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Astrocytes: The missing link in neurological disease?

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Abstract

The central nervous system (CNS) is comprised of numerous cell types that work in concert to facilitate proper function and homeostasis. Disruption of these carefully orchestrated networks results in neuronal dysfunction, manifesting itself in a variety of neurological disorders. While neuronal dysregulation is causative of symptoms manifest in the clinic, the etiology of these disorders is often more complex than simply a loss of neurons or intrinsic dysregulation of their function. In the adult brain, astrocytes comprise the most abundant cell type and play key roles in CNS physiology, therefore it stands to reason that dysregulation of normal astrocyte function contributes to the etiology and progression of varied neurological disorders. We review here some neurological disorders associated with an astrocyte factor and discuss how the related astrocyte dysfunction contributes to the etiology and/or progression of these disorders.

Introduction

Our previous paper described the developmental origins of astrocytes and their diverse roles in the maintenance of the proper functioning of the CNS. This review will focus on neurological disorders that are linked to or associated with astrocyte dysfunction. Since neurons do not exist in a vacuum, surrounded by a milieu of different cell populations that subserve their functions, it follows that the root of many neurological disorders may very well be due to defects in these other cell populations. Due to their broad and diverse roles in CNS function, it stands to reason that a dysregulation of normal astrocyte function contributes to the etiology and progression of neurological disorders. Several neurological disorders are now linked with a specified astrocytic component. These include disorders associated with injury-related reactive astrocyte elements, as well as conditions caused by non-injury related disruptions of normal astrocytic function.

White Matter Disorders

White matter damage is often found in the preterm infant brain and is typically associated with epilepsy, cognitive dysfunction and neurosensory impairments. Most white matter diseases are caused by glial cell-induced inflammation or are the result of ischemic insult on glial cells. Oligodendrocyte precusor cells (OPCs) within the periventricular white matter

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are viewed as a key target for therapeutic intervention because of the impact on oligodendrocytes in these disorders and the capacity of precursor cells to stimulate remyelination.

Leukodystrophies

There is increasing evidence that astrocyte-induced inflammation or ischemic insult to astrocytes results in white matter disorders. White matter-related disorders associated with astrocyte dysfunction include X-adrenoleukodystrophy (X-ALD), a type of leukodystrophy resulting from an excessive amount of very long chain fatty acids (VLCFAs) in the brain due to deficits in ABCD1 and ABCD2 gene(1, 2). Sighj et. al. demonstrated that accumulation of VLCFAs in mouse astrocytes led to inflammatory responses which is hypothesized to induce damage on oligodendrocytes and myelin(1). Canavan disease is another example, where mutation in a gene encoding aspartoacylase (ASPA) hinders the ability to metabolize N-acetyl-L-aspartate (NAA). The presence of NAA in white matter extracellular fluid (ECF) results from metabolism of N-acetylaspartylglutamate (NAAG) by astrocytes and the build up of NAA in white matter ECF could result in increased hydrostatic pressure, thus compromising the myelin sheath(3).

Interestingly, while astrocytes have long been considered the “enemy” in white matter injury, recent studies have demonstrated that the presence of astrocytes is required for the proper remyelination of oligodendrocytes(4–6). Whether or not the presence of astrocytes in a lesion is beneficial or detrimental for the remyelination process has become a hot topic of debate. It has been hypothesized that astrocytes are a “double-edged sword” in this context depending on the molecules that they secrete, the type of cells that are being modulated, and the interaction between these cell types(7, 8). This is one area in particular where an understanding of the cellular diversity of astrocytes could help resolve key questions in the field.

Alexander disease

Alexander disease (ALX) was the first astrocytic genetic disorder reported and demonstrates pathological feature of wide spread presence of Rosenthal fibers, megalencephaly, and demyelination(9–13). ALX is a type of leukodystrophy and demyelinating disease in the CNS white matter that is fatal and believed to occur sporadically in children under the age of 10(14). Detailed analysis revealed that the main component of Rosenthal fibers of ALX is glial fibrillary acidic protein (GFAP) often with a missense mutation. GFAP is an astrocyte intermediate filament and transgenic mouse models with an extra copy of the GFAP gene also demonstrates Rosenthal fibers (15), suggesting that the GFAP allele in ALX is behaving as a hypermorph. This raises the question of how increased GFAP activity or function leads to the progression of ALX. It has been suggested that mutation within GFAP increases the stability of the protein, resulting in its accumulation or alterations in its association with other cellular components(14). In addition, it appears that accumulation of GFAP in ALX does not lead to a loss of astrocytes, but rather creates lethal interactions between astrocytes with oligodendrocytes and subsequent demyelination(14).

Cerebral Palsy

Cerebral Palsy (CP) is a collective term for neurological disorders originating in the cerebral white matter, with chronic deficits in motor functions being the most obvious clinical symptoms(16). The onset for CP ranges from infancy to early childhood and is the result of prolonged external insults on immature white matter, though familial cases have been reported(17). Factors that are known to trigger CP include premature birth, infection during pregnancy, lack of blood and/or oxygen supply in developing brain and severe brain injuries(18). Periventricular white matter is especially prone to these risk factors because the

vascular system in this region is not mature enough to compensate for the reduction in cerebral blood pressure resulting from ischemia (19, 20). The ischemic environment in turn induces the death of astrocytes and OPCs, with the demise of astrocytes conspiring to accelerate the death of OPCs due, in part, to inefficient removal of glutamate by astrocytes (20–22). Adding the involvement of astrocytes to the etiology of this disease compounds its complexity and illustrates how intricate and delicate glial interrelationships are during early development. More detailed studies are certainly needed to uncover the exact role of astrocyte in disease progression.

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic demyelinating and inflammatory disease that is caused by the loss of myelin in the CNS. It is a disease that predominantly occurs in adults, with childhood-onset representing 3 to 5% of total patients (23). Compared to the adult-onset MS, the inflammatory response in Pediatric MS appeared to be stronger, with more frequent relapses (24); nevertheless, evidence suggests similar disease mechanisms between adult and pediatric cases. Clinical symptoms in the majority of patients with Pediatric MS includes severe cognitive impairment, depression and fatigue(25). In the development of MS, white matter lesion begins with the breakdown of the blood-brain-barrier (BBB) followed by the infiltration of inflammatory cells, ultimately leading to the destruction of myelin by the immune system (26, 27). As mentioned previously, the role of astrocytes in the disease progression is to induce inflammation and to form glial scars which hinder remyelination (7, 28). On the other hand, it was also reported that within certain microenvironments, astrocytes also contribute to remyelination (4–6, 8). Regardless of how they influence remyelination in MS, astrocytes remain one of the primary drug targets for combating the disease(29).

Neurodegenerative Diseases

Neurodegenerative disease is a generalized term for any disease that has clinical feature of degeneration in neurons. Historically, the search for the cause of these diseases has focused on neurons. Not surprisingly, more and more studies have reported astrocytic components in the progression of these diseases, with much more attention being given to how reactive astrocytes contribute to both repair and degeneration. Here, neurodegenerative diseases with a known astrocytic contribution will be briefly discussed.

Alzheimer’s disease

Alzheimer’s disease (AD) is the most common type of neurodegenerative disease and it is listed in the top ten causes of death in the United States. Clinically, AD is characterized by memory loss, difficulty in planning or solving simple problems, loss of ability in completing familiar tasks, and motor deficits (30). The pathological features of AD on the other hand are the accumulation of neurofibrillary tangles and Amyloid β (Aβ) (31, 32). An overabundance of reactive astrocytes is present in tissue collected from patients in the early stages of AD (characterized by over expression of GFAP). Reactive astrocytes in this context bind to and endocytose neuron-derived Aβ and other proteins (33), resulting in a toxic accumulation of these materials in astrocytes, subsequent cell lysis and formation of astrocyte-derived amyloid plaques which is believed to be crucial in disease progression (31, 33).

Parkinson’s disease

Parkinson’s disease (PD) is the second most common neurodegenerative disease in the United States and it is estimated 1% of the population over 60 years of age are affected. The clinical symptoms of PD are trembling and rigidity of different body parts, slowness of

movement and loss of postural coordination. The exact cause of PD is unknown but the disease is characterized by significant loss of dopaminergic neurons with soma located in the substantia nigra (SN) and nerve terminal innervated to the striatum and the appearance of α-synuclein and Lewy bodies in the cytoplasm of remaining neurons (31, 34, 35). Astrocytes were found to exert a neuroprotective role in PD as evident by their release of glutathione-peroxidase, superoxide dismutases (SODs) and antioxidant enzymes that are known to be crucial for the survival of neurons after brain trauma (36–38). The reduction or the abnormal expression of these enzymes by astrocytes is believed to exacerbate neuronal death in PD progression.

Huntington's disease

Huntington's disease (HD) is the most common familial inherited neurodegenerative disease. HD is generally an adult onset disease with symptoms of chorea, psychiatric disturbance and dementia(39). It is a fatal autosomal dominant disease caused by trinucleotide CAG repeat in the exon 1 of the huntingtin (*Htt*) gene and once the repeats exceed 36, it forms aggregates within neurons which engulfs other proteins and leads to neuronal degeneration(40–43). Astrocytic contribution to HD involves their role in maintaining the proper level of glutamate in the synapse, which is critical in preventing neuronal excitotoxicity. Astrocyte regulation of glutamate up-take and metabolism is mediated by glutamate transporters GLAST or/and GLT-1 and glutamine synthetase (GS) respectively (22). In the HD mouse model, the astrocytic GLT-1 was found to have lower expression level compared to the wild type control which hinders the glutamate uptake function of astrocytes(44). In addition to neurons, astrocytes also express Htt and Shin et. al. demonstrated through neuron-astrocyte co-culture that mutant Htt expressing astrocytes lost their ability to uptake excess glutamate(45).

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is the most prevalent motor neuron degeneration disease which affects about 4 out of every 100,000 people each year(46). It is an adult onset disease characterized by selective and progressive degeneration of motor neurons in the brain stem and spinal cord. The majority of ALS is sporadic, with familial cases representing ~10% of reported cases; nonetheless, all ALS patients demonstrate marked reduction in the expression level of astrocytic glutamate transporter (EAAT2) (31, 47). In addition to the glutamate transporter, the expression of mutant antioxidant enzyme superoxide dismutase 1 (SOD1) by astrocytes was also reported in some patients with familial ALS(46, 48). Moreover, co-culture of motor neurons with astrocytes expressing mutant SOD1 demonstrated low neuronal survival rate(49, 50) and surprisingly, the toxic effect is specific to motor neurons (50).

Autism Spectrum Disorders

Autism spectrum disorders (ASDs) represent a range of developmental disabilities that are characterized by difficulties in social interactions, communication and repetitive behaviors. The cellular and molecular determinants of ASD's are varied and not well defined. Below are examples of those with a defined genetic basis and astrocytic component.

Rett syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder that has an array of clinical symptoms ranging from microcephaly, autism, seizure, autonomic dysfunction and anxiety, which occur at different stages of disease progression(51, 52). It is an X-linked disease and thus more prevalent among young females with age of onset between 6 to 18 months(51). RTT is characterized by mutation of the Methyl-CpG binding protein 2 (MeCP2) (52, 53)

gene, which functions as a transcriptional repressor throughout the CNS, where it is expressed in neurons, astrocytes, and oligodendrocytes (54–56). The first evidence for astrocytic contribution to RTT was demonstrated by a co-culture of astrocytes from *Mecp2*-null mice with wild-type neurons, which resulted in severely impaired neuronal growth and synapse formation(54). Subsequently, it was demonstrated *in vivo* that re-expression of Mecp2 in astrocytes in a *Mecp2*-null background mouse significantly rescued their characteristic Rett syndrome-like phenotypes(57). Consequently, if the same cellular mechanism is found in human RTT patients, developing methods that can manipulate astrocytic Mecp2 expression could represent a new therapeutic approach. Use of iPS-stem cell technology on tissue from RTT patients could help address these and other questions concerning the cellular basis of RTT.

Fragile X

Fragile X syndrome (FXS) is a form of mental retardation caused by the trinucleotide CGG repeat in the 5′-untranslated region of the *FMR1*, which encodes the protein FMRP(58). Children with FXS demonstrate defects at birth and both genders are equally susceptible to the mutation and disease with the incident rate of approximately 1/2500(59). Patients with FXS have abnormalities in both physical appearance (i.e. longer facial structure and large protruding ears) and cognitive function (i.e. attention deficit, anxiety and autism-liked behaviours)(58, 60). FMRP is widely expressed in the brain and its expression in neurons has been suggested to regulate synaptic plasticity(61). Nonetheless, astrocytes from *FMR1*-deficient mice play a crucial role in the maintenance of dendritic morphology and reduction of pre-synaptic and post-synaptic proteins clusters in a co-culture system(62). Based on this, one can speculate that the dendritic abnormality found in FXS patients might be a result of aberrant interactions between neurons and astrocytes during development.

Other Neurological Conditions

Epilepsy

Epilepsy is a seizure syndrome, diagnosed in about 1% of children in the United States who have recurring, unprovoked seizures (63). Seizure occurs upon spontaneous and synchronous firing of neurons. Symptoms vary widely and in the most extreme cases, the severity and abundance of seizures can damage the developing brain (63). The causes of epilepsy are diverse and include brain damage (trauma or prenatal injury), infectious disease, developmental disorders or even genetic mutations (64, 65). While neurons are responsible for the ictal state, increasing evidences points towards a role for astrocytes in epilepsy. Reactive gliosis has been observed in epileptic brains of both humans and animal models, suggesting that changes in the astrocyte constituency may be linked to chronic epileptic episodes (66). Astrocytes also express receptors that allow them to control the extracellular milieu, which can directly influence neuronal activity and physiology(67–69). During seizures, decreased extracellular Ca^{2+} and increased K^{+} are observed at the site of the seizure focus. Astrocytes sense changes in extracellular Ca^{2+} concentration, leading to intracellular Ca^{2+} oscillations and release of glutamate, which is believed to contribute to the generation of seizures (66, 70). In epileptic brains Kir channels are downregulated and aquaporins are dislocated from the membrane, leading to an impaired K^{+} buffering in the milieu (66, 70). Glutamate regulation, specifically performed by astrocytes through glutamate transporters and glutamine synthase (71, 72), has been involved in epileptic seizure. While there are conflicting reports concerning the deregulation of glutamate uptake during an epileptic seizure, most agree that the glutamate recycling is altered in some way (70, 73). Most of our knowledge on epilepsy is based on adult seizures, which does not take into account the fact that childhood epilepsy occurs in an immature brain. While many studies have shown a strong association of astrocytes with the generation of seizures, a

better understanding of astrocyte development might prove essential in better characterizing its exact components in the generation of an epileptic seizure especially in children

Metabolic disorders

Metabolic disorders are a broad class of diseases in which enzymes involved in metabolic or catabolic pathways are mutated (74), causing either loss of an essential metabolite or accumulation of a toxic by-product. Neurological symptoms, ranging from mental retardation, seizures or even coma, are secondary to the metabolic defects manifest in other organ systems, but are rarely reversible (74), stressing the importance of better understanding the causes underlying these symptoms. In the CNS, astrocytes express most metabolic enzymes and as such are on the front line in the detoxification of the CNS milieu (72), suggesting they may be responsible for many of the neurological symptoms observed in metabolic disorders.

In Menkes disease, ATP7A, a copper transporter expressed by astrocytes, is mutated, resulting in low copper level, neurodegenerartion and possible death (74–78). Urea cycle disorders, hyperammonemia occurs throughout the body and in the CNS resulting in neurological symptoms(74). Astrocytes are the only cells capable of removing ammonia through glutamine synthesis and data suggest that hyperammonemia causes cellular and molecular changes in astrocytes which may be key to brain edema (79). These examples illustrate the potential role of astrocytes in many neurological symptoms observed in metabolic disorders and urge the scientific community to further investigate the link between metabolic disorders and astrocytes to help alleviate debilitating symptoms or even prevent death.

Conclusion/Perspective

In a little over a century, our view of astrocytes has evolved from insignificant “glue” to vital constituents of the CNS. Astrocytes play an essential role in several aspects of CNS physiology and their dysregulation directly contributes to several neurological disorders. In this review, we’ve summarized the current knowledge on astrocytes and their role in neurological and especially neurodevelopmental disorders.

Research in the astrocyte field from the last few decades has significantly altered our view of neurological disorders. Pediatric disorders are developmental in nature and therapeutic goals would benefit from a better understanding of astrocyte development. A more comprehensive understanding of astrocyte development will likely shed light on some of these disorders and point the way for new therapeutic approaches. Importantly, the fact that astrocytes mature postnatally offers a unique therapeutic window where intervention may influence cellular, functional, and, ultimately, neurological outcomes. Another significant aspect of astrocyte biology is their diversity. Morphological and functional heterogeneity has been reported for years, however a clear definition of whether these functions are mediated by subpopulations of astrocytes remains a key question. Application of these paradigms to CNS injury and disease might come in the form of distinct astrocyte subpopulations promoting network and circuit plasticity or simply neuronal repair after insult. Indeed, recent studies suggest that different form of CNS injury result in reactive astrocytes with vastly different properties [80]. Deciphering the who, where, what, and why of such disease-related heterogeneity will be crucial in determining whether an astrocytic intervention for these disorders is possible. Astrocytes could very well be the missing link in our fuller understanding of normal CNS function. Appreciating diverse astrocytic functions may very well be the key to unlocking the mysteries underlying the origins of many varied neurological disorders, better guiding treatments and rehabilitative efforts in managing these disorders.

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