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Mechanisms of astrocyte development and their contributions to neurodevelopmental disorders

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Abstract

The development of functional neural circuits relies upon the coordination of various cell types. In particular, astrocytes play a crucial role in orchestrating neural development by powerfully coordinating synapse formation and function, neuronal survival, and axon guidance. While astrocytes help to shape neural circuits in the developing brain, the mechanisms underlying their own development may play an equally crucial role in nervous system function. The onset of astrogenesis is a temporally regulated phenomenon that relies upon exogenously secreted cues and intrinsic chromatin changes. Defects in the mechanisms underlying astrogenesis or in astrocyte function during early development may contribute to the progression of a variety of neurodevelopmental disorders.

Introduction

The development of the nervous system is no small feat. For decades, neurobiologists have worked to understand how billions of neurons are born, migrate throughout the brain to their respective destinations, and proceed to establish intricate functional circuits. But this is only half the story. As new neurons populate the developing brain they are soon joined by a group of cells known as astrocytes. Astrocytes are not merely passive bystanders of nervous system development; beyond playing critical roles in energy metabolism, K^+ buffering, and neurotransmitter recycling, astrocytes actively contribute to the formation and maintenance of neural circuits by powerfully controlling synapse formation, function, and elimination [1,2••]. In this light, astrocytes may be seen as choreographers of neural circuit formation. Defects in the carefully orchestrated steps required to form functional neural networks are believed to result in a cluster of diseases known as neurodevelopmental disorders. Naturally, this raises the question whether some of these conditions, long assumed to result from neuronal pathogenesis, may share an underlying etiology of astrocyte dysfunction.

Some conjecture that the cognitive abilities observed in humans stem from an increase in the relative size of the cerebral cortex, but the human brain is not the evolutionary outlier that is so commonly assumed. In fact, the human cortex contains precisely the number of neurons that would be expected from a scaled-up primate brain [3]. Human astrocytes, however, are

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quite unique when compared to other animals; they are over 20-times larger by volume and contact up to 10-times the number of synapses as individual rodent astrocytes [4]. Furthermore, transcriptome data of human brains demonstrate significantly increased expression of astrocyte-derived synaptogenic proteins [5]. These data raise the possibility that the non-neuronal dimension of information processing and circuit organization in the human brain may contribute to improved human cognitive ability and complexity. Conversely, the arrival of human neurodevelopmental disorders may therefore represent the end-product of disrupted astrocyte development.

Though we have begun to better understand the contributions of astrocytes to the nervous system throughout various stages of maturation, our insight into how these cells initially develop has been enigmatic. In this review we will focus on astrocyte development through the lens of neurodevelopmental disorders. We will begin with a brief overview of the mechanisms involved in astrogenesis (for comprehensive reviews, see [6–8]) followed by a discussion of emerging evidence suggesting that the pathogenesis of many neurodevelopmental disorders may be attributable to astrocyte dysfunction during development.

Temporal separation of neurogenesis and gliogenesis

Neurons, astrocytes, and oligodendrocytes share a common neuroepithelial origin and are born throughout embryogenesis in a temporally defined manner. In the mammalian system the first divisions of neural stem cells (NSCs) are exclusively neurogenic, either giving rise to neural-restricted intermediate progenitors or directly to young neurons. Once the bulk of neurogenesis has occurred, NSCs become primarily gliogenic. This phenomenon whereby NSCs switch from a largely neurogenic to gliogenic phenotype is also recapitulated in embryonic stem cell (ES) and induced pluripotent stem cell (iPSC) models, indicating that there are inherent temporal mechanisms that underlie the production of neurons *versus* glia.

Astrocytes arise from a number of various sources in the developing nervous system; they may be produced directly from radial glia [9], from a yet-to-be-identified astrocyte-restricted progenitor population, or from the proliferation of newly born astrocytes. In fact, recent reports indicate that the majority of mouse cortical glia arise from clonal divisions of early differentiated astrocytes [10•] and that these clones may specify domains of distinct astrocyte classes [11•]. These data also complement recent findings in the mouse spinal cord that astrocytes are allocated to spatial domains in accordance with their embryonic sites of origin in the ventricular zone [12••].

Activators of gliogenesis

A combination of extrinsic cues and epigenetic factors contribute to fate specification of NSCs during development. The idea that extrinsic signals are required for astrogenesis first arose from the observation that embryonic cortical precursors produce neurons when cultured on embryonic cortical slices, but astrocytes when cultured on postnatal cortical slices [13]. The question then arose as to the identity of these secreted cues and several key experiments soon converged on the IL-6 family of cytokines. The IL-6 subfamily includes ciliary neurotrophic factor (CNTF), leukemia inhibitor factor (LIF), and cardiotriphin-1

(CT-1). Each of these molecules act through the heterodimerization of the signal-transducing coreceptors LIFRb and gp130, which act upstream of the JAK-STAT pathway. Mice lacking either LIFRb or gp130 have pronounced deficits in astrogenesis, and $gp130^{-/-}$ or $LIFRb^{-/-}$ NSCs exhibit significantly impaired astrogenesis *in vitro* [14]. Though both CNTF and LIF are commonly used now for the induction of astrocytes in iPSC and ES models of astrocyte differentiation [15•,16], the relevant *in vivo* ligand of LIFRb and gp130 during development appears to be CT-1 that is secreted from newly born cortical neurons [17]. This creates an inherent timing mechanism whereby the extrinsic cues that are required for astrocyte formation are provided by the neurons whose development initially precedes gliogenesis. Interestingly, IL-6 is a highly versatile cytokine with pleiotropic effects in the nervous system. In addition to its roll in promoting astrogenesis, IL-6 is involved in controlling the intrinsic growth state of neurons. For example, IL-6 levels accumulate following brain injury or inflammation and promote neuronal survival and axonal regeneration [18,19]. Thus, the molecular cues that direct astrogenesis are not necessarily restricted to this purpose. Indeed, it is the intrinsic state of a given cell that dictates how an extrinsic cue is perceived, explaining how identical signals could act as inducers of astrogenesis in NSCs, or conversely as survival signals for distressed neurons.

In addition to IL-6 cytokines, BMPs and Notch signaling molecules are also potent activators of astrogenesis. How do these seemingly independent pathways synergize into a convergent picture of astrocyte development? The common denominator is their association with JAK/STAT activation, the canonical pathway regulating astrocyte gene expression. STAT3 activity is crucial for astrogenesis to occur [20] and is a direct transcriptional activator of the astrocytic genes, *GFAP* and *S100β* [21]. Most significantly, STAT3 does not act alone; it interacts with the p300/CBP co-activator complex to initiate astrocyte gene expression. Furthermore, BMP signaling *via* downstream Smad effector proteins also synergizes with the STAT3:p300/CBP pathway to activate gliogenesis through the formation of a larger Smad1:p300/CBP:STAT3 complex [22]. Not surprisingly, STAT3 has also been implicated as an important player in the astrogliosis that accompanies nervous system damage. Studies focusing primarily in the spinal cord demonstrate that STAT3 knockdown leads to a failure of astrocyte hypertrophy, and pronounced disruption of astroglial scar formation after spinal cord injury [23,24].

Regardless of the inciting source, STAT3 activation alone is insufficient to initiate astrogenesis. During early embryogenesis, chromatin modifications at gliogenic promoters restrict the competence of NSCs by preventing extrinsic cues from triggering astrocyte fate specification. The most striking of these chromatin modification is methylation of the GFAP promoter, which prevents its expression even when STAT3 is activated [25]. This is a transient methylation state; as development continues the Notch effector protein, NFIA, binds to the *GFAP* promoter and induces the dissociation of the DNA methylating enzyme, DNA methyltransferase 1 (*DNMT1*) [26]. The lack of methylation then relaxes the chromatin state and allows the STAT3:p300/CBP complex to initiate transcription.

Notch signaling is another potent regulator of cell fate during embryogenesis with temporally regulated effects. Early in development, Notch activation promotes the maintenance of NSCs and prevents premature neurogenesis, while at later stages it robustly

stimulates gliogenesis. RBP-Jκ, the downstream effector of Notch activation, directly regulates expression of the Hes family of *bHLH* genes. Hes genes inhibit neurogenesis during the neurogenic period and are capable of promoting astrogenesis when ectopically expressed during the gliogenic period [27]. Hes1 itself is capable of inducing phosphorylation and subsequent activation of STAT3 by facilitating interactions between STAT3 and its kinase JAK2 [28]. The Notch target NFIA is another powerful regulator of astrogenesis that functions by repressing excessive Notch activation through the inhibition of Hes1 [29•] while simultaneously encouraging astrogenesis by promoting demethylation at the GFAP promoter [30]. A final Notch target, the HMG box transcription factor Sox9, has also long been known to activate astrogenesis. Now, recent evidence suggests that Sox9 drives NFIA expression and that these two transcription factors complex with each other in order to coregulate genes that are integral to the initiation of gliogenesis [31•]. Overall, Notch signaling is a powerful inducer of astrogenesis both as an extrinsic source of STAT3 activation and by triggering the gliogenic competence of NSCs.

The inhibition of gliogenesis

Gliogenic cytokines are present in the embryonic cortex throughout the neurogenic phase. This raises the question of how astrocytic fates are inhibited during early phases of embryogenesis. The answer is largely due to epigenetic silencing of astrocytic genes (discussed above) accompanied by inhibition of gliogenic transcription factor complexes. Throughout neurogenesis, the proneuronal factor Ngn1 binds and sequesters the p300/CBP complex to prevent its interaction with STAT3 while simultaneously promoting the expression of neuronal genes [32]. Neurotrophins like BDNF are also capable of interfering with JAK/STAT signaling by activating the neurogenic SHP2-Ras-Raf-MEK-ERK pathway. SHP2 has dual effects; it dephosphorylates STAT3 to inhibit JAK/STAT signaling in non-neuronal cells [33] and its expression triggers pro-neural MEK-ERK signaling. Constitutively activating mutations in SHP2 are found in the human neurodevelopmental disorder Noonan syndrome (NS) [34]. NS is a relatively common but complex congenital disorder that presents with an assortment of cardiac, gastrointestinal, musculoskeletal, and hematological dysfunction. Furthermore, most NS children suffer from considerable learning disabilities, a phenotype that new studies are attempting to reconcile with abnormal MEK-ERK signaling during neurodevelopment. In support of this hypothesis and consistent with the neurogenic role of SHP2, mouse models of NS that express mutant constitutively active forms of human NS-SHP2 exhibit excessive neurogenesis and decreased astrogenesis [35•]. This imbalance in the neuron to glial ratio may disrupt normal neural circuit formation and lead to behavioral phenotypes like learning disabilities. A generalized schematic of the mechanisms involved in the activation and inhibition of gliogenesis are summarized in Figure 1.

Neurodevelopmental diseases resulting from abnormal timing of astrogenesis

Disruptions in any of the mechanisms described above that affect the timing or efficiency of neurogenesis and astrogenesis may lead to perturbations in the relative ratios of these two cell types. A prominent example of this phenomenon is a class of syndromes known as

'RASopathies' that result from alterations in the Ras-Raf-MEK-ERK signaling pathway. As seen in NS, these syndromes have a variety of clinical manifestations, but nearly all share a degree of mental impairment [36]. Recent mouse models have demonstrated abnormal astrocyte development and proliferation in several of these disorders including Noonan syndrome [34], Neurofibromatosis-1 [37], Costello syndrome [38], and Cardiofaciocutaneous syndrome [39]. While RASopathy disorders are rare, they represent an excellent example of how precocious astrocyte development can lead to serious neurodevelopmental dysfunction. New data suggest that this phenomenon may also contribute to the pathogenesis of Down syndrome (trisomy 21), a neurodevelopmental disorder with significantly broader prevalence. Histologic findings in Down syndrome patients have long demonstrated reduced neuronal numbers, alteration of synaptic spines, delayed myelination, and increased astrocytes [40]. Now, new evidence is providing some of the first mechanistic clues into what may underlie precocious gliogenesis in these patients. A study from Lu *et al*. suggests that premature exit from neurogenesis may result from increased olig2 expression, a gliogenic transcription factor residing on the trisomic chromosome 21 [41]. Though olig2 is largely recognized for its role in oligodendrocyte formation, its expression is also critical for the formation of white matter astrocytes [42] and may act to drive premature gliogenesis in Down syndrome patients.

Astrocytes driving neuronal pathology in autism

Adequate neurogenesis and gliogenesis represent only the initial steps of nervous system development. Proper neural circuit formation also requires choreographed patterns of neuronal migration, dendritic growth, axon target guidance, and synapse formation. Each of these stages requires appropriate astrocyte-derived factors and raises the question of whether astrocyte dysfunction during these critical steps could contribute to the pathogenesis of neurodevelopmental disorders (Figure 2). Recent evidence of astrocyte involvement in these processes has emerged for a broad class of syndromes known as autism spectrum disorders (ASDs). Observational studies in human ASD patient samples demonstrate elevated expression of GFAP in the superior frontal, parietal, and cerebellar cortices [43] as well as the cerebrospinal fluid [44]. In addition to GFAP, the astrocytic markers *AQP4* and *CX43* also demonstrate abnormal expression patterns in ASD patient samples [45]. More recent reports indicate that astrocytes of autistic patients exhibit reduced branching processes, branching length, and cell body sizes, which may be attributable to decreased Wnt/β-catenin signaling in these individuals [46].

Beyond correlative evidence, what proof exists that astrocytes are capable of driving neuronal aberrations in models of autism? Rodent studies of monogenetic models of autism have provided the best avenues for studying this question. Most significantly, a role for astrocytes has been demonstrated in the progression of Rett syndrome, an X-linked ASD caused by mutations in the transcription factor methyl-CpG-binding protein 2 (*MECP2*). Ballas *et al*. demonstrated that mutant astrocytes from an RTT mouse fail to support normal dendritic morphology in healthy neurons [47••]. Furthermore, astrocyte-specific re-expression of *MECP2* in global *MECP2*$^{-/-}$ mice was capable of rescuing a subset of Rett symptoms [48•]. Now, ChIP-seq and gene expression analyses of MECP2$^{-/-}$ astrocytes are beginning to identify aberrantly expressed target genes that may play a direct role in

astrocyte-mediated disease pathogenesis [49]. Mouse models of another monogenetic form of autism, Fragile-X syndrome, have also demonstrated non-cell-autonomous deleterious astrocyte effects. Co-culture experiments with mutant Fragile X astrocytes and healthy neurons recapitulate *in vivo* observations of delayed dendritic maturation and abnormal synaptic protein expression [50]. Taken together, these studies in monogenetic models of autism provide the most direct evidence that primary astrocyte dysfunction is capable of driving the complex behavioral phenotypes observed in neurodevelopmental disorders.

Many autism-linked genes are also expressed in astrocytes

Most ASDs do not result from monogenetic disorders, but rather from a complex genetic landscape that we do not yet fully understand. As sequencing capabilities have improved, genome wide association studies (GWAS) have provided a nonbiased approach to identify genes that may be implicated in autism. The initial targets that arose from this approach included a number of genes with obvious roles in synaptic function. Considering the integral roles that astrocytes play in synaptic formation and function, we wondered whether any of these autism-associated genes were also expressed in astrocytes. We addressed this question with RNA-Seq mouse expression data from populations of acutely purified cell types (data in preparation). Of the top 46 most significantly autism-linked genes identified in recent GWAS, 30 (65%) are expressed in astrocytes. This only slightly lags behind the 77% found in neurons. Furthermore, a subset of these highly implicated autism genes are predominantly enriched in astrocytes, including the well-known K^+ channel Kir4.1 as well as less studied astrocyte genes like *SYNE1* [51•] and *TSPAN7* [52].

Astrocyte dysfunction underlying neurodevelopmental origins of psychiatric disease

A relatively new avenue of discussion has begun to question whether astrocyte dysfunction may play a role in the neurodevelopmental origins of psychiatric disorders. Like the ASDs, initial evidence has been largely observational in conditions like schizophrenia and major depressive disorder (MDD). Laser capture microdissection of astrocytes in schizophrenic patients reveals alterations of some (*DIO2*, *AQP4*, *S100β*, *EAAT2*, and *TSP*), but not all astrocyte markers (*ALDH1L1* and *VIM*) in the deep layers of the anterior cingulate gyrus [53]. Furthermore, reduced phosphorylated *GFAP* expression has been reported in the frontal cortices of patients with schizophrenia [54] and reduced numbers of glia are well-documented in the anterior cingulate of patients suffering from MDD and bipolar disorder [55]. How could altered astrocyte number and function contribute to the neurobiological foundations of schizophrenia? Recent evidence suggests that decreased astrocyte numbers in deeper cortical layers are accompanied by diminished expression of the astrocytic glutamate transporter, EAAT2 [56]. This fits well with the popular hypothesis that glutamatergic dyshomeostasis contributes to the pathogenesis of schizophrenia [57].

Concluding remarks

The breadth of neurologic disorders that have already been associated with some amount of astrocyte dysfunction is remarkably diverse and easily expands beyond those examples

mentioned above. Several profound questions remain before we can understand how astrocytes might contribute to the pathogenesis of each of these conditions. How developmentally and functionally heterogeneous are astrocyte populations? In the setting of complex disorders like autism, how similar are human and rodent astrocytes? What qualities of astrocyte dysfunction actually contribute to aberrant neural function during development? Numerous new tools are required to answer these questions. New markers of astrocyte maturation and diversity will help to address heterogeneity in the brain. Human iPSC-derived astrocytes from affected patients could help to confirm observations made in rodent models and lead to potential therapeutic screens. We are entering an exciting era of astrocyte biology, and their consideration as drivers of neurodevelopmental dysfunction is of immediate relevance.

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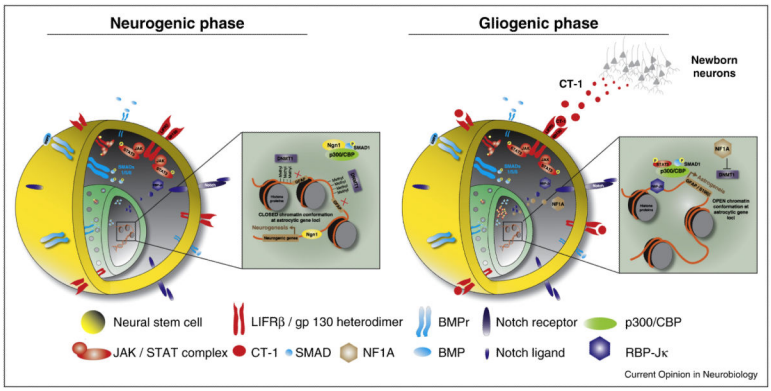

Figure 1.

Molecular mechanisms that govern neurogenic and gliogenic fates in neural stem cells. **(a)** During the neurogenic state, Ngn1 binds and sequesters the p300/CBP complex to prevent interactions with the gliogenic binding partner STAT3. Concomitant DNMT1 expression leads to methylation and subsequent repression of glial gene transcription. **(b)** Later in embryogenesis, proglial signals like BMPs, Notch, and CT-1 lead to the activation of the STAT3:p300/CBP complex. NFIA-mediated repression of DNMT1 helps to eliminate methylation at the GFAP promoter and results in a relaxed DNA confirmation where STAT3:p300/CBP can bind and initiate gliogenic gene transcription.

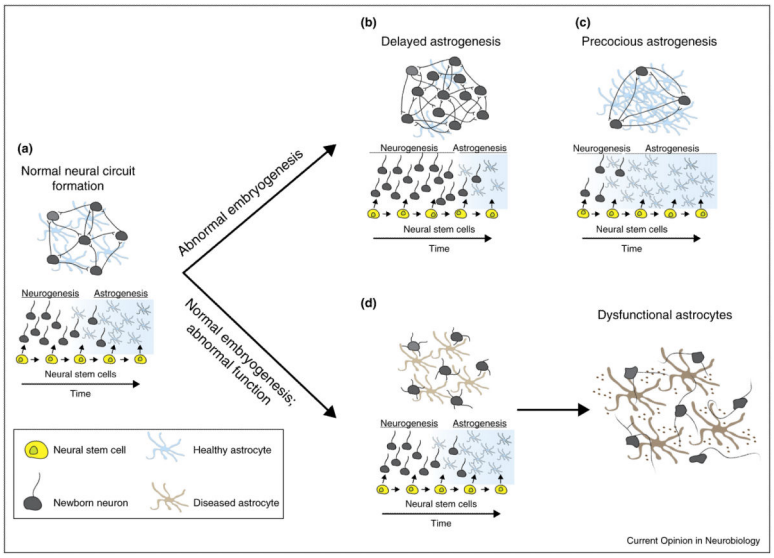

Figure 2.

Mechanisms of astrocyte dysfunction that affect neural circuit development. **(a)** The establishment of appropriate neural circuits requires interplay between both neurons and astrocytes during development. Variations in the precise timing of the neurogenic to gliogenic switch can lead to a dearth **(b)** or surplus **(c)** of astrocytes. Too few astrocytes may eliminate essential cues required for axon guidance, neuronal survival, or synapse formation, while precocious astrogenesis may limit the number of neurons available to contribute to specific circuits. Alternately, neurogenesis and astrogenesis may proceed normally with circuit dysfunction arising from primary astrocyte pathology instead. **(d)** The secretion of toxic factors or the absence of survival and/or synaptogenic signals may contribute to the pathogenesis of aberrant neural circuits.