenous SOD1, although the effect of astrocyte conditioned media on neuronal autophagy was not formally tested [210]. Tripathi et al. (2017) co-cultured motor neurons derived from human embryonic stem cells together with reactive astrocytes from spinal cords of two-month-old SOD1 mutant mice. After 60 days in co-culture, motor neurons developed cytoplasmic inclusions positive for ubiquitin and P62. Neurons also displayed axonal swellings that contained phosphorylation of neurofilament heavy chain (pNF-H) aggregates, characteristic of ALS, which resulted in reduced neuronal viability. This study proposed that TGF-β1, a factor secreted from these reactive astrocytes, mediates autophagy inhibition, since treatment of motor neurons with TGF-β1 resulted in activation of the mTOR pathway and reduced LC3-II turnover [211]. These studies hypothesized that astrocyte-secreted factors have an inhibitory effect on autophagy and that this could mediate some of the detrimental astrocytic effects in ALS.

Other non-cell autonomous roles of astrocytes in autophagy have been studied. Infusion of conditioned media from primary glial cultures into the striatum of the R6/1 mouse model of HD with a 115 CAG expansion resulted in a lower number of mutant HTT inclusions and a higher number of striatal and TH+ neurons after 30 days. This beneficial effect of glial conditioned media was accompanied by an increase in LC3-II levels and a decrease in P62 in whole brain lysates [212]. The antioxidant transcription factor Nrf2 is highly expressed in astrocytes [213] and shows neuroprotection on nearby neurons [213,214]. The factor is also protective in chemically induced animal models of PD and HD [215,216] and in genetically induced models of ALS and PD [217,218]. In this last model, selective astrocyte expression of Nrf2 in a transgenic mouse expressing the human A53T α-synuclein mutant led to extended life span and increased motor neuron survival, as well as reduced accumulation of A53T α-synuclein and activation of microglia and astrocytes. The levels of the autophagy markers LC3-II and P62 are increased in the spinal cord of the A53T α-

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synuclein mutant mice, indicative of defective autophagy, while crossing the A53T α-synuclein mice with mice selectively overexpressing Nrf2 in astrocytes restored autophagy levels, providing evidence that Nrf2-expressing astrocytes could lead to changes in neuronal autophagy [218]. While the exact mechanisms remain unknown, autophagy regulation may explain some of the non-cell autonomous Nrf2-mediated protective mechanisms of astrocytes.

Conclusions and Future Perspectives

Growing evidence has shown that impairment of autophagy and other systems that safeguard protein homeostasis, such as the proteasome, are behind some of the mechanisms underlying neurodegeneration. Autophagy dysfunction in glial cells including astrocytes may also contribute to some of the pathological features which, up to now, have been mostly attributed to neurons. This is particularly important when considering that many of the newly discovered genes associated with increased risk in neurodegeneration are expressed and have fundamental roles in glial cells.

Clearance of aggregate-prone proteins by autophagy is currently being studied for its potential therapeutic use. Besides neurons, astrocytes and other glial cells also accumulate disease-related proteins with potentially harmful effects on astrocytes and surrounding cells. Therefore, strategies that induce autophagy in astrocytes may be considered in the drug discovery pipeline. It is important to note that while further research is needed, autophagy may be regulated differently in neurons and astrocytes, and strategies to induce autophagy will need to investigate how these mechanisms work in different cell types. Importantly, the fact that astrocytes secrete a wide range of molecules, and that the secretion pattern could change during development and disease, provides a wide range of molecules that could potentially act as autophagy regulators, which could be exploited as therapeutic targets for the treatment of these neurodegenerative diseases.

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