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Review

The role of glia in protein aggregation

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ABSTRACT

Protein aggregation diseases involve intracellular accumulation or extracellular deposition of certain protein species in neuronal or glial cells, leading to neurodegeneration and shortened lifespan. Prime examples include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), which are affected by overlapping or specific aggregation-prone proteins. Mounting evidence suggests that dysfunctional glial cells may be major drivers for some diseases, and when they are not causal factors, they could still significantly exacerbate or alleviate disease progression by playing a plethora of detrimental or beneficial roles. Here we review the diverse functions performed by glial cells in a variety of protein aggregation diseases, highlighting the complexity of the issue and the interconnected relationships between these multifaceted effects.

1. Introduction

Protein aggregation is a shared hallmark feature of numerous neurodegenerative diseases (Ross and Poirier, 2004). While some proteins have the tendency to accumulate in more than one types of diseases, others are rather specific to certain conditions. Examples of protein aggregation diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), which in their most stereotypical forms contain aggregates of amyloid beta (Aβ), alpha-synuclein (α-syn), TAR DNA Binding Protein 43 (TDP-43), and huntingtin (HTT), respectively, as part of the pathology. These protein aggregates may occur intracellularly as in the cases of α-syn, TDP-43 and HTT, or mainly form extracellular deposits such as Aβ plaques. Regardless of these variations, they are all possible causes of neuronal cell death.

In the past, the neuron-centric perspective has steered research focus primarily on mechanisms related to aggregates that are inside the neuron or have a direct impact on neuronal functions, despite unequivocal presence of such protein aggregates in many types of glial cells (Miller et al., 2004). This biased approach is beginning to change, as it is increasingly recognized that glial cells actively participate in nearly very aspects of central nervous system (CNS) development and function. Furthermore, technological advances in human genetics has made it possible to perform large scale genome-wide association studies, which uncover numerous neurodegenerative disease risk genes that are abundantly or sometimes exclusively expressed by glia (Efthymiou and Goate, 2017). This has led to intensive research efforts trying to address what glial cells do in these protein aggregation diseases.

As a matter of fact, histological changes of glial cells have always been considered as part of neurodegenerative pathology (Bruck et al., 2016; Radford et al., 2015; Strohm and Behrends, 2020; Wyss-Coray, 2006). These changes, collectively called gliosis, involve proliferation and hypertrophy of glial cells which usually display increased immunoreactivity to selective antigens near the damaged CNS cores. These observations, however, are traditionally thought to be only secondary responses to neuronal death (Wyss-Coray, 2006). Even when the significance of glial functions in disease is acknowledged, their functions are often oversimplified as proinflammatory with an overall negative connotation. To the contrary, we now know that glial cells play very diverse and complex roles in protein aggregation diseases, and in many cases, these multifaceted roles can dynamically change, and intertwine with one another along disease progression.

As there is a large array of protein aggregates, and various glial cell types may be involved in different aspects of a disease, we do not intend to discuss all possible combinations in this review. Rather, we provide

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recently discovered examples for each general category of glial functions, focusing on detrimental *versus* beneficial outcomes to disease. Such logic may be applied to many different scenarios.

2. Detrimental roles of glia in protein aggregation

2.1. Glia as agents of protein aggregate formation and spread

Protein aggregates within glia, such as glial cytoplasmic inclusions (GCIs), have long been observed in neuropathology (Ikeda et al., 1998; Nishimura et al., 1995; Papp et al., 1989). In many instances the presence of the same protein aggregated in glia, compared with neurons, is associated with distinct neurodegenerative diseases. For instance, tau aggregates are observed within neurons in frontotemporal dementia (FTD) and AD, whereas tau is observed aggregated in oligodendrocytes and astrocytes in progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (Ferrer et al., 2014). These glial aggregates could be taken up from the extracellular space or originate from endogenous protein expression within the glial cell. Interestingly, a recent study shows that in the absence of neuronal tau, oligodendrocytes, but not astrocytes, can still propagate PSP-tau and CBD-tau aggregates *via* white matter tracts (Narasimhan et al., 2020), suggesting distinct modes of interactions between tau strains and neural cell types.

In the case of oligodendrocyte aggregates, one major consequence of their accumulation is to cause cell death and subsequent demyelination, which is frequently observed in neurodegenerative diseases (Ettle et al., 2016). This is possibly due to loss of critical functions in the aggregation-prone genes, and/or such protein aggregates interfering with other cellular processes. It has been shown that in mouse models of ALS, removal of disease causal mutation SOD1 specifically in oligodendrocytes can rescue white matter degeneration, thereby delaying disease onset and prolonging lifespan (Kang et al., 2013). Similarly, the normal function of TDP-43 is also required for oligodendrocyte survival and myelination (Wang et al., 2018). These animal studies are consistent with the observation that in ALS patient samples, oligodendrocytes with GCIs have decreased levels of myelin basic protein (MBP) (Lorente Pons et al., 2020). Therefore, myelination defect may be an important driver for protein aggregation disease pathology.

Besides these cell-autonomous effects, a more dramatic consequence is that glia may facilitate prion-like seeding and spreading of aggregates throughout the CNS (Hopp et al., 2018; Valdinocci et al., 2017). The prion-like spread of many protein aggregates, such as Aβ, tau, α-syn and HTT, has been well documented to occur in neurons and across neuronal networks (Vaquer-Alicea and Diamond, 2019); however, this phenomenon attributed to glial cells has been relatively less explored. A great example is provided by an elegant recent study on synucleinopathies in which oligodendroglial α-syn is more potent in seeding protein aggregation compared to α-syn from neurons (Peng et al., 2018). Particularly, the cellular environment of oligodendrocytes in multiple system atrophy (MSA) generates a distinct α-syn aggregate form, which is much more efficient—up to 1000 times more efficient in some cases—in converting endogenous α-syn monomers into aggregates, compared with neuronally derived α-syn in Parkinson's disease (PD) and Lewy-body dementia. When two forms of aggregates are transplanted into the mouse CNS, there is no cell type preference in the uptake between aggregates of two origins, but the oligodendrocyte-derived aggregates are much more aggressive in their spread and, interestingly, spread across distinct anatomical networks (Peng et al., 2018). This raises interesting questions as to what cellular machinery is present in oligodendrocytes but not neurons that compacts aggregates in this distinct way, leading to different disease outcomes. The cellular components of such compaction machinery in oligodendrocytes could be new attractive therapeutic targets for MSA.

This discovery of the special oligodendrocyte cellular milieu in packing aggregates makes one wonder whether other glial cell types may spread or produce unique aggregate forms. It is possible that microglia or astrocytes, which have a greater capacity for compression and compaction of cellular debris through lysosomal degradation, could generate other cell type-specific aggregate species, when the cells lack the ability to fully degrade them. Although there have been few studies implicating microglia in the spread of aggregated α-syn, they seem to contribute to tau propagation *via* secreted exosomes (Asai et al., 2015). Moreover, phagocytic glia in Drosophila have been shown to be necessary for the spread of the mutant HTT (Pearce et al., 2015). Interestingly, eliminating P16+ senescent astrocytes and microglia in a mouse model of tauopathy reduces the amount of phosphorylated tau in neurons (Bussian et al., 2018), which may suggest that senescent glia facilitate the spread of phosphorylated tau. Alternatively, these results could be due to the elimination of negative secreted factors from senescent glia. One unique capacity of microglia that could facilitate aggregate spread throughout the CNS is their high degree of motility (Nimmerjahn et al., 2005), although stereotypic propagation patterns across neuronal networks, when existing, would require some coordination in microglia migration. On the other hand, recent evidence suggests that α-syn fibrils can be taken up by astrocytes and spread among astrocytes through tunneling nanotubes (Rostami et al., 2017). This phenomenon, however, was only demonstrated with exogenously added pre-formed α-syn fibrils in stem-cell models of human astrocytes, and its *in vivo* relevance remains to be determined. While how aggregate seeding and spread among glial cells accelerate disease progression is an emerging topic of investigation, a large body of research has been focusing on the negative factors glia secrete in response to aggregates.

2.2. Secretion of negative factors by glia in response to protein aggregates

Reactive microglia and astrocytes, as prominent neuropathological features of most protein aggregation diseases, can induce neuroinflammation resulting in disruption of CNS homeostasis. It is now widely accepted that reactive glial cells are heterogeneous and highly context-dependent by expressing distinct subsets of signature genes (Friedman et al., 2018; Liddelow and Barres, 2017; Zamanian et al., 2012). The transcriptional state and molecular triggers of one type of harmful reactive astrocytes have been recently uncovered (Liddelow et al., 2017). These astrocytes are termed A1 (analogous to the proinflammatory M1 state of microglia), which not only lose supportive functions for neuronal survival and outgrowth but also release some unidentified neurotoxic factors. Such toxins can powerfully kill neurons and mature oligodendrocytes. As A1 are present in many neurodegenerative diseases, they may be important drivers underlying the massive cell death in these conditions (Liddelow et al., 2017).

Interestingly, A1 reactive astrocytes may be induced by activated microglia-secreted signals (Liddelow et al., 2017). It has been known for decades that microglia adjacent to aggregates, such as amyloid plaques, exhibit a unique activation state that stimulates the secretion of inflammatory cytokines such as IL-1α (Mrak et al., 1995; Sheng et al., 1995). As the resident innate immune cells of the brain, it is thought that the activated state of microglia is triggered by damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) from either the aggregates themselves or by proteins and debris from neurons or other glia (Venegas and Heneka, 2017). These so called proinflammatory microglia are present in many neurodegenerative diseases. They secrete an array of inflammatory cytokines including IL-1β, IL-6, IL-12, IFN-γ, and TNF-α, which may directly cause neuronal death or interact with other cellular components in the CNS to induce damages (Floden et al., 2005; Wang et al., 2015).

One mechanism underlying microglia activation that has come into view in recent years is through the NLRP3 inflammasome, a multiunit protein complex that results in the secretion of IL-1β and the ASC (apoptosis-associated speck-like protein containing a CARD) specks. While multiple cell types in the brain express the machinery for inflammasome components, the NLRP3 inflammasome seems to be

particularly active in microglia (Heneka et al., 2018). In a similar fashion to most inflammasomes, the NLRP3 inflammasome is initiated by innate immune receptors which induce expression of pro-IL-1β and NLRP3. Upregulated NLRP3 can then be activated to form inflammasomes consisting of a helical fibrillar complex of NLRP3 and the adaptor protein ASC. These inflammasomes lead to formation of ASC specks, which activate Caspase-1 to generate mature IL-1β and meanwhile are also released into the extracellular space themselves (Heneka et al., 2018). Notably, this cascade of inflammasome activity can be induced in microglia by either aggregated tau (Stancu et al., 2019) or Aβ oligomers (Luciunaite et al., 2019). Consistent with these observations, NLRP3 inflammasome activation has been observed in both FTD and AD human brain tissues (Ising et al., 2019).

Inflammasome activation is of particular importance, because not only does it lead to the release of IL-1β but the ASC specks produced during the process are released into the extracellular space where they remain active in a 'prionoid' like form (Franklin et al., 2014). These extracellular ASC specks may propagate the wave of inflammation in the CNS as well as cross-seed Aβ aggregate formation (Venegas et al., 2017). Remarkably, these ASC speck-Aβ aggregates can also drive tau pathology (Ising et al., 2019). The series of events from aggregates stimulating the inflammasome leading to extracellular ASC specks release could be causing an especially pathological feed forward loop in multiple neurodegenerative diseases. Therefore, inhibition of NLRP3 inflammasome activation and/or preventing the formation of ASC specks may provide a novel therapeutic approach to treat protein aggregation diseases.

2.3. Aberrant elimination of synapses in response to protein aggregates

Microglia and astrocytes not only impact neurons by the factors they secrete, but they also sculpt neuronal circuitry by phagocytic engulfment of synapses (Chung et al., 2013; Schafer et al., 2012; Stevens et al., 2007) and axons (Watts et al., 2004). For example, microglial synapse elimination mediated through the complement pathway is required for proper neurodevelopment in multiple regions of the brain (Anderson et al., 2019; Schafer et al., 2012; Stevens et al., 2007). Removing immature synapses is crucial for establishing functional neural network during development; however, the same mechanism may be aberrantly reactivated in diseases of neurodegeneration. Indeed, synapse loss is a major reason for cognitive decline in many protein aggregation diseases, and its occurrence may even precede aggregate formation (Hong et al., 2016).

The first bridge between glial synaptic phagocytosis and neurogenerative disease came with a study showing *in vitro* and *in vivo* that oligomeric Aβ (oAβ), but not the monomeric peptide, is sufficient to induce neuronal C1q expression and synaptic elimination by microglia (Hong et al., 2016). This microglial activity is blocked in C3R knockout mice, suggesting that the microglial synaptic elimination in response to oAβ is complement dependent. Because microglia predominantly express this complement receptor within the CNS, their hyperactive phagocytosis is considered as the culprit for synapse loss in AD and some other neurological diseases. Furthermore, hippocampal long-term potentiation is also impaired due to the glial synaptic pruning in this paradigm, which can be reversed with a C1q antibody. Can this synapse loss explain the cognitive defects in mouse AD models? Strikingly, APP/PS1;C3 KO mice show enhanced cognitive ability in a spatial learning behavioral task compared to APP/PS1 mice (Shi et al., 2017). In addition, C3 KO also partially spares neuronal and synaptic loss in the APP/PS1 mouse model. Despite the improvements in behavior and synapse density due to the inhibition of microglial phagocytosis in the C3 KO, Aβ burden is actually increased in APP/PS1;C3 KO mice compared with APP/PS1 alone, suggesting that, through the complement pathway, microglia regulate synapse elimination and Aβ removal independently, and that synaptic restoration is more relevant to functional recovery. This observation is also consistent with the poor correlation between cognitive scores and plaque levels previously reported in human patients (Nelson et al., 2012).

Surprisingly, the Tau-P301S transgenic mice, a distinct neurodegenerative mouse model, also show an increase of C1q localized to and tagging hippocampal synapses for microglial engulfment (Dejanovic et al., 2018). The synapse density loss in this tauopathy mouse model can be rescued with a C1q blocking antibody. This work is complemented by other studies showing that C3R KO also reduces spine density loss, brain atrophy and behavioral deficits in Tau-P301S mice (Wu et al., 2019). Interestingly, an additional recent study demonstrates a reduction of tauopathy and microglial synaptic phagocytosis with C3aR KO in the background of the PS19 tauopathy mouse model, suggesting that different complement pathways may be engaged in parallel to modulate synapses (Litvinchuk et al., 2018). Consistent with the significance of complement in disease, variants in the complement components, CR1 and CLU have been identified as AD risk factors (Lambert et al., 2009). Together these studies suggest a potentially powerful and broadly applicable point of therapeutic intervention by putting the brakes on aberrant microglial synapse phagocytosis through inhibition of the complement pathway in AD and other tauopathies. Evidence supporting the feasibility of therapeutically targeting this pathway in the CNS can be seen in the recent AAV based approaches that inhibit the complement-mediated synapse phagocytosis in preclinical models of multiple sclerosis (Werneburg et al., 2020).

3. Beneficial roles by glia in protein aggregation

3.1. Glial uptake of protein aggregates

Protein aggregation can not only cause loss of normal functions of these proteins, but also produces gain of toxicities to neurons and glia. Removing protein aggregates, mostly done by glial cells, is generally beneficial to restore brain physiology and homeostasis. As professional phagocytes in the CNS, microglia play important roles in synapse elimination and clearance of cellular debris during development and disease (Li and Barres, 2018), and a recent study showed that restoration of phagocytosis in aged microglia can improve cognitive function during aging (Pluvinage et al., 2019). Meanwhile, astrocytes can also perform similar functions with their high expression of phagocytic receptors (Cahoy et al., 2008; Chung et al., 2013; Jung and Chung, 2018; Zhang et al., 2014). Interestingly, recent human genetic studies have demonstrated that increasing susceptibility in diseases with protein aggregation are associated with variants in many glia-specific genes, such as triggering receptor expressed on myeloid cells 2 (TREM2), CD33, complement receptor 1 (CR1) and progranulin (PGRN), which are involved in phagocytic processes (Brown and Neher, 2014). Therefore, direct or indirect uptake of protein aggregates by glia has neuroprotective effects, which might be compromised due to these gene mutations.

3.1.1. Amyloidosis

The most extensively studied glial uptake of aggregates is microglial clearance of Aβ in Alzheimer's disease. There are various forms of Aβ with different solubility, such as monomers, oligomers, fibrils and compact plaques, some of which are more toxic to neurites than others (Chen et al., 2017). Early work using cultured microglia demonstrated their ability to phagocytose fluorescently labeled Aβ fibrils, although electron microscopy (EM) data pointed to inefficient degradation of ingested material in microglial phagosomes (Frackowiak et al., 1992; Paresce et al., 1996). Cell surface receptor complex comprising scavenger receptors (both class A and class B) and α6β1 integrin seems to control this phagocytic activity (Koenigsknecht and Landreth, 2004; Paresce et al., 1996). However, conflicting observations have been reported about microglial competence of engulfing Aβ *in vivo*. Time lapse *in vivo* imaging in APPPS1 mice shows that the sizes of plaques fluctuate in relation to the volumes of surrounding microglia, and plaque-

associated microglia can robustly internalize injected amyloid-binding dye (Bolmont et al., 2008). Furthermore, engulfed Aβ colocalizes with lysosomal markers, suggesting microglia are capable of amyloid clearance at least in this model. In contrast, another imaging study using the CRND8 model and fibril *versus* soluble Aβ antibodies, demonstrates that plaques are stable over months, and the authors concluded that microglia only uptake soluble forms of Aβ but not fibrils in AD (Liu et al., 2010). Indeed, microglia can engulf soluble Aβ *via* P2Y4 receptor-mediated macropinocytosis *in vitro* (Li et al., 2013; Mandrekar et al., 2009).

Consistent with limited microglial phagocytic ability, EM studies fail to detect significant levels of intracellular amyloid fibrils in microglia of APP23 mice as well as *post mortem* human tissues (Frackowiak et al., 1992; Stalder et al., 2001). Moreover, depletion of microglia for about 1 month genetically (CD11b-HSVTK in APPPS1 and APP23 mice) or pharmacologically (CSF1R inhibitor in 5XFAD mice) does not alter the compact plaque load (Grathwohl et al., 2009; Spangenberg et al., 2016). However, when microglia are depleted for only 1 week (CX3CR1-iDTR in APPPS1), individual plaques that are tracked by *in vivo* imaging show 13% increase in volumes over the following week (Zhao et al., 2017b). This data seems to suggest that microglia play a role in limiting plaque load, although it did not address if such action is mediated by phagocytosis and if so which forms of Aβ are engulfed. Alternatively, microglia can be functioning through confining and compacting plaques (see below). Despite some discrepancies in these studies, which may be attributed to different animal models, age of mice, and methods used, active Aβ immunization is able to trigger more efficient removal of amyloid plaques both in animal models and human patients (Condello et al., 2018). Collectively, the emerging picture is that although microglia are capable of amyloid uptake, at least for the soluble form, this activity is somehow inhibited in disease conditions and becomes very limited especially for fibrillar Aβ.

In addition to microglia, astrocytes also phagocytose amyloid, and this was first shown using *in vitro* assays and brain sections from hAPPJ20 mouse models (Wyss-Coray et al., 2003). A later study demonstrated that low-density lipoprotein receptor (LDLR) may serve as an astrocytic receptor to which Aβ binds for its clearance (Basak et al., 2012). This notion is further corroborated by immuno-EM on AD or aged human brain samples, in which nonfibrillar Aβ are found in astrocytes (Funato et al., 1998; Kurt et al., 1999). Interestingly, Aβ can also stimulate gene expression of APP processing enzymes in astrocytes, which presumably increases amyloid levels (Zhao et al., 2011). This paradox may be explained by changes in astrocyte reactivity during disease progression, where astrocytes initially may be responsible for Aβ uptake but gradually change to an activated phenotype with lower phagocytic activity, higher Aβ production, and a tendency to undergo lysis causing content (including Aβ) release and aggregate spread (Nagele et al., 2004).

Besides direct uptake, extracellular Aβ can also be internalized by microglia and astrocytes through binding to chaperone proteins such as APOE. APOE is mainly produced by astrocytes and microglia. Interestingly, it is downregulated in astrocytes but upregulated in microglia in AD (Mathys et al., 2019). These glial cells also express apolipoprotein receptors, such as LDLR and LRP1, for APOE-Aβ uptake (Fan et al., 2001). The ApoE4 isoform confers the strongest genetic risk for late-onset AD, perhaps by disturbing its interaction with Aβ leading to poorer clearance (Castellano et al., 2011). A recent study shows that another AD risk factor, TREM2, also binds to APOE (and APOJ), which facilitates Aβ uptake by microglia (Yeh et al., 2016). It remains unknown how microglia and astrocytes coordinate Aβ clearance with changes of their reactive states in different disease stages.

3.1.2. Diseases with Intracellular aggregates

While it is established that engulfment of extracellular aggregates in the case of amyloidosis is beneficial, the role of glial phagocytosis is less clear for other diseases containing mainly intracellular aggregation of proteins, such as tau, superoxide dismutase proteins (SOD), TDP-43, and α-syn. Despite their intracellular localization, these proteins can also be secreted into extracellular space through direct exocytosis or exosomes (Iguchi et al., 2016; Kim et al., 2013; Urushitani et al., 2006). Moreover, during neurodegeneration, which is shared among protein aggregation diseases, aggregates and other toxic factors may be released into the microenvironment, leading to inflammation and other secondary damages. Therefore, timely removal of dying cells and the relevant protein aggregates is beneficial for these conditions as well.

ALS is a common motor neuron disease, which shares pathological features with FTD, including cytoplasmic accumulation of TDP-43 (Radford et al., 2015). Using an inducible human TDP-43 (hTDP-43) model, it has recently been demonstrated that microglia switch to a reactive state only after hTDP-43 expression is halted, and these activated microglia efficiently clear neuronal hTDP-43 debris leading to functional motor recovery (Spiller et al., 2018). This phagocytic activity is thought to be neuroprotective, as motor neuron functions fail to recover when microglia are pharmacologically removed. Interestingly, TDP-43 itself seems to negatively regulate microglial phagocytosis. Knocking out TDP-43 in microglia promote amyloid clearance, providing a possible explanation for low occurrences of AD among ALS patients (Paolicelli et al., 2017). However, this should not be interpreted as solely beneficial, because this elevated phagocytosis also causes synapse loss.

Regarding α-syn aggregation, seen in PD and MSA, microglia can efficiently engulf extracellular and secreted α-syn *in vitro* (Bruck et al., 2016). In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD, activated microglia, instead of infiltrating myeloid cells, are found to preferentially phagocytose retrogradely labeled dopamine neuron debris (Depboylu et al., 2012). TLR2 and TLR4 seem to mediate both α-syn uptake and inflammatory response (Fellner et al., 2013; Kim et al., 2013; Stefanova et al., 2011). Interestingly, these two receptors have also been shown to remove Aβ in AD (Chen et al., 2006; Tahara et al., 2006), pointing to converging mechanisms of controlling protein uptake and inflammation *via* TLRs in microglia.

Astrocytes also phagocytose α-syn fibrils for degradation *in vitro* and on *ex vivo* brain sections (Loria et al., 2017; Tremblay et al., 2019). Furthermore, using a rat model of 6-hydroxydopamine induced dopaminergic denervation in the striatum, dopaminergic debris as well as α-syn is observed in astrocytes 2–5 days after injury, suggesting that astrocytes may play a beneficial role in clearing damaged cellular components during early stages of PD (Morales et al., 2017). Later in disease, however, astrocytes may be polarized towards A1 reactive state, which is less phagocytic but highly cytotoxic to neurons and oligodendrocytes (Liddelow and Barres, 2017).

3.1.3. Double effects for glial engulfment

As discussed earlier, although phagocytic elimination of protein aggregates and inflammation-inducing debris by glia is generally neuroprotective, increasing phagocytosis can cause synapse loss, along with some other detrimental effects. In the case of PD, for example, microglia with elevated phagocytic activity may remove distressed live neurons, and hence, knocking out AXL and MER (two phagocytic receptors) in α-syn transgenic mice spares these neurons leading to prolonged lifespan (Fourgeaud et al., 2016). Similarly, a common familial PD allele in LRRK2 (G2019S) may promote microglia to phagocytose otherwise recoverable dopamine neurons by interacting with actin cytoskeleton machinery (Kim et al., 2018). Interestingly, the same gene mutation also seems to compromise lysosomal degradation of engulfed material in astrocytes, which may eventually lyse up and release more α-syn causing spreading of the disease in later stages (Henry et al., 2015). Indeed, many protein aggregates, including α-syn, can be internalized by phagocytic cells initially as a neuroprotective mechanism, but overloading or altered glial functions over time could provide opportunities for aggregates release and prion-like disease transmission as

discussed in the previous section (Brundin et al., 2010).

3.2. Extracellular degradation of protein aggregates

Clearance of protein aggregates may also occur without internalization, and one mechanism is through degradation by glia-derived ectoenzymes. Because diseases like PD and ALS contain intracellular aggregates, enzymatic or alternative degradation mechanisms there would be mainly cell autonomous to neurons. We will focus this section on amyloidosis and its clearance.

Glial cells can produce metalloendopeptidases, such as neprilysin (NEP), the insulin degrading enzyme (IDE), and the endothelin-converting enzymes (ECEs), which all hydrolyze monomeric Aβ (Nalivaeva et al., 2012). NEP is an ectoenzyme containing an extracellular catalytic domain for digesting peptides up to 50 amino acids. NEP downregulates with age in neurons and reduces expression in AD patients (Apelt et al., 2003). Overexpression of NEP in neurons attenuates amyloid burden and the associated cytopathology in APP transgenic mice (Leissring et al., 2003). Interestingly, reactive astrocytes near amyloid plaques express higher levels of NEP, which may be neuroprotective (Apelt et al., 2003; Nalivaeva et al., 2012). Similar to NEP, ECEs are able to degrade Aβ *in vitro* and *in vivo* (Eckman et al., 2001). While ECE2 expression seems broader in neural cell types, ECE1 is predominately expressed by endothelial cells (Zhang et al., 2014). Activation of PKC pathway can increase ECE1 expression, resulting in Aβ degradation (Choi et al., 2006). IDE is another metalloendopeptidase that can digest Aβ both *in vitro* and *in vivo* (Ries and Sastre, 2016). IDE is expressed in neurons and different glial cells. Although it is mainly intracellular due to the lack of a secretory signal, IDE can be exported outside of the cell through exosomes (Bulloj et al., 2010). IDE expression is decreased in aging and AD mouse models, highlighting its disease relevance. Again, genetic manipulation of IDE, by knockout or overexpression, increases or decreases Aβ load in AD transgenic mice, respectively (Ries and Sastre, 2016).

Matrix metalloproteinases (MMPs) are another class of proteases involved in Aβ degradation. Many MMPs are secreted, and MMP2 and MMP9 are two well studied members, which can digest both monomeric and fibrillar Aβ (Ries and Sastre, 2016; Yan et al., 2006). They are expressed by reactive astrocytes surrounding amyloid plaques in AD mouse models (Ries and Sastre, 2016). Interestingly, an endogenous inhibitor of MMPs, TIMP metalloproteinase inhibitor (TIMP) is at higher levels in the CSF of neurodegenerative disease patients than healthy controls (Lorenzl et al., 2003), providing a possible mechanism for Aβ accumulation.

Cathepsin B (CTSB) is a lysosomal cysteine protease, which can be secreted by microglia, making it suitable for Aβ degradation both intracellularly within the lysosomal compart and extracellularly (Nalivaeva et al., 2012). As such, enhancing CTSB levels by genetically removing its endogenous inhibitors is beneficial in AD animals (Sun et al., 2008). However, CTSB may also function as an alternative β-secretase to produce Aβ. Consistent with this scenario, CTSB inhibition alleviates disease pathology (Hook et al., 2010). These seemingly conflicting observations might not be contradictory, but could be due to different models and approaches used in the studies, which also highlights the complexity of Aβ regulation by CTSB and others. Despite promising therapeutic potentials for these enzymes, their *in vivo* cell type-specific functions remain elusive. Given that many of these ectoenzymes are expressed, or sometimes predominantly expressed in non-neuronal cells, it is quite possible that the beneficial effects observed are attributed to glial function.

3.3. Glial barrier

Recent advances in imaging technologies have facilitated the discovery of microglial barrier function, particularly in AD. Given that microglia cluster around amyloid plaques, and given that microglia are professional phagocytes, engulfment of Aβ by microglia has been most extensively studied, which yielded some conflicting results (Condello et al., 2018) (also see above). One of the approaches was to use *in vivo* two-photon imaging to monitor microglia and fluorescently labeled Aβ species in AD models over time (Condello et al., 2015). Surprisingly, compact plaques, which were stable during weeks to months imaging period, showed little sign of engulfment by microglia (Condello et al., 2015). Instead, a major function in this context suggests that microglial processes form a physical barrier to compact plaque microregions so that neurotoxic Aβ42 fibrils cannot be incorporated.

As genetic variants of the microglia-specific gene, TREM2, have been reported to strongly increase the odds ratios of late-onset AD (Guerreiro et al., 2013; Jonsson et al., 2013), similar imaging-based investigation was performed in TREM2 mutants (Wang et al., 2016; Yuan et al., 2016). Remarkably, in TREM2 haplodeficiency, microglia no longer clustered around plaques owing to a combination of reduced proliferation, increased cell death and compromised metabolic fitness (Condello et al., 2018). Consistent with loss of the barrier function, super resolution microscopy shows more diffused plaques with greater fibril branching, which is associated with more profound axonal dystrophy (Yuan et al., 2016). This defect is phenocopied by mice lacking DAP12, a known signal transducer of TREM2. Importantly, impairment of the microglial barrier is also observed in the disease-linked TREM2 R47H carriers, suggesting a conserved mechanism for this beneficial role played by microglia in AD.

Another well-established glial barrier is glial scar formed by reactive astrocytes during severe CNS injury or neurodegenerative disease (Sofroniew, 2009). It is commonly accepted that astrocytic reactivity is not a simple “all-or-none” process, but on a graded continuum where scar forming is an extreme (Liddelow and Barres, 2017). Although these astrocytes have long been considered as detrimental to disease recovery, a series of elegant genetic studies recently challenge this century-old dogma by showing that scar-forming astrocytes are beneficial at least in the context of acute injuries (Anderson et al., 2016; Liddelow and Barres, 2017). They not only are permissive to axon regrowth through the scar, but also provide supportive factors to stimulate regeneration, in addition to confining the inflammatory milieu within the lesion cores. The beneficial role of such reactive astrocytes is in line with molecular profiling studies, where astrocytes isolated from ischemia, termed A2, are predicted to be neuroprotective (Liddelow and Barres, 2017; Zamanian et al., 2012). As reactive astrocytes are prevalent in almost all protein aggregation diseases, it is tempting to speculate that similar A2 population may exist in these scenarios, in which they provide certain barrier functions with the benefits of promoting recovery and limiting inflammation.

3.4. Secretion of neurotrophic factors

Under certain conditions, glia cells also release various neurotrophic factors to actively promote recovery in disease. Although the factors that we will discuss below are generally thought to play beneficial roles, and they are expressed by non-neuronal cells, their glia-specific functions are often understudied and, in many cases, unknown.

Brain-derived neurotrophic factor (BDNF) is perhaps the best studied neurotrophic factor, playing numerous developmental and functional roles in the CNS (Lu et al., 2013). Notably, cortical astrocytes express higher levels of BDNF than neurons, and such astrocyte-derived BDNF is functionally relevant in synaptic regulation (de Pins et al., 2019; Zhang et al., 2014). Human glial cells also express BDNF, which is upregulated in PD, leading to increased numbers of BDNF-positive glial cells surrounding dying nigral neurons (Knott et al., 2002). These cells may represent A2 reactive astrocytes identified in ischemia which upregulate BDNF among other trophic factors (Zamanian et al., 2012). Interestingly, astrocytes surrounding amyloid plaques in the APP23 transgenic mice have also been shown to express BDNF, although its functional relevance is unclear (Burbach et al., 2004). In another study,

when BDNF is overexpressed using GFAP promoter in reactive astrocytes of the 5XFAD mice, improvement in behavior as well as functional recovery of synapses is observed, pointing to overall beneficial functions of astrocytic BDNF in disease conditions (de Pins et al., 2019). Consistently, adenovirus-mediated overexpression of BDNF in the striatal astrocytes of R6/2 transgenic mice (modeling HD) delays onset of motor neuron defects, suggesting the broad applicability of using glia-producing BDNF to treat degenerative disease (Arregui et al., 2011).

Glial cell line-derived neutrophic factor (GDNF), which was intially isolated from cultured cell lines, is one of the most potent neurotrophins that promote dopamine neuron survival, differentiation and function (Lin et al., 1993). When exogenously applied, GDNF brings promising therapeutic outcomes by delaying or rescuing disease pathology in various PD animal models (Poyhonen et al., 2019). *In vitro* studies suggest that unidentified neuronal signals triggerd by chemical injuries seem to be able to induce GDNF expression in astrocytes (Saavedra et al., 2006). In addition, cultured midbrain astrocytes may release GDNF, which appears anti-inflammatory to activated microglia. A major caveat of these studies is that astrocytes and microglia cultured with serum may be activated and not represent their endogenous states. Therefore, despite the strong neuroprotective effects, which have mainly been demonstrated *in vitro*, presence and function of GDNF under physiological conditions are still poorly understood.

Insulin-like growth factor 1 (IGF-1), besides its well-known metabolic functions in the periphry, is generally thought to be neuroprotective for its ability to modulate neuronal survival, metabolism, and plasticity in the CNS (Bassil et al., 2014; Labandeira-Garcia et al., 2017; Yang et al., 2018). IGF-1 is expressed by neurons and microglia, in which microglia-derived IGF-1 is crutial for layer V cortical neuron survival and CNS myelination during postnatal development (Li and Barres, 2018; Ueno et al., 2013; Wlodarczyk et al., 2017). Impairment of insulin signaling, as well as lower serum IGF-1, correlates with AD and PD dementias, which leads to many preclinial and clinical studies evaluating the efficacy of available anti-diabetic drugs to treat neurodegenerative diseases (Westwood et al., 2014; Yang et al., 2018). The results have been controversial: some suggest that IGF-1 is capable of Aβ clearance in AD models possibly by increased carrier proteins (Gasparini and Xu, 2003), but others report lack of such effects (Lanz et al., 2008). Interestingly, recent single-cell RNA sequencing study reveals a common disease-associated microglia subset, which highly upregulates IGF-1 (Keren-Shaul et al., 2017; Krasemann et al., 2017; Li et al., 2019). Functional significance of it in this microgilal population remains to be determined.

Vascular endothelial growth factor (VEGF) is a family of neurotrophic factors, which modulate vasculature system in brain and spinal cord, and also directly control multiple aspects of neuronal development and function (Llado et al., 2013). Astrocytes and microglia produce VEGF, which signals to one of its major receptors, VEGFR2, expressed on a variety of neuronal and glial cells (Llado et al., 2013). VEGF signaling has been extensively explored in the context of ALS, following the observation that mutant mice with lower VEGF expression develop ALS-like motor neuron degeneration (Oosthuyse et al., 2001). Moreover, the VEGF mutation exacerbates disease outcomes in SOD1G93A mice (Lambrechts et al., 2003). Consistent with its pathogenic role, certain haplotypes causing lower VEGF expression in human increase ALS susceptibility in males, and both VEGF and VEGFR2 are downregulated in the motor neurons of ALS patients (Brockington et al., 2006; Lambrechts et al., 2009). On the other hand, increasing VEGF signaling, either by genetically overexpressing VEGF (or its receptor) in neurons or by intracerebroventricular injection of recombinant VEGF, attenuates ALS disease pathology in animal models (Storkebaum et al., 2005; Wang et al., 2007). Mechanistically, the PI3K/Akt pathway downstream of VEGFR2 activation seems to antagonize the excitotoxicity effect, a common reason for neuronal death in ALS (Llado et al., 2013). Future work should address glial cell type-specific roles of these neurotrophic factors in different protein aggregation diseases.

4. Patient-derived glia and their functions in protein aggregation

Animal models, especially rodents carrying human disease mutations, allow functional manipulation of the systems and have tremendously contributed to our understanding of protein aggregation disease mechanisms. This is largely due to relatively close relationship in evolution between rodents and humans, which share cellular and structural similarities in their nervous systems. Despite significant conceptual advances being made and promising results from preclinical animal studies, the sober reality is that numerous clinical trials failed to prove efficacy in treating these devastating diseases (Dawson et al., 2018). Caveats of using animal disease models have been increasingly acknowledged, which are particularly relevant when considering glial contributions to disease pathology, because: (1) there are important morphological, gene expression and perhaps functional differences between rodent and human glial cells (Gosselin et al., 2017; Zhang et al., 2016); (2) some key disease risk genes have poor sequence conservation among orthologues of different species (*e.g.* only about 50% identity for TREM2, a microglia-specific gene involved in AD) (Penney et al., 2020); (3) disease-related mutant animals often show very weak or no phenotypes and therefore overexpression of mutant genes, a non-physiological condition, is commonly used; (4) a vast majority of disease cases are sporadic with unknown genetic links, which cannot be easily modeled in animals. On the other hand, human cells, especially those generated from patient-derived induced pluripotent stem cells (iPSCs), can circumvent certain limitations and have provided important new insights into the pathological roles of glia in protein aggregation.

In previous studies, human astrocytes have been a major focus in modeling non-cell-autonomous effects of glial cells on neuronal dysfunction. To study astrocyte-specific contribution to PD, di Domenico et al. generated iPSC-derived astrocytes and neurons from familial PD patients carrying mutant LRRK2 or healthy controls, and performed co-culture experiments (di Domenico et al., 2019; Simmnacher et al., 2019). Remarkably, disease astrocytes cultured with healthy neurons led to neuronal accumulation of astrocyte-derived α-syn and neuronal cell death, while healthy astrocytes cultured with disease neurons partially rescued the neuronal defects. Impairment of chaperon-mediated autophagy in astrocytes seems to underlie the pathological role of PD astrocytes and neurodegeneration.

Similar non-cell-autonomous neurotoxicity by astrocytes has also been observed in ALS (Ferraiuolo, 2014). Consistent with animal studies in which mouse astrocytes harboring SOD1 mutations can kill neurons, human astrocytes derived from post-mortem spinal cord neural progenitor cells, which were harvested from familial (SOD1) or sporadic ALS patients, demonstrated toxicity towards motor neurons (Haidet-Phillips et al., 2011; Nagai et al., 2007). This observation is further supported by other co-culture studies using different strategies to produce ALS astrocytes, such as primary human astrocytes, direct lineage conversion from fibroblasts, or iPSC-derived astrocytes (Birger et al., 2019; Meyer et al., 2014; Re et al., 2014). These studies expand the neurotoxicity effect of astrocytes to other familial cases of ALS, such as C9orf72 mutants, and link neuroinflammation, oxidative stress and necroptosis to the mechanisms of neurodegeneration. However, inconsistent results have also been reported. In one study, iPSC-derived C9orf72 astrocytes lacked toxicity to neurons despite their negative impacts on neuronal physiology (Zhao et al., 2020). Similarly, in another study, iPSC-derived TDP-43 astrocytes displayed clear pathology in protein aggregation but did not affect motor neuron survival (Serio et al., 2013). These discrepancies may be due to differences in cell derivation methods, culturing conditions, and/or genetic backgrounds of patients.

In terms of AD, iPSC-derived astrocytes with familial AD mutations in PSEN1 show severe defects, including increased Aβ production,

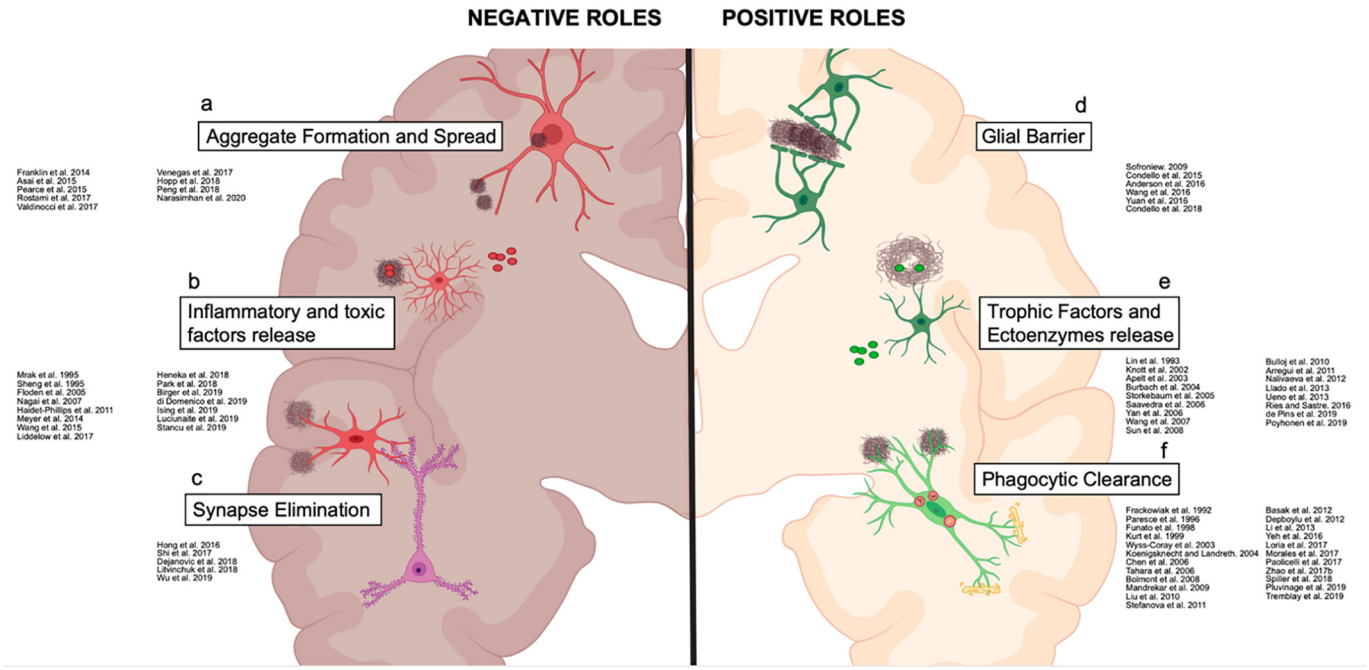

Fig. 1. Glial roles in protein aggregation diseases. Detrimental glial functions in relation to aggregates are depicted on the left, and beneficial functions on the right. (a) formation and spread of prion-like aggregates by glial cells glial; (b) release of proinflammatory/toxic factors and Aβ cross-seeding of inflammasome-mediated ASC specks by activated microglia; (c) aberrant phagocytosis of synapses by Aβ or phosphorylated tau triggered microglia; (d) glial barrier formation around extracellular aggregates or CNS lesions; (e) release of neurotrophic factors and ectoenzymes to degrade extracellular plaques; (f) phagocytic clearance of extracellular aggregates and cellular debris.

altered cytokine profiles and dysregulated metabolism, which compromise their normal supportive functions to neurons (Oksanen et al., 2017). Such astrocyte-specific pathology has also been illustrated in sporadic AD, in which astrocytes generated from human iPSCs carrying homozygous APOE4, compared to APOE3, manifest reduced levels of lipidation in lipoprotein particles, as well as less effectiveness in promoting neuronal survival and synaptogenesis (Zhao et al., 2017a). A recent study has further dissected the detrimental effects of APOE4 in various cell types, including iPSC-derived neurons, astrocytes and microglia-like cells, which all showed drastic changes in gene expression compared with those generated from isogenic APOE3 cells (Lin et al., 2018). These gene expression changes in APOE4 were accompanied by functional alterations for each cell type, with neurons showing increased synapses number and Aβ secretion, while astrocytes and microglia-like cells showing reduced Aβ uptake. Notably, microglial cells have recently attracted intense research interest, partly because many immune genes, including some microglia-specific ones, have been associated with late-onset AD (Kunkle et al., 2019). In light of these findings, a number of iPSC-based methods have been developed to generate human microglia, which will expedite efforts to pinpoint microglial dysfunctions underlying sporadic AD, although cautions should be taken due to challenges in maintaining endogenous microglial gene expression under *in vitro* conditions (Abud et al., 2017; Haenseler and Rajendran, 2019; Li and Barres, 2018).

A new frontier using patient-derived cells to model human disease involves the incorporation of multiple neural cell types in a complex 3D system, with the benefits of capturing cell-cell interactions as an important part of disease pathology. For example, Park et al. developed a triculture system comprising neural progenitor cell- or iPSC-derived neurons and astrocytes, along with immortalized microglial cells to model AD (Park et al., 2018). This system recapitulated all key features of AD, such as amyloid plaques, neurofibrillary tangles, neuroinflammation and neurodegeneration, providing a platform to dissect cell type-specific functions and neural-glial interactions in the future. It should be noted that such technology is still at its infancy and has its own limitations. For instance, even though it is possible now to incorporate more mature astrocytes and myelinating oligodendrocytes in iPSC-derived 3D organoids, human glial cells take years or decades to reach adult levels of maturity (Marton et al., 2019; Sloan et al., 2017). In addition, aging is the strongest risk factor for many protein aggregation diseases, yet reprogramming eliminates age-related epigenetic marks that may be essential for understanding disease mechanisms (Penney et al., 2020). Finally, as endothelial cells and systemic factors also greatly contribute to disease pathology (Pluvinage and Wyss-Coray, 2020), more faithful reconstruction of human brain with these critical players will be needed in the future. These modern technological advances will undoubtedly open many exciting opportunities to reveal new roles glial cells play in these diseases and novel targets for therapies.

5. Conclusions

It is increasingly recognized that glial functions are a “double-edged sword” in neurodegenerative disease. In this review we have described their opposing effects in protein aggregation diseases, by providing examples to show that on one hand, glia can themselves drive prion-like protein spread and that they are the main drivers of aggregate-induced neuroinflammation, while on the other hand, glia are the main defense mechanism against aggregates through phagocytic engulfment, forming a protective barrier in the CNS to restrict the damage, and secreting neuroprotective factors (Fig. 1). One emerging theme is the importance of precise regulation of phagocytosis by microglia and astrocytes in the presence of aggregates. In some cases, phagocytic glia maintain homeostasis by clearing extracellular aggregates, cellular debris, and apoptotic cells. In other contexts, phagocytic glia may destroy neural networks and drive neurodegenerative disease by excessively phagocytosing synapses or even live neurons. Therapeutic interventions that modulate phagocytic mediators, such as C1q or C3, may prove beneficial. An exciting new area of glial research regarding their protective functions is the insulation barriers formed by gliosis, which could be

amenable to therapeutic intervention for instance by modulating the immune receptor TREM2 in microglia, or STAT3 signaling in astrocytes (Anderson et al., 2016). Future research into the cell type-specific mechanisms for these different yet interconnected modes of actions along disease progression, may provide molecular handles allowing to tip the balance in glia towards protective states as opposed to the more damaging inflammatory states commonly observed in protein aggregation diseases.

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