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Glia in neurodegeneration: drivers of disease or along for the ride?

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Abstract

While much of the research on neurodegenerative diseases has focused on neurons, non-neuronal cells are also affected. The extent to which glia and other non-neuronal cells are causally involved in disease pathogenesis versus more passively responding to disease is an area of active research. This is complicated by the fact that there is rarely one known cause of neurodegenerative diseases; rather, these disorders likely involve feedback loops that perpetuate dysfunction. Here, we will review genetic as well as experimental evidence that suggest that non-neuronal cells are at least partially driving disease pathogenesis in numerous neurodegenerative disorders, including Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, and Parkinson's disease.

Keywords

Glia; astrocytes; microglia; oligodendrocytes; oligodendrocyte precursor cells; neurodegeneration

Introduction

Neurodegenerative diseases have traditionally been defined as diseases in which particular populations of neurons degenerate, leading to specific symptoms in patients depending on the population affected (Przedborski et al., 2003). It is not surprising, therefore, that historically, much of the research on these disorders focused on those particular neuronal populations. However, while neurons may degenerate in those brain regions,

it is by no means clear that the degeneration is cell-autonomous (Lobsiger and Cleveland, 2007).

Glial cells – astrocytes, oligodendrocyte precursor cells, oligodendrocytes, and microglia – are present throughout the brain, in high numbers. These cells are present in areas of neurodegeneration, and frequently show phenotypic changes in disease states. While not traditionally considered glia, endothelial cells and pericytes are found throughout the brain as well as the rest of the body; in the CNS, these cells gain specific characteristics, most obviously around the formation and maintenance of the blood-brain barrier or blood-spinal cord barrier (Daneman et al., 2010a; 2010b). As critical components of the neurovascular unit, they interact with neurons and glial cells and have been implicated in some aspects of neurodegeneration as well; therefore, we will include these other non-neuronal populations in the CNS in this review of glial involvement in neurodegeneration.

Glial cells, particularly astrocytes and microglia, are typically (and somewhat opaquely) defined as "reactive" or "activated" in disease states, and are highly sensitive to perturbations of the brain. Markers of reactive astrocytes (Ben Haim et al., 2015) or activated microglia (Lull and Block, 2010; Sarlus and Heneka, 2017) are robust biomarkers for many neurodegenerative disease states. However, this terminology, in addition to being fairly imprecise, specifically implies that the altered state of these cells is downstream of some causal change elsewhere.

Most neurodegenerative disorders are unlikely to have one discrete cause; these complex conditions likely contain multiple feedback loops that can perpetuate dysfunction or attempt repair, such as the cyclical nature of relapse and remission in multiple sclerosis (MS) (Dendrou et al., 2015) or positive feedback loops involving amyloid β and reactive oxygen species in Alzheimer's disease (AD) (Doig, 2019; Nortley et al., 2019). Therefore, identifying any one particular cell type as causal in disease is a difficult proposition. Still, recent technological advances have increased our ability to dissect the relative contributions of distinct cell populations in the disease process, through both genetic analysis and experimental manipulations. Here, we will discuss recent evidence from large-scale genomic screens and systems-biology transcriptomic studies as well as multiple experimental approaches that address the question of the fundamental role of glia in neurodegenerative disease: are these cells drivers of the disease process or passengers along for the ride?

Genetic evidence of glia as drivers of neurodegenerative disorders

Genomic data

Some forms of neurodegeneration have been associated with mutations in one particular gene. Huntington's disease is almost always caused by expansions of a CAG trinucleotide repeat in the gene huntingtin (The Huntington's Disease Collaborative Research Group, 1993), and familial, rather than sporadic, forms of AD, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD) have all been identified (Pihlstrom et al., 2017), in which a particular gene is mutated and causes disease.

Still, most neurodegenerative disorders are not caused by a single gene; rather, they arise sporadically within the population. As genomic sequencing gets faster and more affordable, it has become possible to identify rare gene variants that impact the risk of developing a particular neurodegenerative disease using genome-wide associate studies (GWAS) (for a recent review, see Pihlstrom et al., 2017). Similarly, rare but highly penetrant monogenic forms of disease may be identified through whole exome or whole genome sequencing. Discovering the expression patterns and function of these genes has become a priority in many areas of neurodegenerative disease research, with the goal of identifying causal mechanisms of disease and potential intervention strategies.

In the cases of Mendelian inheritance of neurodegenerative disease, identifying the gene in question has largely not implicated one particular cell type or brain region (although an exhaustive discussion of the cellular localization of all genes associated with familial neurodegeneration is beyond the scope of this review). Huntingtin (HTT) is widely expressed (Sari, 2011). Amyloid precursor protein (APP), mutations in which can cause familial AD, exists in multiple isoforms which may have some cell-type specificity (Rohan de Silva et al., 1997); presenilins 1 and 2 (PSEN1 and PSEN2), also mutated in some cases of familial AD, are found in both neurons and glia (M. K. Lee et al., 1996). Familial PD has been linked to a number of genes, none of which appear to be specifically enriched in glia (Gasser, 2011); this is also the case for ALS (Taylor et al., 2016). One exception to this pattern may be found in MS. While monogenic, highly penetrant genes causing MS have been more elusive, a recent report (Maver et al., 2017) suggests that *NRLP1*, a gene predominantly found in microglia and endothelial cells (Zhang et al., 2014; 2016), may provide a genetic basis for disease.

In contrast, several of the genes associated with increased risk of developing neurodegenerative disease are predominantly glial genes, particularly in the case of AD. *APOE* was identified as a risk factor gene for AD prior to the modern sequencing era (Corder et al., 1993); one copy of the E4 isoform increases the risk of AD two- to three-fold, while two copies increases risk twelve-fold (Pihlstrom et al., 2017). APOE is predominantly, though not exclusively, expressed in astrocytes in the healthy brain (Xu, 2006). GWAS analyses have identified a number of additional risk factor genes in AD

which, while not conferring the same degree of risk as *APOE*, are still associated with disease. Many of these genes are primarily expressed in non-neuronal cells, including *CLU* and *FERMT2* (astrocytes); *BIN1* and *NME8* (oligodendrocytes and microglia); and *CASS4, CD33, CR1, CD2AP, HLA-DRA, INPP5D, MS4A6A*, and *TREM2* (microglia) (Figure 1, adapted from Zhang et al., 2016) (reviewed in Verheijen and Sleegers, 2018). *TREM2*, in particular, has been the focus of much attention, as *TREM2* variant R47H is associated with a three-fold increase in AD risk (Guerreiro et al., 2013; Jonsson et al., 2013). Given that astrocytes and microglia are specifically enriched for two genes conferring dramatically increased risk of AD, *APOE* and *TREM2*, it is reasonable to suggest that these cells may play important roles in the development of AD.

GWAS studies have also implicated microglia in the development of MS. A recent GWAS study identified 200 variants associated with MS (International Multiple Sclerosis Genetics Consortium*†, 2019); while these largely represent peripheral immune processes, MS genes were also enriched in human microglia but not astrocytes or neurons. From this, the authors come to the intriguing conclusion that, while MS may originate as an autoimmune response in the periphery, microglia may play a role in the brain-specific targeting characteristic of MS. This would place microglia in a downstream, but still critical, role in MS development.

Transcriptomic data

An important caveat to the genomic studies discussed above is that regulation of many genes is altered in response to disease: while a particular cell type in a healthy brain may not express a particular gene or express it only in low levels, in a disease context that gene may well be upregulated. This complicates the interpretation of a risk factor gene having an effect due to expression in a specific cell population. For example, APOE, while predominantly expressed in astrocytes, can be upregulated in microglia (Keren-Shaul et al., 2017) and neurons (Xu, 2006) under pathologic conditions. Therefore, identifying which cell populations may be mechanistically involved in disease requires additional approaches.

One way to explore risk factor association with a particular cell type or cellular process is by analyzing transcriptomic datasets with a network analysis approach. Network analysis approaches, such as Weighted Gene Correlation Network Analysis (WGCNA), identify patterns of genes that change in a correlated fashion across many samples; genes that change in a correlated pattern are frequently associated with a similar biological function. This is an unbiased way to group genes into biologically relevant modules. By comparing these modules with genes known to be enriched in particular cell types, it can be possible to identify a module as being

associated with a specific cell type. These analyses are not absolute; many modules include genes from different cell types that are involved in similar cellular processes or cell-cell interactions, leading to correlated expression patterns that are not associated with only one cell type. In addition, genes typically associated with one cell type may show altered expression patterns particularly in disease, complicating the interpretation. Nevertheless, WGCNA can be a valuable tool, leveraging the relative ease, affordability, and depth of bulk RNA sequencing. Further, one can then generate testable hypotheses regarding the roles of specific cell types or biological pathways in disease (Kelley et al., 2018).

In a recent particularly compelling use of WGCNA and systems biology to understand underlying mechanisms of neurodegeneration, Swarup et al. used extensive RNAseq datasets and WGCNA to explore the biological pathways that alter in tauopathies, specifically frontotemporal dementia (FTD) and AD (Swarup et al., 2019). By performing RNAseq on tau P301S mutant mice crossed to three distinct background strains, the authors generated strain-independent datasets of region-specific transcriptomic changes in tauopathy, specifically comparing regions that are sensitive to tau-related neurodegeneration with the cerebellum, which is spared. They identified four gene modules that correlated with disease state, two of which were associated with hyperphosphorylated tau. They then tested the robustness of these two modules with other neurodegenerative RNAseq datasets, including four additional AD/FTD models as well as human AD and FTD datasets of affected and unaffected brain regions, and found that the modules were preserved in only the affected samples, suggesting that these gene modules are relevant not only to animal models of tauopathies, but to human patients as well. Intriguingly, these two modules were specifically enriched with genes for astrocytes, microglia, and endothelial cells, or for neurons, suggesting involvement of neurons vs non-neuronal cells in separate and distinct disease processes. The non-neuronal module contained multiple AD risk factor candidate genes (*APOE*, *CLU*, *PICALM*, *C1q*, *TREM2*) and was specifically enriched in inflammatory genes. In contrast, the neuronal module contained several FTD or progressive supranuclear palsy (also a tauopathy) risk factor genes (*SLC32A1*, *NSF*, *ELAVL2*). From this, the authors suggest that genetic risk for the different tauopathies act via distinct mechanisms – glial vs neuronal – but converge on downstream processes, including immune activation. While this is not conclusive evidence of a causal role of glia in the development or progression of AD vs FTD, these extensive bioinformatic findings are intriguing, and can be used to shape future experiments.

WGCNA has also been used in another recent FTD study, to explore how progranulin deficiency, a gene associated with familial FTD, changes transcriptomic profiles during aging in different brain regions in mice (Lui et al., 2016). The authors sequenced cortex, hippocampus, and cerebellum

from mice of five different ages, in wild type, progranulin heterozygotes, and progranulin knockout animals. A module significantly associated with age-related changes in the cortex proved to be associated exclusively with microglial genes, and this and other modules suggested an interaction with innate immunity and lysosomal function. On the strength of these data, Lui et al. further explored the role of microglia in progranulin-deficient animals and discovered that these cells infiltrate and phagocytose inhibitory synapses in the ventral thalamus, leading to circuit dysfunction and behavioral abnormalities. These data not only suggest a critical role for microglia in progranulin deficiency-related neurodegeneration, but also demonstrate the power of bioinformatic tools in directing hypothesis-driven experiments.

Different brain regions are selectively affected by different neurodegenerative disorders, which has reasonably lead to studies comparing the transcriptomes of various regions in both health and disease. Smaller-scale heterogeneity, however, such as differential gene expression specifically in cells surrounding Aβ plaques in AD or lesions in MS, have been more challenging to study at the transcriptomic level. Recent technological advances in single cell sequencing (Macosko et al., 2015) and single cell transcriptomics (Eng et al., 2019; Rodriques et al., 2019) have made it increasingly possible to resolve transcriptomic differences in small populations of cells. For example, a recent study by Mathys et al. transcriptomically profiled over 80,000 single nuclei from the prefrontal cortex of AD patients (Mathys et al., 2019). The authors identified four clusters of astrocytes; interestingly, one cluster showed preferential expression of *CLU*, a risk factor, confirming the finding that *CLU* can be preferentially upregulated in reactive astrocytes and that, in AD, this likely represents a subset of astrocytes. Similarly, Falcão et al. performed single-cell RNAseq of oligodendrocyte lineage cells in a mouse model of MS, combined with validation studies in patient samples (Falcão et al., 2018). Intriguingly, the authors identified a subset of oligo lineage cells that express immunomodulatory genes and appear to take on immune functions as well, suggesting that a specific subpopulation of oligo lineage cells may play a role in disease pathology distinct from the rest of that cellular population. Studies of this sort are increasingly feasible and will dramatically increase our understanding of the transcriptomic landscape of neurologic disease in its full complexity.

Experimental evidence of glia as drivers of neurodegenerative disorders

While there are clearly cases in which genomic or transcriptomic data suggest glial involvement in the development or progression of neurodegenerative disease, these data are largely more suggestive than

conclusive. Further, they do not speak to the mechanisms that may be involved or the ways in which these disease processes may be prevented or reversed. In the cases in which glial involvement in the development or progression of neurodegenerative disease seems clear, are glia gaining a toxic function or losing a protective one? To answer these types of questions, experimental manipulations are necessary, and increasingly possible with recent technical advances. The increasing development of glial-specific Cre lines (Kaiser and Feng, 2019; Srinivasan et al., 2016); more advanced protocols for isolation of specific cell types for downstream applications (Zhang et al., 2016; 2014); protocols for the development of glial induced pluripotent stem cells (iPSCs) (Krencik et al., 2011; S. Wang et al., 2013); the development of cortical organoids or spheroids as model systems for the human brain (Sloan et al., 2017); and more advanced transcriptomic approaches (Macosko et al., 2015; Sanz et al., 2009) have all made it possible to explore the role of glia in neurodegeneration in a more specific and detailed fashion.

One well-established approach to exploring cell type causality in the progression of neurodegeneration is to limit disease-causing mutations to specific cell types. This can take the form of *in vitro* co-cultures of cell types from different transgenic backgrounds: culturing glia from transgenic animals with disease-causing mutations with neurons from wild-type animals, or vice-versa. A similar approach can be used in vivo, relying on floxed disease-causing mutations and cell-type-specific Cre drivers to induce gene expression only in one cell type, or to exclude expression only from one cell type, and evaluate the effect on disease onset or progression. There are caveats to these strategies: they are largely limited to familial forms of disease, although the advent of glial iPSCs has opened up the possibility of using patient iPSC lines to evaluate how sporadic forms of disease may affect a given outcome measure; they are dependent on the efficacy of cell isolation approaches or transgenic specificity, although, as mentioned, both of these have improved in recent years; and going from an initial finding of a cell-type specific role in disease pathogenesis to a mechanistic understanding of that role or a related therapeutic approach is still extremely challenging. Additionally, it has become increasingly clear in recent years that glial heterogeneity is a key feature of both the healthy brain and in disease (Chai et al., 2017; Hammond et al., 2019; Keren-Shaul et al., 2017; Liddelow et al., 2017), and subtype-specific or region-specific manipulation of particular cell types may be necessary to more fully understand the contributions of these cells to disease pathogenesis. Nevertheless, studies manipulating disease-causing mutations in particular cell types and the more mechanistic studies they have led to are quite suggestive as to a primary role for glia in neurodegenerative disease.

Amyotrophic Lateral Sclerosis

The co-culture approach has been used in ALS models to suggest that mutated Cu/Zn superoxide dismutase (SOD1) in astrocytes can drive the death of motor neurons (Di Giorgio et al., 2007; Nagai et al., 2007). Similarly, mouse stem-cell derived motor neurons cultured with astrocytes derived from postmortem neural precursor cells from patients with familial or sporadic ALS died faster than neurons cultured with astrocytes derived from non-ALS patients (Haidet-Phillips et al., 2011). However, a specific secreted toxic factor has not been identified, complicating the interpretation of these results, and indeed may reflect the loss of a homeostatic or protective function in these ALS-model astrocytes. Loss of two different forms of mutant SOD1 from astrocytes using conditional mutant animals showed that astrocytes can play a role in both disease onset and progression, depending on the mutation involved (L. Wang et al., 2010; Yamanaka et al., 2008), further suggesting a critical role for astrocytes in ALS, although it should be noted that these studies both used constitutive GFAP-Cre transgenic mice to delete mutant SOD1 from astrocytes, which also affects adult neural stem cells and some neuronal populations.

A number of mechanisms by which astrocytes may influence neuronal death in ALS have been proposed, as either gain of a toxic function, such as release of a toxic factor, or loss of a protective function. One potential gain-of-function mechanism suggests that SOD1 mutant astrocytes induce a decrease in major histocompatibility class I (MHCI) molecules on motor neurons, and that this leads to neuronal death, although how astrocytes induce this downregulation and how the loss of MHCI leads to neuronal death are still unclear (S. Song et al., 2016). Among the most prominent loss-of-function hypotheses is that decreased astrocytic buffering of glutamate through loss of the transporter Glt1 can lead to excitotoxicity (Howland et al., 2002). An intriguing potential loss-of-function mechanism suggests that mutant SOD1 prevents astrocytes from inducing expression of the calcium-impermeable AMPA receptor subunit GluA2, leading to increased calcium entry through calcium-permeable AMPA receptors and therefore excitotoxicity (van Damme et al., 2007). This finding is particularly suggestive in light of recent results identifying a protein, Chordin-like 1, that is secreted from astrocytes and induces GluA2 expression (Blanco-Suarez et al., 2018), although it is unknown if this particular mechanism is affected in ALS.

Although a single unifying mechanism underlying a potential primary role of astrocytes in ALS onset or progression has not been identified, these studies support a role for astrocytes in non-cell-autonomous loss of motor neurons in ALS, which has led to interest in astrocyte transplantation as a therapeutic strategy. Injection of rodent glial-restricted progenitor cells into the spinal cord of SOD1-mutant rats extended survival and slowed motor neuron loss (Lepore et al., 2008), although similar approaches with human-derived glial progenitors have been less successful (Hefferan et al., 2012; Lepore et al.,

2011). Modified approaches to astrocyte transplant, such as a wider delivery approach (Izrael et al., 2018) or injection of an astrocyte line specifically modified to deliver growth factors (Thomsen et al., 2018) have shown more benefit, and clinical trials with astrocyte transplant in ALS patients have begun (Glass et al., 2016).

Astrocytes are not the only glial cells strongly implicated in ALS pathogenesis. Deleting mutant SOD1 in myeloid lineage cells, including microglia, increased animal survival, largely due to slowed disease progression (Boillee et al., 2006). Transplanting mutant SOD1 microglia into a mouse lacking microglia as well as several other immune cell types did not induce motor neuron degeneration, but transplanting wild-type microglia into SOD1 mutant mice lacking microglia extended survival (Beers et al., 2006). While these early studies are suggestive of a role of microglia in disease progression, it is important to note that neither rule out a critical role of peripheral macrophages rather than CNS-resident microglia.

Most studies of cell type-specific roles in ALS have used SOD1 mutations, which are found in a small number of ALS patients. Expansions in *C9orf72* are the most common cause of ALS and FTD, and cause decreased expression of the gene. Knockout in mice induces a dramatic pro-inflammatory profile in myeloid lineage cells, including microglia (O'Rourke et al., 2016). Although glial-specific *C9orf72* expansion mice have not yet been reported and a causal role of glia in *C9orf72* expansion-mediated disease is still an open question, multiple links between C9orf72 and astrocytes and microglia have been reported (see Rostalski et al., 2019 for a recent review).

TDP-43 is a protein that is found in cytoplasmic aggregates in the vast majority of ALS patients; this can be modeled in transgenic mice, in which the formation of aggregates of the human TDP-43 protein is controlled by doxycycline administration. Surprisingly, inducing the formation of TDP-43 aggregates in neurons, even to the point of motor neuron loss, produced only minimal microglial activation; in contrast, suppressing further aggregate formation after allowing them to form for some time induced dramatic microglial proliferation, from CNS-resident microglial populations rather than peripheral infiltration (Spiller et al., 2018). Further, this proliferation is necessary for animal recovery from motor phenotypes induced by TDP-43 aggregate accumulation in neurons. While this study does not speak to a causal role of microglia in ALS – TDP-43 aggregation was limited by design to neurons – it suggests that, in sporadic ALS, CNS-resident microglia specifically may act to promote recovery if inclusion formation is sporadic. Intriguingly, the authors found little evidence for activated microglia in the ventral horn of the spinal cord based on Iba1 staining in cases of sporadic ALS or patients with a *C9orf72* expansion, although in SOD1 mutation patients, microgliosis was pronounced. Others have found activated

microglia in both sporadic ALS as well as *C9orf72* cases, but only overt LAMP1 lysosome accumulations in *C9orf72* (O'Rourke et al., 2016), collectively reinforcing the idea that patients with familial mutations may have very different disease features from sporadic cases.

Additionally, there is some evidence for a critical role of oligodendrocytes in ALS. Oligodendrocytes provide metabolic support of axons through a lactate transporter, which is reduced in both animals models of ALS as well as in patients (Y. Lee et al., 2012). In a SOD1 mouse model of ALS, oligodendrocytes degenerate with disease progression, and OPCs proliferate but do not fully differentiate into mature oligodendrocytes. Deletion of the SOD1 mutation from OPCs within the first month of life using an inducible NG2-CreERT2 mouse line delayed onset of disease, suggesting that oligo lineage cells play a part in the development of ALS, although there was no change in survival time after disease onset, indicating they may not have a role in disease progression (Kang et al., 2013).

Alzheimer's disease

There is compelling evidence that multiple non-neuronal cellular populations are involved in the pathogenesis of AD. Vascular dysregulation may be the earliest AD biomarker (Iturria-Medina et al., 2016), and a breakdown of the blood-brain barrier (BBB) has been proposed as the first step in AD pathogenesis (Sweeney et al., 2018). Vascular lesions are found along with the classic AD signs of amyloid plaques or neurofibrillary tangles in up to half of dementia cases; although distinguishing AD from vascular dementia can be complicated (see review in Iadecola, 2013), it is becoming increasingly clear that vascular pathology is a common and early symptom in AD.

The blood-brain barrier and blood flow regulation in the brain, while still not fully understood, are influenced by multiple cell types, including endothelial cells, pericytes, astrocytes, microglia, and neurons (Chen et al., 2014; McConnell et al., 2017; Thurgur and Pinteaux, 2019). How these cells independently or collectively contribute to vascular pathology and BBB leak in AD is an area of active investigation, but several key elements have emerged. A recent study found that amyloid-β peptides (Aβ) may act in part by increasing reactive oxygen species generation in pericytes, which in turn contract capillaries and decrease blood flow in both animal models of AD and in patients (Nortley et al., 2019). Decreased blood flow, in turn, may lead to synapse and neuronal loss. Pericytes have also been reported to degenerate in AD (Sengillo et al., 2013), leading to BBB breakdown. BBB breakdown in AD may act through several mechanisms to influence AD pathogenesis, including deposition of proteins from the plasma into the brain, in particular fibrinogen and its cleavage product, fibrin. Fibrin can then activate microglia, triggering a neuroinflammatory cascade (Petersen et al., 2018).

BBB breakdown may also affect Aβ clearance. Failed Aβ clearance from the brain has emerged as a prominent hypothesis in the pathogenesis of AD (Tarasoff-Conway et al., 2015), and multiple glial cells are implicated in this process. As discussed above, APOE4 dramatically increases the risk of developing AD. The mechanisms by which APOE isoforms alter AD pathology are complex, and a comprehensive discussion of these mechanisms is outside of the scope of this review (for a recent review of the interactions of glia with APOE, see Fernandez et al., 2019), but one function of APOE appears to be clearance of Aβ from the brain. By culturing wildtype or APOE null astrocytes on top of mouse brain sections from animals overexpressing human amyloid precursor protein, (Koistinaho et al., 2004) found that APOE was required for astrocytic uptake of Aβ. Indeed, Aβ clearance from the brain has been linked to uptake by astrocytes and microglia, as well as by transport across the BBB and other mechanisms, many of which involve glial cells (see recent review by Ries and Sastre, 2016). Pericytes can also play a role in Aβ clearance in a APOE-allele dependent fashion (Ma et al., 2018).

A recent study explored the question of interactions between APOE allele and tauopathy, crossing the tau P301S mouse with different human APOE knockin lines for alleles that modify AD risk (2, 3, and 4) or APOE knockout (Shi et al., 2017). APOE2 confers some protection against AD risk; APOE3 is the most common allele; APOE4 increases risk. P301S/APOE4 mice showed the greatest degree of brain atrophy, microglial activation, and reactive astrocytosis, while the P301S/APOE knockout animals showed the least, on par with wildtype animals. The authors co-cultured mixed glial cultures from the three APOE allele mice or APOE knockout animals with P301S tau neurons. Knockout APOE glial cultures maintained the highest levels of neuronal survival, while APOE4 glial cultures had the highest neuronal death, coinciding with transcriptomic data suggesting that astrocytes in these animals may take on a form of reactivity that includes neurotoxicity (A1-type astrocytes; Liddelow et al., 2017), although the data are also consistent with loss of a protective function of normal astrocytes rather than gain of a toxic function. These data suggest that one way APOE4 may impact AD pathogenesis is through astrocyte-induced loss of neurons.

Microglial phenotype in AD may also be regulated by AD risk factor genes, with higher APOE expression in microglia found closely associated with Aβ plaques in both an animal model of AD as well as human samples (Krasemann et al., 2017). These cells express a number of pro-inflammatory genes; intriguingly, loss of the risk factor gene TREM2 prevented the development of this microglial phenotype. While the mechanisms by which TREM2 variants impact AD risk are still being elucidated, TREM2 appears to at least partially regulate the ability of microglia to take on a disease-related phenotype (Keren-Shaul et al., 2017; Krasemann et al., 2017). Indeed, a loss-of-function TREM2 variant that increases disease risk, R47H, decreases

microglial clustering around plaques in both patients (Yuan et al., 2016) and AD model mice expressing the humanized TREM2 variant (W. M. Song et al., 2018). (See (Zhou et al., 2018) for a more thorough discussion of TREM2 in microglia.) Together, these results suggest that the two most common risk factor genes for AD, APOE and TREM2, both impact microglial clustering around plaques.

How this disease-associated microglial phenotype relates to AD pathogenesis, though, is still largely an open question. Microglia clustering around Aβ plaques has been proposed to act to protect neurons in the vicinity (Zhou et al., 2018), and indeed, the fact that loss of microglial clustering in TREM2 deficiency increases AD risk supports the idea that microglia can act to decrease AD pathogenesis. However, microglia can preemptively phagocytose synapses in response to soluble Aβ (Hong et al., 2016), and depletion of microglia in an AD model prevents dendritic spine loss and neuronal loss (Spangenberg et al., 2016), suggesting a possible pathogenic role for these cells as well. Further complicating the matter is the question of microglial heterogeneity in disease, with recent work suggesting the presence of a subpopulation of disease-associated microglia in AD (Keren-Shaul et al., 2017). Distinct glial subpopulations may have different roles in disease pathogenesis, but further work will be needed to dissect out these features.

While genetic factors modify the risk of neurodegenerative disease, age is the primary risk factor. Intriguingly, a recent study (Bussian et al., 2018) using a neuronal tauopathy mouse model suggests that senescent astrocytes and microglia specifically accumulate during disease progression and cause neuronal degeneration. Using a transgenic strategy that eliminates these cells as they become senescent, the authors could prevent the formation of neurofibrillary tangles, neuronal loss, and cognitive decline, suggesting that senescent microglia and astrocytes are heavily involved in the development of neurodegeneration. How senescent state aligns with other disease-related features of microglia or astrocytes is still an open question, and reinforces the idea that different populations of these cells may have distinct roles in disease pathogenesis.

Huntington's disease

Interestingly, symptom onset in HD patients is not associated with classical signs of astrocyte reactivity, nor is there evidence of the more recently described A1-type neuroinflammation-related astrocyte reactivity (Diaz-Castro et al., 2019; Tong et al., 2014). However, less obvious alterations in astrocytes have been associated with HD progression. Astrocyte-specific overexpression of mutant huntingtin (mHTT) can recapitulate some features of HD, although combining both astrocytic and neuronal mHTT expression

produces more extreme phenotypes (Bradford et al., 2010), suggesting that astrocytes may play an important role in HD but are not the sole drivers of disease. Astrocytic impact on HD pathogenesis may relate to altered neuronal excitability, through mHTT-mediated decreases in astrocytic glutamate transporters (Faideau et al., 2010) and decreased astrocytic expression of the inwardly rectifying potassium channel Kir4.1 (Tong et al., 2014). (See Khakh et al., 2017 for a recent review.) Indeed, selectively removing mTT from astrocytes improves behavioral phenotypes in a mouse model of HD; this manipulation normalizes evoked NMDA currents in medium spiny neurons as well, again suggesting a link between astrocytic mHTT expression and neuronal excitability (Wood et al., 2019).

To ask how human glial cells may impact HD disease pathogenesis, Benraiss et al. took the intriguing approach of making chimeric mice, transplanting human glial progenitor cells expressing mHTT (either patient-derived or overexpressing a viral mHTT construct) or normal HTT into the striatum of immunodeficient neonatal mice (Benraiss et al., 2016). Animals receiving mHTT cells showed impaired motor coordination and hyperexcitable medium spiny neurons in the striatum. Conversely, transplanting wildtype human glial progenitor cells into a mouse model of HD rescued some of the phenotypes of HD, including improved motor coordination and longer survival times, although these improvements were somewhat subtle, and partially rescued medium spiny neuron electrophysiological properties. The majority of these cells were Olig2+, with a subpopulation of GFAP+ cells, suggesting a role for astrocytes or OPCs in these effects.

Less is known about the role of other glial cell types in HD, although a recent study found mHtt in microglia was neither necessary nor sufficient to induce HD associated phenotypes in a mouse model of the disease (Petkau et al., 2019). Microglia in HD patients and mouse models have been reported to express pro-inflammatory factors (Yang et al., 2017), suggesting that it is possible that microglia may modulate HD pathogenesis through inflammation.

Multiple sclerosis

MS is characterized by focal inflammatory lesions that induce demyelination but largely spare axons. As such, a causal role for non-neuronal cells in MS has long been accepted, as peripheral immune cells are thought to infiltrate the CNS through a disrupted BBB and mount an autoimmune response in the brain (Dendrou et al., 2015). Still, the extent to which CNS resident cells play a role in MS pathogenesis has been more debated. MS, unlike other neurodegenerative disorders, typically involves periods of more acute disease progression followed by periods of partial recovery (relapsing-remitting MS). Therefore, identifying a causal role for glia in MS could refer to

a role in either state: as a driver of disease progression or acting to effect repair.

Microglia have long been thought to play a role in MS onset and progression (for a recent review, see O'Loughlin et al., 2018). It has traditionally been challenging to distinguish a role for CNS-resident microglial as opposed to infiltrating monocyte-derived macrophages in disease, as these cells express many of the same markers. However, new approaches are making it more feasible to distinguish these cells. Yamasaki et al. employed distinct fluorophore labels for these two populations of cells based on CCR2 labeling of peripheral monocytes and CX3CR1 labeling of CNS-resident microglia. This approach led to the intriguing result that peripheral monocyte-derived macrophages initiate demyelination in a mouse model of MS (experimental autoimmune encephalitis, EAE) (Yamasaki et al., 2014). In contrast, others have found that CNS-resident microglia may in fact play a role in active lesions. Using the microglial-specific marker TMEM119 to identify microglia as opposed to macrophages in human tissue, Zrzavy et al. found that roughly 45% of the macrophage-like cells in an active lesion were microglia (Zrzavy et al., 2017), although precisely how reliable TMEM119 is at distinguishing the two cell types in disease states is unknown. Using CX3CR1-Cre mice, Goldmann et al. found that microglial-specific deletion of a proinflammatory cytokine-activated kinase, Tak1, prevented the onset of EAE (Goldmann et al., 2013). It may be possible to more clearly distinguish between the roles of microglia vs macrophages in active MS lesions using newer microglial transgenic strategies (Kaiser and Feng, 2019), which may resolve some of the discrepancies.

Oligodendrocytes are the primary cells lost in MS, but have generally been thought of as innocent victims of inflammatory and autoimmune processes. These cells may play active roles in disease pathogenesis, however. Oligodendrocytes' ability to respond to the cytokine interferon gamma affects EAE severity (Balabanov et al., 2007), and a number of immune genes are upregulated in subpopulations of oligodendrocytes in both EAE and in patient samples (Falcão et al., 2018), suggesting that these cells may take on new immune-related phenotypes in disease.

Oligodendrocyte precursor cells can mature into new oligodendrocytes, and are necessary for remyelination of MS lesions; however, this process fails to keep up with disease progression (Franklin, 2002), suggesting that a failure of OPCs to sufficiently replace lost oligodendrocytes is a critical component of disease pathogenesis, albeit downstream of the demyelination that creates the need. In order to remyelinate active lesions, OPCs must proliferate, migrate, differentiate, and remyelinate (for a recent review, see Miron et al., 2011). It has been proposed that the latter two are the rate-limiting steps, and can be overcome pharmacologically (Mei et al., 2014). OPC differentiation and remyelination may require the presence of reactive

astrocytes, as areas lacking astrocytes do not remyelinate after ethidium bromide-induced demyelination (Talbott et al., 2005), suggesting yet another glial cell type may play a part in MS pathogenesis and repair. In addition, however, in EAE OPCs have recently found to be capable of phagocytosis and activation of T cells (Falcão et al., 2018), suggesting these cells may have a more active role in disease processes beyond remyelination.

Parkinson's disease

While there is relatively little evidence yet suggesting a causal role of astrocytes in PD pathogenesis, astrocytes do express many of the genes implicated in PD, and astrocyte-specific knockout of many of these genes can affect astrocyte physiology (for a recent review, see Booth et al., 2017). Astrocytic expression of a disease-related α-synuclein mutant induced progressive paralysis in mice, associated with reactive astrocytosis, microglial activation, and neuronal degeneration (Gu et al., 2010), although interestingly, there is little evidence for overt astrocyte reactivity in patients with PD (Mirza et al., 2000). Astrocytes (Loria et al., 2017) and microglia (H.-J. Lee et al., 2008) may both act to clear α-synuclein inclusions, and loss of these functions due to PD-associated mutations has been proposed to impact disease progression (Filippini, 2019). Intriguingly, a recent study by Lau et al. suggests that distinct strains, or conformational states, of α-synuclein may target different cell types: while one strain showed accumulation only in neurons, a different strain accumulated in neurons and astrocytes (Lau et al., 2019). The two strains were both capable of inducing neurologic deficits in a synucleinopathy mouse model, but with different time courses and symptoms, suggesting that different conformational states of α-synuclein may affect disease course, potentially through differential effects on astrocytes and neurons.

A recent study suggests that microglia may be the primary site of action of a glucagon-like peptide-1 receptor (GLP1R) agonist, a potential PD neuroprotective agent. In this study, Yun et al. used injection of α-synuclein pre-formed fibrils to model PD. Treatment with a GLP1R agonist starting one month later dramatically mitigated disease, both in terms of tissue outcome measures and behavioral effects (Yun et al., 2018). The authors found that GLP1R expression in the substantia nigra in PD patients or models is primarily microglial, and show *in vitro* that the GLP1R agonist acts on microglia to decrease the production of inflammatory factors, including IL-1α and TNFα, and complement component C1q, three factors that have been reported to trigger a neurotoxic phenotype in neighboring astrocytes (A1; Liddelow et al., 2017). By treating microglial cultures with α-synuclein pre-formed fibrils and then treating astrocyte cultures with media from those experiments, the authors found that the microglial response to α-synuclein fibrils induces a form of astrocyte reactivity that recapitulates some features of A1-type neuroinflammatory reactive astrocytosis. Further, this reactivity is

largely blocked, both *in vitro* and *in vivo*, by GLP1R agonist treatment. These results suggest that microglial reactivity in response to α-synuclein fibrils may act as a driver of PD pathogenesis, upstream of neuroinflammation and astrocyte reactivity, and, excitingly, that this process can be interrupted by GLP1R agonists.

Future directions in understanding glial causality in neurodegeneration

This should not be considered an exhaustive review of all evidence of glial involvement in neurodegenerative disease, but rather a series of vignettes that collectively support the idea that glia can act as drivers of disease pathogenesis. As such, further research is merited into the mechanisms by which glia influence disease and ways in which they might be targeted therapeutically. There are any number of interesting directions that research might go; we suggest several particular facets of glial biology that should be kept in mind along the way.

A common feature across many neurodegenerative diseases is the presence of inflammation; note its appearance as a potential mediator of disease in virtually every section of this review. Inflammation may well have a primary role in many disease processes; certainly in the progression of disease, if not as commonly in disease onset. Does inflammation therefore represent a common mechanism by which glial cells drive neurodegeneration? While microglia are typically considered the resident immune cells in the brain, astrocytes are also actively involved in neuroinflammation (Colombo and Farina, 2016), and OPCs are increasingly recognized as having a neuroimmune role as well (Falcão et al., 2018; Fernández-Castañeda et al., 2019). Identifying ways to evaluate the complex mechanisms of neuroinflammation and integrate them into a framework of understanding disease pathogenesis will improve our understanding of disease causality moving forward.

Further, while much of the work to date has focused on uniform single cell types or the interactions of non-neuronal cells with neurons, different subpopulations of glial cells and glial-glial interactions are likely to play critical roles in many diseases; our understanding of these interactions is in its infancy. There is increasing evidence of glial heterogeneity in healthy tissue (Chai et al., 2017; De Biase et al., 2017; Hammond et al., 2019; Marisca et al., 2020; Molofsky et al., 2014), and how heterogeneity intersects with disease is an area of active investigation. Heterogeneity may arise between brain regions or within a particular brain region; both of these forms of heterogeneity are likely relevant to disease processes. Similarly, glial-glial interactions are increasingly recognized as having critical functions in both

the healthy brain and in disease (for a recent review, see Vainchtein and Molofsky, 2020).

Our understanding of both glial heterogeneity and cell-cell interactions are being dramatically transformed by the recent development of new techniques, particularly single-cell transcriptomics (Macosko et al., 2015) and spatial transcriptomics (Eng et al., 2019; Rodriques et al., 2019). As discussed, single cell transcriptomics have been used to identify subpopulations of astrocytes in human AD samples (Mathys et al., 2019) as well as oligodendrocyte lineage cells that express immunomodulatory genes in a model of MS (Falcão et al., 2018). Similarly, Masuda et al. used single cell RNAseq to explore the response of microglia in both a mouse model of MS and human patients, revealing multiple disease-associated microglial clusters with potentially relevant roles in disease pathology (Masuda et al., 2019). While spatial transcriptomic approaches are at slightly earlier stages in development, they will no doubt dramatically improve our understanding of localized changes in transcriptomic profiles, allowing researchers to specifically assess transcriptomic changes in cells immediately adjacent to relevant tissue landmarks, such as Aβ plaques, MS lesions, or TDP-43 aggregates. Further, spatial approaches will make it possible to begin to query the interactions between different glial populations and assess how those interactions influence disease state. These advances will make it increasingly possible to understand the complexity and variability of glial cell responses in both animal models and patients.

Finally, as progress is made in identifying the drivers of neurodegeneration and developing strategies to slow or stop these processes, these studies may be complemented by work addressing repair and regeneration to potentially reverse damage. We and others have done extensive work to study the mechanisms of regeneration after acute neurologic injuries such as stroke, spinal cord injury, or optic nerve crush. Increasingly, this work has included ways in which non-neuronal cells may be critical in repair processes, showing that peri-infarct angiogenesis promotes neuroblast migration and recovery post-stroke (Ohab et al., 2006); the astrocytic scar acts to promote specific neuronal outgrowth after spinal cord injury (Anderson et al., 2016)
; the lack of myelination in regenerating neurons critically impairs neuronal functionality in optic nerve crush (Bei et al., 2016); and OPC-astrocyte signaling temporally regulates the proliferation and differentiation of OPCs and subsequent myelin repair in white matter stroke (Sozmen et al., 2019), among many other studies. While the extent to which the mechanisms discovered in acute injury models may be applicable to repair in neurodegeneration is unknown, they may provide common pathways to repair worth investigating. A more complete understanding of the roles of glia in both the progression of disease and its potential recovery will be critical to ultimately understanding neurologic disease and identifying therapeutic strategies.

Acknowledgments

Figure 1. Different AD risk factor genes are expressed in all cell types, but show enrichment in glia, particularly astrocytes and microglia. Adapted from Zhang et al., 2016; z-score for individual cell type calculated by subtracting log value of mean expression data from all cell types in Zhang et al. (www.brainrnaseq.org) from individual cell type, divided by standard deviation from all cell types.

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