Implications of Microglia in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

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Abstract

Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative disorders with clear similarities regarding their clinical, genetic and pathological features. Both are progressive, lethal disorders, with no current curative treatment available. Several genes that correlated with ALS and FTD are implicated in the same molecular pathways. Strikingly, many of these genes are not exclusively expressed in neurons, but also in glial cells, suggesting a multicellular pathogenesis. Moreover, chronic inflammation is a common feature observed in ALS and FTD, indicating an essential role of microglia, the resident immune cells of the central nervous system, in disease development and progression. In this review, we will provide a comprehensive overview of the implications of microglia in ALS and FTD. Specifically, we will focus on the role of impaired phagocytosis and increased inflammatory responses and their impact on microglial function. Several genes associated with the disorders can directly be linked to microglial activation, phagocytosis and neuroinflammation. Other genes associated with the disorders are implicated in biological pathways involved in protein degradation and autophagy. In general such mutations have been shown to cause abnormal protein accumulation and impaired autophagy. These impairments have previously been linked to affect the innate immune system in the central nervous system through inappropriate activation of microglia and neuroinflammation, highlighted in this review. Although it has been well established that microglia play essential roles in neurodegenerative disorders, the precise underlying mechanisms remain to be elucidated.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by a progressive loss of motor neurons in the brain and spinal cord. The disease has a prevalence of 5 in 100,000 in the worldwide population, making it the most common motor neuron disease, with no curative treatment currently available [1]. ALS is a lethal, rapidly progressing disease, with a typical age of onset around 55 years, and a median survival of 3–5 years after appearance of symptoms [2]. Patients usually present with both upper motor neuron and lower motor neuron signs, resulting in muscle weakness and paralysis, eventually causing respiratory failure, and thus death [1]. Most ALS cases are sporadic, but 5%–10% of all cases have been identified as familial, typically with dominant inheritance [3]. Over the past decades, a wide range of pathogenic mutations in genes have been identified and associated with ALS. These genes include *ORF 72 on chromosome 9* (*C9orf72*), *superoxide dismutase 1* (*SOD1*), *FUS RNA Binding protein* (*FUS*), and *TAR DNA-binding protein* (*TARDBP*) [4–8]. Many of these genes have also been associated with frontotemporal dementia (FTD), confirming not only a clinical overlap as previously observed but also significant similarities on both genetic and pathological level [9].

FTD is the second common cause of dementia, with a mean prevalence of 15 in 100,000 of the worldwide population aged 45–65 years [10]. This neurodegenerative disorder is characterized by progressive degeneration of the frontal and temporal lobes, causing altered behavior, personality and language dysfunction [11]. It has been established that ALS and FTD can co-occur in the same individuals

based on clinical evaluations. Furthermore, it has been observed that up to 50% of patients with ALS develop FTD symptoms, whereas 15% of patients with FTD show motor neuron dysfunction typically associated with ALS [11,12]. The identification of disease-causing genes has led to a better understanding of the significant relationship between these two disorders, showing direct overlaps on a cellular and molecular level affecting the same biological pathways, which will be elaborated on in the following sections.

Genetic Contributions

A number of genes have been identified as causes or risk factors of both ALS and FTD, some purely restricted to one end of the ALS/FTD spectrum, such as *SOD1* for ALS and *microtubule-associated protein Tau* (*MAPT)* for FTD, while some have been described with a clear connection to both conditions. These include the *C9orf72*, *TARDBP, Valosin-containing protein (VCP), ubiquilin-2 (UBQLN2)* and *Sequesterome-1 (SQSTM1)* [13]. An overview of genes with confirmed disease-causing mutations associated with ALS and FTD is displayed in Fig. 1, showing a clear genetic overlap between the disorders.

FTD-associated genes

MAPT encodes Tau, a protein essential for assembly of microtubules, mainly expressed in neurons. Missense or splice-site mutations in this gene were the first identified genetic link to FTD [14]. *MAPT* mutations accounts for 2%–11% of familial FTD cases, causing both neuronal and glial inclusions, that promotes neurodegeneration [3]. Since this discovery further genes have been associated with the disease, including mutations in *granulin* (*GRN*). *GRN* encodes progranulin (PGRN) and is expressed in both neurons and microglia in the central nervous system (CNS). PGRN is suggested to have growth factor properties promoting neurite outgrowth [9,15]. In addition, it has been suggested that it functions as an anti-inflammatory molecule preventing inflammatory-induced neurotoxicity. Loss-of-function mutations in this gene have been identified as a common cause of FTD, causing lysosomal dysfunction, TDP-43 aggregation and neurodegeneration. Consequently, these cellular pathologies suggest a role of PGRN in autophagy regulation [16]. Both *MAPT* and *GRN* mutations have mainly been linked to FTD and are not commonly observed in ALS, representing one end of the spectrum, whereas other genetic discoveries have been linked to both disorders.

ALS/FTD-associated genes

Non-coding repeat expansions of the *C9Orf72* gene have been identified in both sporadic and familial forms of ALS and FTD [5]. This is recognized as the most common known mutation in the two disorders and has been identified in 40% of familial ALS (fALS) and 25% of familial FTD (fFTD) cases, in addition to 6% and 7% of sporadic forms of ALS (sALS) and FTD (sFTD), respectively [5,17,18]. The mutation affects a hexanucleotide repeat expansion of GGGGCC nucleotides. This nucleotide stretch and can be found extended by hundreds to thousands in affected patients, compared to a normal amount of 0 to 30 copies in healthy individuals [19]. *C9Orf72* encodes a protein important in regulation of endosomal trafficking, interacting with RAB proteins involved in autophagy and endocytic transport. Such hexanucleotide repeats can result in loss of function and lead to accumulation of dipeptide repeat protein aggregates that could have a pathogenic effect in ALS and FTD patients [20,21]. In addition, decreased *C9Orf72* expression has been linked to altered microglial function and neuroinflammation. *C9Orf72* is highly expressed in myeloid cells, and haploinsufficiency has been observed to cause increased levels of pro-inflammatory cytokines, lysosomal accumulation and hyper-reactive immune responses, thus altering myeloid cell function and immunity [19]. Up-regulation of microglial activation genes, such as *TREM2*,

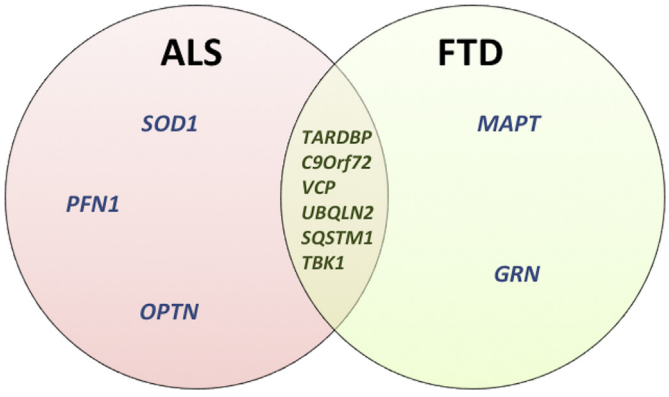

Fig. 1. Overview of genetic contributions in ALS and FTD. Distinct ALS and FTD associated genes, and genes linked to both disorders, indicating a clear genetic overlap and suggesting a common pathological disease spectrum.

has been demonstrated in mice with knocked down *C9Orf72* expression, indicating a link between *C9Orf72*, microglia and neuroinflammation in these disorders. Deficiency of C9Orf72 in microglia is thus suggested to directly alter microglia function, resulting in neuroinflammation [19].

Although *C9Orf72* is now considered the most common cause of ALS and FTD, several other genes are associated with lower incidence of mutations for both disorders. Mutations in *TARDBP* and *FUS*, encoding TDP-43 and FUS, respectively, have been linked to 9% of fALS and 2% of sALS and have rarely been observed in FTD cases [4,17,22]. *FUS* encodes a protein that plays a role in transcription, pre-mRNA splicing and mRNA transport. Patients with such mutations display deposits of FUS protein in cytoplasmic inclusions [6,23]. Since a genome-wide association study has only uncovered non-significant association to FTD, it still remains to be seen if mutations in *FUS* can indeed be directly associated with FTD pathology. Nevertheless, few cases of FTD display FUS aggregation in postmortem brain analyses [24]. One possibility could be that mutations in *FUS* and *TARDBP* induce neurodegeneration by altering the processing of mRNA. TDP-43 plays a role in transcriptional regulation of RNA splicing and stability, and a majority of inclusions in both FTD and ALS cases have been found to contain this protein [3].

Mutations in *VCP* have been associated with familial forms of both ALS and FTD. VCP functions via the ubiquitin–proteasome pathway, targeting a variety of substrates for degradation [25]. It is known to play a role in a wealth of cellular functions such as the reassembly of the endoplasmic reticulum (ER) and Golgi, proteolysis, spindle disassembly, DNA replication and damage response, autophagy and protein degeneration. Mutations in this gene cause accumulation of ubiquitinated substrates and deficient proteolysis [26]. *VCP* was first identified as an FTD-related gene, but mutations have now become apparent in 1%-2% of patients with fALS [27].

Another gene involved in this pathway is *UBQLN2*, and mutations in this gene occur in inherited forms of the two disorders. This gene encodes ubiquilin-2, important in regulating the degradation of ubiquitinated proteins. Patients show accumulation of ubiquilin-2 in inclusions, and such pathology has also been identified in sporadic cases of ALS/FTD [28]. Other reported mutations affect *SQSTM1* or *p62,* which is linked to protein degradation, and is important in cell survival and death. Mutations in this gene have been discovered in both fALS and fFTD, indicating an important role of deficient proteolysis in ALS/FTD pathology [29,30]. Mutations in these genes have thus been reported in both ALS and FTD patients, supporting a correlation between the two disorders.

ALS-associated genes

On the other side of the spectrum, some genes have been identified as strongly associated with ALS but are rarely seen in FTD, including *SOD1*. *SOD1* was the first causative gene identified in fALS and accounts for 12%–20% of all ALS cases. Mutations in *SOD1* have also been found in 1%–2% of sALS cases [8,31]. SOD1 normally provides a protective function in cells, by converting superoxide radicals into oxygen and hydrogen peroxide, thus relieving the cells from oxidative stress [9,33]. It has been debated whether mutations in this gene cause a loss of function or a gain of function, but animal models support the latter. *SOD1* mutations promote misfolding and aggregation of proteins, which in turn can cause alteration and a block of protein degradation and autophagy, in addition to mitochondrial defects [34–37].

Mutations in the above-described genes can cause abnormal aggregation of proteins in both neurons and glial cells. The presence of ubiquitinated, cytoplasmic inclusions, is a common feature present in both ALS and FTD. Such protein inclusion pathology is a hallmark of both disorders, mainly consisting of TDP-43. In addition, FUS protein inclusions have been observed in both disorders, whereas Tau inclusions are common for FTD cases, and SOD1 inclusion pathology can be observed in some ALS cases [9,11]. These reports clearly suggest a pathogenic connection between the two disorders, underlining the statement of a common ALS/FTD spectrum, also in terms of disease pathophysiology. An overview of the most common mutated genes in relation to ALS and FTD, their function and disease contribution is presented in Table 1.

The genes associated with ALS/FTD are involved in various cellular pathways, including inflammation, RNA toxicity, DNA/RNA homeostasis and protein dysfunction. Mutations in these genes can disrupt these pathways and contribute to neurodegeneration [38]. Research within neurodegenerative disorders has until recently mainly focused neural pathology. However, microglia and astrocytes are getting more and more recognition as being important for disease development and progression, which also applies to ALS and FTD. Alterations of the pathways mentioned in the previous sections not only can compromise neural function but also disturb microglia and astrocytes function. This can affect the homeostasis of the brain and glia–neuron communication and intercellular dependencies [39]. In addition, most of the genes identified as underlying causes of the disorders are expressed not only in neurons, but also in glial cells, suggesting a multicellular pathogenesis. Moreover, reactive gliosis is an occurring feature in both ALS and FTD, characterized by microglial proliferation and astrocytic

Table 1. Overview of genes with disease-causing mutations in ALS and FTD, showing type of mutation, frequency of such mutations in disease cases and gene function

Gene	Mutation	Frequency	Function
FUS	Missense	4% fALS/1% sALS 1% fFTD	RNA processing
TARDBP	Missense/Nonssense	5% fALS/1% sALS 1% FTD	RNA processing
C9Orf72	Non-coding expansion	40% fALS/7% sALS 25% fFTD/6% sFTD	Guanine nucleotide exchange factor for GTPases (Rab)
VCP	Missense	1%–2% fALS 1% fFTD	Proteasome pathway
UBQLN2	Missense	1% fALS/fFTD/2% sALS	Protein degradation
SQSTM1	Missense/Deletion	1% fALS/4% sALS 2% fFTD	Protein degradation
SOD1	Missense	12–20% fALS/1% sALS	Oxidative stress
MAPT	Missense/Splice-site	11% fFTD	Microtubule assembly
GRN	Missense	20% fFTD/5% sFTD	Growth/tissue repair, anti-inflammatory

hypertrophy, representing neuroinflammation of the brain. The ALS/FTD inflammatory phenotype is present in areas with inclusion pathology and neuronal loss, and it has been suggested that both astrocytes and microglia have an impact on disease progression and spreading [40–43]. There is clear evidence that microglia and astrocytes play an important role in ALS/FTD pathology, affecting inflammation and phagocytosis. However, the exact role and functional mechanisms glial cells play in these still need to be elucidated.

Microglia and Neuroinflammation

Microglia are the main resident immune cells of the brain, crucial to the CNS based on their important function in homeostasis, phagocytosis and synaptic pruning, removing toxic material and optimizing neurotransmission [42,44]. These microglia have the capability to sense any disruption in brain homeostasis, respond through a change in their morphology, release different cytokines and chemokines in order to clear pathogens and prevent further damage or injury. In response to such activating stimuli, microglia express major histocompatibility II (MHC-II), CD80 and CD86, associated with antigen presentation. In the case of chronic neurodegeneration other myeloid cells infiltrate the brain and contribute to the breakdown of the blood–brain barrier. Myeloid cells and microglia work together to eliminate the damage [45]. Activated microglia are present in most disorders of the CNS, including ALS and FTD, but there has been a debate in terms of their role in the diseases, and whether such activation is in fact a cause or a consequence of the disease. However, it has been established that these immune cells play a role in neurodegeneration, and the genetic discoveries in specific immune genes conferring an elevated risk of such diseases, support this theory [46].

Microglia can clear pathogens or apoptotic cells through phagocytosis, and altered phagocytosis has been identified in a number of neurodegenerative disorders [47]. Mutations in phagocytosis-associated genes expressed by microglia in the CNS have been identified as risk factors for both ALS and FTD. These include missense mutations in *TREM2*, which is exclusively expressed by microglia in the brain. Mutations in this gene have been linked to loss of function of the TREM2 protein, leading to altered inflammatory responses and reduced microglial phagocytosis [7,48,49]. Mutations in *GRN* on the other hand have been directly associated with FTD and may also confer a certain risk of developing ALS. *GRN* is expressed by both neurons and microglia and enables a process by which microglia recognize toxic elements and apoptotic cells [50]. Mutations in this gene have thus been observed to cause dysfunctional phagocytosis. Lack of PGRN causes microglia specific dysregulation of complement gene expression, impaired synaptic pruning and an overall alteration of microglial function [51,52]. On the other side of the spectrum, mutations in *PFN1,* encoding Profilin, have been identified as a causative mutation in ALS. Profilin is important for regulation of actin dynamics and thereby necessary for phagocytosis and phagosome formation [53]. Mutations in *PFN1* have been demonstrated to activate microglia [54]. The fact that the mentioned genes are either highly expressed in microglia, or observed to activate microglia when mutated, indicates that there is a link between microglial phagocytosis, neuroinflammation and neurodegeneration (Fig. 2).

Mice overexpressing human mutant *SOD1* have been used as the most common disease model of ALS. These mice show signs of motor neuron disease and share both clinical and pathological features present in ALS patients. Transgenic mice overexpressing fALS associated mutations in a constitutive manner develop ALS pathology. However, mice expressing human SOD1 with the G37R mutation, driven by the neurofilament light chain promoter (restricted expression in motor neurons) did not cause significant motor neuron disease. This

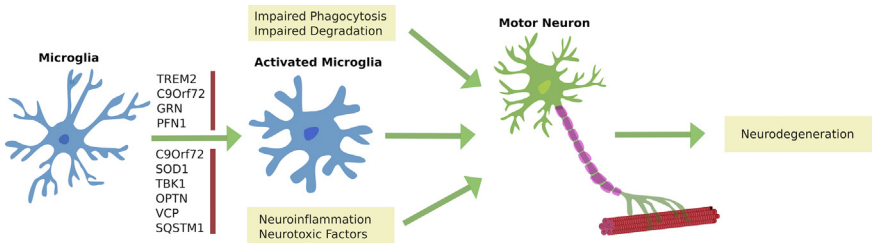

Fig. 2. Microglia and inflammation in ALS/FTD. Mutations in genes such as *C9Orf72*, *SOD1*, *TBK1*, *OPTN*, *VCP* and *SQSTM1* have been shown to activate microglia, increasing the production of neurotoxic factors and thus neuroinflammation, whereas mutations in *TREM2*, *C9Orf72*, *GRN* and *PFN1* have been observed to compromise microglial phagocytosis and associated degradation pathways. Alterations in these systems cause further damage of neurons, such as motor neurons in ALS, leading to neurodegeneration, promoting disease progression.

indicates that expression of mutant SOD1 in motor neurons is not sufficient to trigger disease pathology. These studies provide further indication of non-neuronal, such as microglial, involvement in disease progression [55,56]. Studies have shown that wild-type motor neurons develop features of ALS pathology, such as ubiquitin-containing aggregates, in the presence of mutant microglia, further emphasizing a non-neuronal involvement in disease pathology. Damage or mutations in glial cells could thus provoke disease development [57]. On the other hand, mutant SOD1 motor neurons have been demonstrated to survive longer when surrounded by wild-type microglia, indicating that glial cells have the ability to reduce the toxicity to such neurons, hence slowing down the disease progression [58].

Cultured microglia also show the same tendency. Microglia expressing mutant *SOD1* promote neural death. They become more activated than wild-type microglia and are more toxic to cultured neurons [59]. Furthermore, microglial activation appears to precede the clinical onset and increase during disease progression. A direct link between mutations in *SOD1* and microglial function has thus been identified in ALS, and both removal of the mutation itself, and inhibition of cytokines produced by activated microglia enhanced survival in mice, indicating a direct microglial influence on the progression of ALS [58].

To further investigate the role of microglia in neurodegenerative disorders, it is important to consider how these cells become activated. In terms of ALS, microglial activation might be triggered by misfolded protein accumulation, one of the pathological hallmarks of the disease. When activated, microglia have been shown to display neuroprotective properties during presymptomatic stages, but shift to a neurotoxic phenotype in later stages, further enhancing disease progression [60].

Animal and *in vitro* culture studies show a clear correlation between *SOD1* mutations, microglial function, neuroinflammation and ALS disease progression, and many of the other main ALS/FTD genes share these connections. *C9Orf72* is highly expressed in myeloid cells, and deficiency has been reported to cause lysosomal accumulation and hyper-activation of immune responses, altering the myeloid cell function and causing overall systemic neuroinflammation. This is accompanied by increased expression of pro-inflammatory cytokines such as IL-1β and IL-6 [5,18]. Moreover, reduced expression of *C9Orf72* has been observed to cause up-regulation of microglial activation genes, such as *TREM2*. This could contribute to altering the function of microglia, resulting in chronic neuroinflammation and thereby promoting neurodegeneration [19].

The recently discovered mutation in the gene *TANK-binding kinase 1* (*TBK1*) provides further evidence of altered immunity in ALS/FTD cases, emphasizing the role of glial cells and neuroinflammation in disease pathogenesis [61]. TBK1 is a known regulator of the innate immune system, influencing the production of interferon-α (IFNα) and interferon-β (IFNβ), and is thereby directly involved in neuroinflammation [62]. Optineurin (OPTN), SQST1 and VCP have also been linked to neuroinflammation and microglia, as they, together with TBK1, can regulate nuclear factor-kappa beta (NF-kβ), one of the crucial regulators of glial activation and neuroinflammation [63–67]. In addition, these proteins are similarly important within the autophagy and lysosomal pathways as PGRN and UBQLN2, clearly emphasizing the role of autophagy and lysosomal dysfunction in ALS/FTD patients and disease progression [16,51,68]. The fact that genes involved in these systems are expressed in both neurons and microglia indicates that both cell types might promote abnormal protein accumulation in neurons and altered inflammatory responses in microglia, that in combination leads to neurodegeneration. Disease-associated mutations in these genes have been documented to cause partial loss of function resulting in impaired autophagy induction, which seems to be a key mechanism in ALS/FTD pathology. This mechanism appears to be especially important in microglia, and many of these genes are highly expressed in such

cells, suggesting a molecular link between autophagy, neuroinflammation and microglia [19,69].

Microglial Inflammation and Autophagy

Autophagy is a general term for pathways in which cytoplasmic materials, such as misfolded or ubiquitinated proteins and damaged organellesm are delivered to lysosomes for degradation. This autophagic process has been documented as being compromised in a number of neurodegenerative disorders, including ALS and FTD. Autophagy is important for cell homeostasis and survival and three different types of autophagy have been described: macroautophagy, microautophagy and chaperone-mediated autophagy, with macroautophagy being the dominant form of autophagy within cells [70,71]. The autophagy system consists of autophagy-related proteins, known as ATGS, essential for mediating autophagosome formation [72]. Strikingly, it has recently been discovered that this pathway and its related proteins can influence inflammation and immunity. It appears that autophagy proteins can function as both suppressers and inducers of inflammatory responses. On the other hand, inflammatory signals can influence autophagy, thereby indicating a clear connection between the two pathways [73,74]. As both autophagy and microglia-induced inflammation have been proven to play an important role in neurodegenerative disorders, the relationship between these two mechanisms has recently gained increased interest.

Autophagy has been observed to influence microglial function, both in terms of phagocytosis and inflammation. Both autophagy and phagocytosis share many similarities, relying on formation of vesicular structures, the autophagosomes and phagosomes, respectively. Both processes engulf and deliver intra-cellular (autophagy) and extra-cellular (phagocytosis) molecules to lysosomes for degradation and are essential for maintaining cell homeostasis [69]. These processes may share similar functions in microglia, and it has been suggested that autophagy can regulate phagocytosis on multiple levels. A correlation between the two has been observed by the discovery of LC3-associated phagocytosis in macrophages, where the autophagy machinery is translocated to the phagosome for intracellular processing of the extra-cellular material that has been engulfed. Thus, autophagy is required for proper, complete phagocytosis [75,76]. Deficiency of autophagy-associated proteins has been suggested to alter the expression of phagocytic receptors, such as TREM2, providing further correlation between autophagy and microglial phagocytosis [77]. Increasing evidence thus suggests that autophagy might modulate phagocytosis in microglia, and alterations in autophagy seen in ALS/FTD can hence influence this function.

Moreover, autophagy is associated with immunity, and evidence indicates that this pathway regulates the inflammatory response in microglia. Autophagy has been shown to indirectly inhibit the production of IL-1β and IL-18. This is achieved via digestion of abnormal, dysfunctional mitochondria, which in turn reduces production of reactive oxygen species (ROS) production. Increased amounts of ROS are known to activate the inflammasome, promoting maturation and secretion of pro-inflammatory cytokines [78]. Strikingly, autophagosomes can also target such inflammasome complexes for degradation, which even further prevents cytokine production and inflammatory responses [79]. Moreover, autophagy can engulf pro-inflammatory cytokines, providing an additional regulatory step. All of these autophagic actions linked to inflammatory responses clearly underline the role of the autophagy machinery in microglia and inflammation [78,80]. If this system is compromised, such as in ALS and FTD, it can cause accumulation of both proteins and defective mitochondria and an increase in the release of inflammation activators [81]. Impaired autophagy or inhibition of this system has been shown to induce increased production of IL-1β along with other cytokines, promoting inflammation and microglial activation [78,82]. Overall, emerging evidence indicates that autophagy normally promotes an anti-inflammatory phenotype of microglia, by preventing inflammasome activation and blocking the release of pro-inflammatory cytokines. Dysregulation of this system can thus influence microglial function, and potentially contribute to chronic neuroinflammation as seen in neurodegenerative disorders [69] (Fig. 3).

Biomarker Evidence for Microglial Involvement

Microglial activation can be assessed via neuroimaging of biomarkers and has provided further evidence of microglial involvement in ALS. Using radioligands for the 18-kDA translocator protein (TSPO), present in activated glial cells combined with PET imaging, it has become possible to analyze microglial activation *in vivo* in ALS patients at an early disease stage [83,84]. Proteomic studies have identified novel biomarkers and potential targets for neuroinflammation-focused therapy. A recent study demonstrated elevated levels of three macrophage-derived chitinases: chitotriosidase (CHIT1), chitinase-3-like protein 1 (CHI3L1) and chitinase-3-like protein 2 (CHI3L2) in the cerebrospinal fluid of ALS patients. These proteins are primarily released by activated macrophages. Since microglia are the most abundant macrophages of the CNS, these observations likely relate to increased microglial activity [85].

The ability to analyze microglial activation *in vivo* using such biomarkers provides great potential in

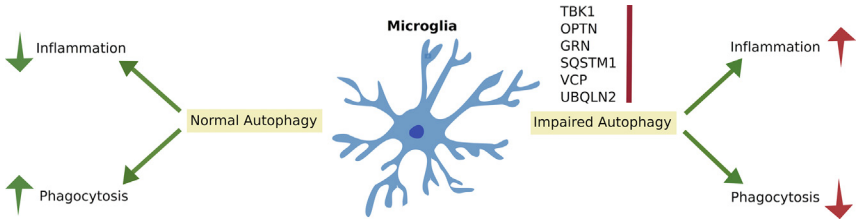

Fig. 3. Correlation between autophagy and microglial function. Normally, autophagy is suggested to play an anti-inflammatory role, promoting phagocytosis and reducing maturation and release of inflammatory cytokines and neurotoxic factors. When this system is compromised, it can, however, negatively regulate microglia and inflammatory responses. Mutations in the genes *TBK1*, *OPTN*, *GRN*, *SQSTM1*, *VCP* and *UBQLN2* have been shown to alter the autophagy machinery. Deficiencies of these proteins cause impaired autophagy, which results in increased inflammation, activation of the inflammasome and impaired phagocytosis. This indicates a disease-relevant correlation between autophagy, microglial function and neuroinflammation.

terms of improving our understanding of neuroinflammatory mechanisms in neurodegenerative disorders as well as allowing monitoring disease progression and treatment. Riluzole received marketing authorization in 1995 and has until recently been the only Food and Drug Administration–approved treatment option for ALS available. In 2017, the Food and Drug Administration also approved the drug edaravone [86]. However, these are only capable of delaying the disease progression, and there is a clear unmet need for new treatment strategies. It is now 20 years ago that riluzole was the first available drug for ALS on the market. Since then, a number of clinical trials with ALS patients have been performed, but have all failed to demonstrate clinical efficiency. This includes drugs with an anti-inflammatory mechanism of action. Several neuroinflammation modulators have shown preclinical efficiency in rodent ALS models, but have failed to improve function in human patients in advanced stage-clinical trials [87]. One of the reasons behind this endless failure could be the fact that the causal mechanisms of the diseases are still poorly understood. ALS is a heterogeneous disease, in terms of cause, progression and symptoms, making it challenging to model the disease and thus optimize treatment options. The drugs developed over the past years have been unsuccessful in clinical trials due to lack of efficacy, tolerability problems, or simply lack of convincing phase 3 clinical trial data. The success of such trials might be improved by designing better trials, and possibly focus on patients where the disease is rapidly progressing, to better monitor the effect of the treatment. The recent genetic discoveries provide a better understanding of specific disease pathways, giving new hope for future therapeutic approaches. The technology of creating personalized disease models using cellular reprogramming and induced pluripotent stem cells could contribute to new therapeutic insights, making it possible to work with a patient's own cells. Both the genetic contributions and increased understanding of both the microglial and neuronal disease involvement, as well as the interaction between the different players provide a new drive for future drug development [88].

Conclusion and Future Directions

It is evident that significant similarities in a clinical, pathological aspect and even cellular level exist between ALS and FTD. The identified genetic mutations correlated to both diseases reveal commonly affected pathological pathways promoting the idea of a mutual ALS/FTD disease spectrum. Many of the disease-associated mutations are not only expressed in neurons, suggesting a multicellular pathogenesis, and especially microglia have been implicated to play an important role in disease pathology and progression. Chronic inflammation is a common feature of both disorders, and increased activation of microglia has been observed in FTD and ALS. Several genes associated with ALS and FTD have been reported to disturb microglial function, by altering phagocytic activity, directly activating inflammatory pathways, or leading to protein aggregation and degradation defects that can trigger microglial activation, causing neuroinflammation and neurodegeneration. In addition, it is evident that autophagy plays a direct role by preventing inflammation. Impairments of the autophagic machinery, as seen in ALS and FTD, influence microglia through impaired phagocytosis, inflammasome activation and release of inflammatory cytokines. The fact that many of the disease-associated mutations are found in genes encoding for proteins important in autophagy, phagocytosis and inflammatory responses emphasizes a possible correlation between autophagy and microglial inflammation, highlighting the role of glial cells in neurodegenerative disorders.

It is clear that microglial function is essential in the pathogenesis of ALS and FTD, and this insight provides new possibilities in terms of potential therapeutic approaches in treatment of these disorders. One interesting approach would be to identify

compounds that increase the autophagic and phagocytic activities in both neurons and microglia. This approach could be valuable for many neurodegenerative diseases in which misfolded protein aggregate and impaired autophagy and neuroinflammation represent pathological hallmarks. Further research is needed to confirm the specific role of microglia in disease progression. Specifically, it would be relevant to gain more insights into how specific mutations and genetic risk factors affect the autophagic machinery and the link to immune function.

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ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; CNS, central nervous system; ROS, reactive oxygen species.

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