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1 Do astrocytes play a role in intellectual disabilities?

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15

16 **Keywords**

17 astrocytes, intellectual disability, Fragile X syndrom, Down syndrom, Rett syndrom, tripartite
18 synapse

19

20 **Abstract**

21 Neurodevelopmental disorders, including those involving intellectual disability, are
22 characterized by abnormalities in formation and functions of synaptic circuits. Whereas
23 traditionally, research on synaptogenesis and synaptic transmission in health and disease
24 focused on neurons, a growing number of studies have highlighted the role of astrocytes in
25 this context. Tight structural and functional interactions of astrocytes and synapses indeed
26 play important roles in brain functions, and the repertoire of astroglial regulations of
27 synaptic circuits is large and complex. Recently, genetic studies of intellectual disabilities
28 have underscored potential contributions of astrocytes in the pathophysiology of these
29 disorders. Here we review how alterations of astrocytes' functions in disease may interfere
30 with neuronal excitability and the balance of excitatory and inhibitory transmission during
31 development, and contribute to intellectual disabilities.

32 Main text

33 **Intellectual disabilities**

34 Intellectual Disability (ID, also called learning disability, mental retardation, or cognitive
35 deficit) is defined by an overall Intelligence Quotient (IQ) lower than 70 associated with
36 deficits in conceptual, social and practical adaptive skills with an onset before the age of 18
37 years. The clinical spectrum of cognitive deficit varies widely from non-syndromic ID to
38 Autism Spectrum Disorder (ASD) and is estimated to affect 1 to 3 % of the population. The
39 causes of ID are heterogeneous and include genetic and/or environmental factors that
40 influence the development and function of the central nervous system (CNS) during the pre-,
41 peri-, or post-natal period. Genetic causes, including chromosomal abnormalities, such as in
42 Down syndrome (DS), and monogenic causes, in Rett and Fragile X syndromes (RS and FXS,
43 respectively), seem to be responsible for 40 to 50 % of moderate to severe ID (IQ < 50).
44 Environmental factors, including neurotoxic insults, maternal exposure to infections
45 (toxoplasmosis, cytomegalovirus and rubella), or teratogenic molecules (alcohol),
46 malnutrition and brain lesions during early development, primarily contribute to mild ID (50
47 < IQ < 70). In theory, genes that are involved in cases of ID in which CNS organization is
48 preserved at a gross anatomical level (i.e., normal MRI scan), are likely to encode proteins
49 that are necessary for neural circuit development, in a manner that ultimately contributes to
50 impaired cognitive function. Though at first sight, it may appear that these proteins are very
51 diverse, upon closer analysis, functional commonalities between these proteins emerge
52 (e.g., transcription and chromatin remodeling factors, cell adhesion molecules, processing,
53 modification, and transport of RNA, protein ubiquitination, and fatty acid metabolism
54 function). Compelling evidence indicates that a major functional group of ID-related proteins
55 corresponds to proteins that are enriched at synaptic compartments, and recent
56 investigations point out the crucial role of these synaptic proteins in the regulation of
57 dendritic spines morphogenesis and synaptic activity [1,2].

58 Of note, new findings regarding the role of astrocytes in brain development and functions
59 have emerged. These raise many questions regarding the contribution of neuroglial
60 interactions in the pathogenesis of neurodevelopmental diseases. Here we review the
61 alterations in the morphological and functional properties of astrocytes occurring in DS, RS
62 and FXS and how this may affect neuronal development and functions. We also briefly

63 address alterations and potential contributions of astrocytes in environmental forms of IDs
64 (Box 1).

65

66 **Intrinsic astroglial alterations in ID?**

67 ***Neuropathies: a restrictive vision of ID***

68 Expression of genes involved in ID, initially viewed as mainly confined to neurons, was
69 recently described in astrocytes, suggesting that deficient astrocytes contribute to ID [3].
70 RNA sequencing technologies of brain cells [4,5] revealed that most ID genes [6] are indeed
71 expressed not only in neurons, but also in astrocytes (about 70% of ID genes). These genes
72 encode for proteins enriched in mitochondria and lysosomes and that play roles in
73 oxydoreduction functions known to be altered in several brain diseases[7,8]. Notably, FMRP
74 and MeCP2, whose genes are mutated in FXS and RS respectively, as well as several genes of
75 human chromosome 21 (HSA21) that are triplicated in DS (SOD1, DYRK1A, S100 β and
76 OLIG2), are expressed in astrocytes. Other glial cell types also express ID genes and show
77 alterations in IDs, including FXS, RS and DS, and accordingly, these cell types may contribute
78 to these disorders as well [9–13].

79 It is still unclear however whether ID proteins have similar or different functions when
80 expressed in neurons or in astrocytes. ID proteins indeed may interact, regulate or target
81 different sets of proteins or genes during development in a cell specific manner. In FXS, for
82 instance, the FMRP protein regulates mGluR5 expression in astrocytes, but not in neurons.
83 This leads to regulation of GLT1 glutamate transporter expression and associated glutamate
84 uptake in astrocytes [14]. Notably, FMRP can also control glutamate transport in neurons,
85 but via the direct regulation of the VGLUT1 vesicular transport [15].

86 Similarly, the MeCP2 protein, which binds to methylated DNA, increases or decreases
87 expression of different sets of genes in neurons [16] and astrocytes [17,18] through
88 chromatin structural changes [19]. Among the downregulated genes in astrocytes, two
89 encode for membrane receptors that mediate calcium signaling (mGluR3R and S1P1R) and
90 one for an ion channel involved in potassium uptake (Kir4.1) [20]. In addition, astrocytes
91 from MeCP2 deficient mice show a reduction in the expression of stathmin-like 2, a protein
92 involved in microtubule stability [21] and both mouse and human astrocytes showed altered
93 microtubule dynamics and vesicular secretion [22]. Thus, the cell-specific functions of ID

94 proteins are a great source of information that should lead to a better understanding of the
95 contribution of astrocytes in ID.

96

97 ***Abnormal astrocytic development and state***

98 Whereas most IDs and other related pathologies are presented as neurodevelopment
99 disorders (with a focus on the neural compartment), the development of astrocytes is also
100 affected, and changes in astrocyte number may impact the CNS development. Studies in DS
101 showed an increase of astrocytes (more mature in their morphology) and radial glial cells in
102 frontal lobe of fetuses at different stages [23]. Similarly, an increase of astrocytic
103 differentiation from neuronal stem cells (NSC) has been observed in RS [24].

104 Recent evidence indicates that mutant astrocytes display an abnormal state in most IDs
105 (Table 1 and Figure 1). Several astrocytic markers such as GFAP and S100 β are indeed
106 altered, and this is associated with a less complex morphology and thicker branches,
107 suggesting astrocytic reactivity [25,26]. For instance, Rett patients have increased GFAP
108 expression compared to matched controls [27], possibly because MeCP2 directly represses
109 GFAP expression [28]. Increase in GFAP, but also S100 β expression, was also found in
110 astrocytic cultures of MeCP2-deficient mice [29]. However, the modulation of GFAP
111 expression is not as clear in the case of FXS, as both increase [30] or no change in GFAP
112 expression [31,32] have been reported. In DS, dysregulated astrocytes were also observed in
113 human brain tissue and differentiated cells from induced pluripotency stem cells (IPSCs)
114 [25,33]. Interestingly, the human chromosome 21 carries the gene coding for S100 β , which is
115 triplicated in DS and leads to higher level of S100 β protein (75 times more) than control
116 astrocytes [33]. Moreover, mutated astrocytes overexpress the GFAP protein (5 times more)
117 although its gene is not located on the 21 chromosome, suggesting that astrocytes reactivity
118 is not directly linked to the gene triplication. Whether astrocyte reactivity reported in some
119 IDs applies to all astrocytes or subpopulations is currently unknown. It will thus be of interest
120 to analyze the transcriptomic datasets of astrocytes in IDs and search, for instance, for
121 markers of toxic A1 and trophic A2 astrocytes, as recently described [34].

122 Notably, dysregulation of astrocytic markers in IDs is associated with alterations in typical
123 functional properties of astrocytes, such as glutamate sensing and clearance, as detailed
124 below.

125

126 **Astrocytes: the unusual suspect in ID**

127 ***Neuronal morphological alterations resulting from astroglial dysfunction***

128 A common feature of most IDs is altered neuronal morphology. Reduced dendritic
129 branching, long thin immature spines and reduced spine motility have indeed been reported
130 in FXS, RS and DS, suggesting that synaptic networks remain in an immature state [35–37].
131 Interestingly, recent data indicate that astrocytes are involved in the formation and
132 maturation of neuronal networks by acting at multiple levels, such as dendritic growth,
133 synaptogenesis, synapse maintenance and pruning [38,39]. These astroglial regulations of
134 synaptic networks are likely altered in IDs, as suggested by several studies (Table 1). Deletion
135 of FMRP in astrocytes *in vitro* inhibits neuronal growth as well as delays formation of
136 excitatory synapses and dendritic arborization [40,41], while *in vivo*, it increases the density
137 of immature dendritic spines [32]. Similarly in RS, astrocytes derived from iPSCs
138 differentiation alter neuronal morphology, and *in vivo*, re-expression of MeCP2 in astrocytes
139 from constitutive MeCP2-deficient mice rescues dendritic branching and number of
140 excitatory synapses through a non-cell autonomous effect [42,43]. Finally, DS astrocytes co-
141 cultured with wild type neurons decrease spine density [44,45]. Yet, the mechanisms
142 underlying astroglial dysregulation of synapses in IDs remain unclear. Several studies suggest
143 that secreted factors are implicated in this context. Among these factors, thrombospondin-1
144 (TSP-1), known to stimulate excitatory synapse formation [46], is decreased in astrocytes
145 from FX [47] and DS models [45]. In addition, conditioned media from wild type astrocytes or
146 exogenous TSP1 restores in co-cultures spines and excitatory synaptic abnormalities of
147 neurons [45,47]. Further work is needed to unravel the molecular determinants of astroglial
148 regulations of synapses.

149

150 ***Dysregulation of neuronal excitability due to astrocytic failure***

151 - **Glutamate and potassium extracellular homeostasis**

152 Astrocytes are involved in the clearance of extracellular glutamate through GLT1 and GLAST
153 glutamate transporters. They also sense glutamate levels via metabotropic glutamate
154 receptors (mGluRs), which mediate calcium release from intracellular stores. In FMRP-
155 deficient mice, GLT1 and astrocytic mGluR5, as well as GLAST, are reduced during
156 development, causing an excess of extracellular glutamate, which contributes to neuronal
157 hyperexcitability [14,31]. By contrast, in cultured astrocytes from MeCP2 deficient mice,

158 glutamate clearance is increased in response to extracellular glutamate rise, most likely due
159 to higher expression of GLT1 and GLAST [29]. Somewhat similarly to MeCP2 deficient
160 astrocytes, DS astrocytes express higher levels of GLAST, and also of mGluR5 than control
161 astrocytes, however with no change in GLT1 expression, leading to a higher rate of
162 glutamate uptake [33,48]. In vivo, contradictory observations have been reported regarding
163 the levels of glutamate in DS [7]. Altogether, astroglial glutamate uptake is altered in most
164 IDs (Table 1) but the alterations in extracellular glutamate do not seem to account for the
165 cognitive deficits in ID.

166 Astrocytes also possess high permeability to potassium ions and are able to spatially
167 redistribute the local excess of synaptic potassium through gap junctions in neighboring
168 regions. Transient increases in extracellular potassium levels caused by neuronal activity are
169 indeed buffered by astrocytes, which prevents network hyperactivity. Interestingly, several
170 IDs including FXS and DS are associated with changes in neuronal excitability resulting from
171 alteration in the expression or activity of several neuronal potassium channels [49–51]. Some
172 of these channels, such as BK channels or KCNJ6 and KCNJ15, are expressed in astrocytes
173 [52] and may therefore also be dysregulated in FXS and DS.

174
175 In addition, other non-neuronal potassium channels expressed in astrocytes and mediating
176 most of the activity-dependent potassium uptake can also be dysregulated, as shown in RS
177 (Table 1 and Figure 1). MeCP2 is indeed a positive regulator of the *Kcnj10* gene which
178 encodes the Kir4.1 channel [20], and whose expression is drastically reduced in MeCP2
179 deficient-astrocytes, resulting in disruption of extracellular potassium homeostasis [53]. This
180 may contribute to the epileptic activity observed in about 70% of Rett patients [57]. Such
181 astrocytic potassium channels may therefore represent a novel therapeutic target for ID.

182
183 Connexins, the astroglial gap junction proteins, are also known to contribute to glutamate
184 and potassium extracellular homeostasis [54] and epileptic activity [55] and may thereby
185 also be implicated in the alterations in neuronal excitability and seizures in IDs. Interestingly,
186 mutations in Cx43 gene (GJA1), which codes the main gap junction channel subunit of
187 astrocytes, can cause oculo-dento-digital dysplasia whose neurological manifestations
188 include both ID and epilepsy [56].

189

190 Of note, beyond astroglial proteins whose expression is altered in ID and which contribute to
191 epileptic activity such as Kir4.1 [57] and GLT1 [58] or Cx43 [55], astrocytes also express some
192 ID genes which are functionally implicated in seizures. The interleukin-1 receptor accessory
193 protein like 1 (IL1RAPL1) gene, for instance, which codes a synaptic adhesion protein, is an ID
194 gene [59] which is also expressed in mouse astrocytes [5] and whose deletion has been
195 recently associated with startle epilepsy in humans [60]. Furthermore, mutations in nuclear
196 distribution protein nudE homolog 1 coded by the NDE1 ID risk gene [61], which is crucial for
197 cell positioning during cortical development and is strongly expressed by astrocytes [5],
198 increases susceptibility to convulsions in *C. Elegans* and can cause human cortical
199 malformation termed lissencephaly associated with epilepsy [62].

200

201 - **Calcium signalling**

202 Astrocytes, unlike neurons, do not exhibit action potentials, but they do display intracellular
203 calcium signaling, thought to represent their excitability. Such signaling occurs in response to
204 several stimuli, and mediates various responses, including release of neuroactive molecules,
205 which can regulate neuronal excitability or synaptic transmission. A couple of studies
206 indicate that astroglial calcium signaling is enhanced in ID gene related pathologies (Table 1).
207 For instance, in FX associated tremor/ataxia syndrome, astrocytes exhibit increased
208 spontaneous asynchronous calcium oscillations [63]. In a DS mouse model, astrocytes basal
209 calcium levels are also enhanced and evoked calcium responses are reduced likely due to an
210 accumulation in organelles that may buffer cytosolic calcium [64]. Finally, aberrant calcium
211 signaling also occurs in DS-patient-derived astroglia, with more frequent and increased
212 spontaneous calcium fluctuations, independently of functional astroglial maturation [65].
213 The functional impact of the elevated astroglial calcium signaling still remains elusive, but
214 the elevated calcium levels are likely to alter neuronal excitability, as reported for DS
215 astroglia, where prominent calcium signaling reduces excitability of control co-cultured
216 neurons [65].

217

218 ***Excitation/Inhibition imbalance resulting from astroglial dysfunction?***

219 The balance between excitatory and inhibitory transmission (E/I) is commonly altered in FXS,
220 RS and DS [37]. This effect may result from changes in the number of synapses or from

221 regulation of ionic gradient and homeostasis altering the effect of neurotransmitters (Table
222 1 and Figure 1).

223 - **Reduction in excitatory synapses**

224 As mentioned above, astrocytes in IDs participate to the immature excitatory spines
225 phenotype. This likely results in decreased excitatory transmission and altered E/I balance.
226 The overall astroglial control of E/I balance is however still unclear, partly because few data
227 are available regarding the role of astrocytes in the formation, maturation and elimination of
228 inhibitory synapses [66,67].

229

230 - **Regulation of the Cl⁻ homeostasis**

231 Astrocytes have been shown to accelerate the developmental changes in chloride gradient
232 of cultured neurons [68]. This suggests an additional mechanism that may control the E/I
233 balance via regulation of the GABA switch occurring during early development, and which
234 has been reported to be dysregulated in ID [69,70].

235 While activation of GABA_A receptors in adult neurons induces an hyperpolarization due to an
236 entry of chloride into neurons, their activation during early development is thought to lead
237 to a depolarization resulting from a net release of chloride [71]. This GABA switch results
238 from variations in the expression of NKCC1 (decrease) and KCC2 (increase), two chloride co-
239 transporters. These co-transporters are present not only in neurons [72] but also in
240 astrocytes, suggesting that glial cells may also participate to chloride homeostasis regulation
241 [5]. Of note, both NKCC1 and KCC2 expression are dysregulated in IDs. Specifically, a delay in
242 KCC2 expression occurs in humans and mouse model of RS as well as in FMRP deficient mice,
243 suggesting a developmental delay in the switch to inhibition, which may also alter the
244 excitation/inhibition balance during developmental critical periods [69,70]. Similarly, a
245 dysregulation of the Cl⁻ equilibrium leading to an excitatory effect of GABA was observed in
246 the Ts65Dn mouse model of DS, in this case stemming from NKCC1 overexpression [73].
247 Interestingly, KCC2 and NKCC1 are strongly regulated by BDNF and its receptor TrkB [74,75]
248 and BDNF levels are altered in FXS, RS and DS mouse models [76–78]. Since astrocytes are
249 now recognized as an alternative source for BDNF expression and secretion [79], they may
250 thereby also regulate the GABA switch.

251

252 **Concluding remarks and future perspectives**

253 Genetically-linked IDs, including DS, RS and FXS are now well recognized to present neuronal
254 alterations at the synaptic level. More recently, glial dysfunctions have also been reported in
255 such diseases, yet their contribution remains elusive. Only in a few cases, for instance FXS
256 and RS, astrocyte dysfunctions have been directly shown to contribute to synaptic defects.
257 These defects relate, in particular, to the formation of excitatory synapses, dendritic
258 branching and the density of dendritic spines. However, the mechanisms underlying
259 astroglial dysregulation of synapses in IDs remain to be further studied. In particular, do
260 mutations in ID genes disrupt astroglial pathways involved in the physiological control of
261 synapse formation, maintenance or pruning [80] ? Or do these mutations selectively activate
262 other astroglial pathways which differentially regulate synapses?

263

264 In addition, whether astroglial dysfunctions also contribute to the cognitive decline and
265 behavioral changes associated with synaptopathies is not yet clear . One study, in MeCP2-
266 deficient mice, reported that re-expression of MeCP2 in astrocytes significantly improved
267 locomotion and anxiety levels, restored respiratory abnormalities to a normal pattern, and
268 prolonged lifespan compared to globally null mice [42,81]. These data, to our knowledge, are
269 the first to directly indicate that astrocytes, like neurons, may be integral components of the
270 neuropathology of RS. This urges the study of astroglial contribution to behavioral changes
271 in other synaptopathies, such as autism spectrum disorders. At least in one case, the
272 principles as observed in MeCP2-deficient mice, do not seem to directly generalize: in FXS,
273 re-expression of FRMP in astrocytes does not restore normal behavior, in particular related
274 to motor learning [32]. But an involvement of a non-neuronal cell population does seem
275 relevant, in this model, since deletion of FRMP in a large proportion of neurons (~ 60 %) did
276 not induce a behavioral phenotype [15]. Altogether, these data suggest that the behavioral
277 alterations in FXS may result from the interactions between dysfunctional neurons and
278 astrocytes, rather than from cell-specific defects. In fact, dysfunctions in IDs have typically
279 been studied either in neurons or astrocytes, but little is currently known on the nature of
280 the alterations in neuroglial interactions at the morphological and functional level. Studying
281 the astroglial coverage of synapses using super resolution imaging, as well as bidirectional
282 neuroglial calcium signaling at the tripartite synapse using cell-specific approaches is likely to
283 provide further insights into the role of dysfunctional astrocyte-synapse interaction in IDs.

284

285 One could envision that targeting pathways involved in neuroglial interactions, rather than
286 solely neurons or astrocytes, may pave the way for novel alternative therapeutic approach in
287 IDs. Since astrogliogenesis mainly occurs during the postnatal period of neurodevelopment,
288 there might also be a timely temporal window for therapeutic intervention to improve these
289 neuroglial interactions and compensate for some neuronal deficits acquired before birth.

290

291 Finally, at a more fundamental level, understanding how astrocyte dysfunctions alter the
292 development of functional synaptic circuits, should provide new conceptual frameworks for
293 mechanistic understanding of neurodevelopmental disorders such as ID, thus setting ground
294 for future clinical investigations.

295

296 **Glossary**

297 **Intellectual disability**

298 Neurodevelopmental disorders characterized by a low intellectual quotient associated with
299 deficits in adaptability including sociability, conceptualization, and practical skills prior to age
300 of 18.

301 **The tripartite synapse**

302 Revised concept of the synapse defined as a functional unit formed by the pre- and
303 postsynaptic elements as well as the surrounding astrocyte. The astrocyte integrates the
304 moment-to-moment synaptic activity via its ion channels, neurotransmitter receptors and
305 transporters, and provides feedback modulation of neurotransmission through uptake or
306 release of neuroactive substances.

307 **Gliotransmission**

308 Release of neuroactive substances such as glutamate, ATP, D-serine, or lactate from
309 astrocytes to modulate neuronal activity.

310 **GABA switch**

311 Neurodevelopmental phenomenon where NKCC1 activity decreases whereas KCC2 activity
312 increases, leading to an inversion of the Cl⁻ gradient. This inversion explains the transition of
313 the effects of GABA on neuronal activity from depolarizing during early development to
314 hyperpolarizing at later stages.

315 **Channelopathy**

316 A term describing pathologies related to the dysfunction of one or more ion channels,
317 leading to an alteration in ionic homeostasis and defects in neuronal transmission.

318

319

320 **Box1. Astrocyte alterations in non-genetic forms of IDs.**

321 Among IDs, the genetic forms have been the ones mostly studied thanks to the use of
322 genetic animal models enabling to address cell-type specific roles. The involvement of
323 astrocytes emerges however also in environmental forms of IDs, i.e. ones that can result for
324 instance from malnutrition, infection and toxics exposure during early development.

325 Severe prenatal malnutrition can result in a range of cerebral dysfunctions including ID. In a
326 rat model of protein malnutrition, a delay in the emergence of GFAP expression and a
327 reduction in astrocyte number has been observed, suggesting astrocytes as possible
328 contributors to neurodevelopmental disorders [82]. Moreover, in a rat model of neonatal
329 overnutrition, increases in primary projections of GFAP positive cells and in GFAP/vimentin
330 levels suggest a modification in glial coverage. The levels of glucose (GLUT-1, GLUT-2) and
331 glutamate transporters (GLAST and GLT-1), all expressed in astrocytes, are also increased in
332 those rats, and associated with a decreased synaptic transmission, suggesting alterations in
333 glucose and glutamate responses [83].

334 Another example where astrocytes seem to play a role is congenital cytomegalovirus (CMV)
335 infection. Human CMV is the most common cause of congenital infections in developed
336 countries. CMV infection causes serious neurodevelopmental sequelae, including ID. Lesions
337 due to infection include ventricular dilation, white matter gliosis, atrophy and cortical
338 malformations [84]. It has been shown that CMV can reduce the capacity of human neural
339 cells to differentiate into astrocytes and thereby contribute to brain development
340 abnormalities associated with congenital infection [85].

341 Astrocytes may also be involved in fetal alcohol spectrum disorder, a common cause of ID in
342 the western world, causing cognitive and sensory impairments after birth [86]. The effects of
343 fetal alcohol exposure (FAE) on the brain can vary throughout gestation according to the
344 targeted neurodevelopmental stage and the corresponding dominant neuronal maturation
345 event, progressing through proliferation, migration and differentiation. Alcohol exposure can
346 strongly affect proliferation of glia and neuronal precursors, leading to microcephaly,
347 hydrocephaly and ocular malformations [87]. FAE can also lead to abnormal migration of

348 cortical neurons and later affects synaptogenesis, leading to persistent deficits in neuronal
349 plasticity [88]. Of note, alcohol exposure at the neonatal stage can also induce alterations,
350 such as reductions in cell number, maturation and survival of adult-born neurons and
351 synaptic plasticity in the hippocampus [89]. The neuronal defects are accompanied by
352 changes in glial development and function, including differentiation [90], impaired
353 astroglialogenesis [91] and reduced glial cell survival [92]. Recently, it has also been
354 demonstrated that FAE leads to a permanent change in the astrocyte secretome [86].
355 Astrocytes, by regulating circuit maturation, could thus participate in neuronal alterations
356 underlying the spectrum of ID symptoms observed in FAE.

357

358 **Figure legend**

359 **Figure 1. Astrocytes and the tripartite synapse in normal physiology versus ID.** Schematic
360 representation of normal physiological conditions (normal physiology, left panel) and
361 putative pathophysiology in ID (ID, right panel) based on main alterations found in FXS, RS
362 and DS. A number of common features have been reported to be altered in ID astrocytes,
363 including changes in (1) astroglial complexity and reactivity; (2) synthesis and secretion of
364 astroglial factors that support neuronal growth; (3) pruning of synapses by astrocytes
365 leading to immature dendritic spine formation; (4) the synthesis and activity of astrocytic
366 channels that regulates K^+ buffering, which prevents network hyperexcitability; and (5),
367 expression of receptors (mGluR5) and transporters (GLT1, GLAST) enabling glutamate
368 sensing and clearance.

369

370 **Table 1. Astroglial implication in different IDs.**

Astroglial changes implicated in different IDs		Rett Syndrome	Down Syndrome	Fragile-X Syndrome
Abnormal astrocytic expression profile	Signalling	MeCP2 deficiency in the neural cell lineage increases astrocytic differentiation from multipotent neural stem cells [93]	Dysregulation of astrocytic MiR-146 and MiR-155, key regulators of the innate immune response [94]	
		Candidate target genes expressed in astrocytes (ApoC2, Cdon, Csrp, Nrep) that may contribute to the RS phenotype [18]		
	Reactivity	Increased GFAP expression in Rett patient [27]	Overexpressed GFAP protein in mutated astrocytes [33]	Increased expression of TNFR2, LIF, S100 β , GFAP in FXS mouse model [30]
		Regulation of GFAP expression by MeCP2 [28]	Increased S100 β protein expression [33]	No consensus regarding the modulation of GFAP expression in FXS patients [32]
			Higher level of reactive oxygen species induced by elevated levels of S100 β and other molecules [33,95]	Reactive astrocytes, but no apparent peripheral immune system activation [96]
	membrane receptors/ ionic channels	Alteration in transcriptional regulation of GLT-1 in MeCP2 astrocytes leading to abnormal clearance of glutamate [29]	Increased expression of mGluR5 in human astrocytes [48]	Downregulation of mGluR5 and GLT-1 dysregulation [14,31]
Downregulation of genes coding for membrane receptors that mediate calcium signaling (mGluR and SUPIR) [20]		Higher level of GLAST in DS astrocytes leading to a higher rate of glutamate uptake [33]	Imbalance between glutamate and GABA in astrocytes [97]	
Downregulation of genes involved in potassium uptake [20]		Increased spontaneous calcium fluctuation in astrocytes [65]		
Impairments in supporting neuronal maturation		Astrocytes regulate dendritic branching and density of excitatory synapses (rescue experiment) [42]	Decreased spine density of wild-type neurons co-cultured with DS astrocytes [44,45]	Inhibition of in vitro neuronal growth and delay in the formation of excitatory synapses in absence of FMRP in astrocytes [40,41]
		Astrocytes fail to support normal dendritic morphology due to altered protein secretion [81]	Deficits in TSP-1 secretion leading to spine and synaptic pathology [45]	Deficits in TSP-1 secretion leading to spine and synaptic pathology [47]
		Abnormal astroglial regulation of BDNF, cytokines production and p38MAPK pathway that may induce adverse effects on neuronal morphology [98]	Reduced astroglial intracellular ionic zinc involved in cellular processes related to growth and differentiation [99]	Alterations in neuronal proliferation due to astrocyte secreted factors [100]
		Adverse effects of mutant astrocytes differentiated from RS patients-specific iPSCs on wildtype neurons [101]	Dysregulation of the mTOR pathway regulating essential physiological functions including cell growth and synaptogenesis [44]	Increased spine density and altered dendritic development in an astrocyte-specific Fmr1 KO mouse model [32,102]
		Dysregulation of astrocytic secreted protein Chromogranin B and lipocalin-2 may exert negative non-cell autonomous effects on neuronal properties, notably dendritic morphology [17]		Abnormal dendritic development due to an excess of astrocyte-derived Neurotrophin-3 [96]

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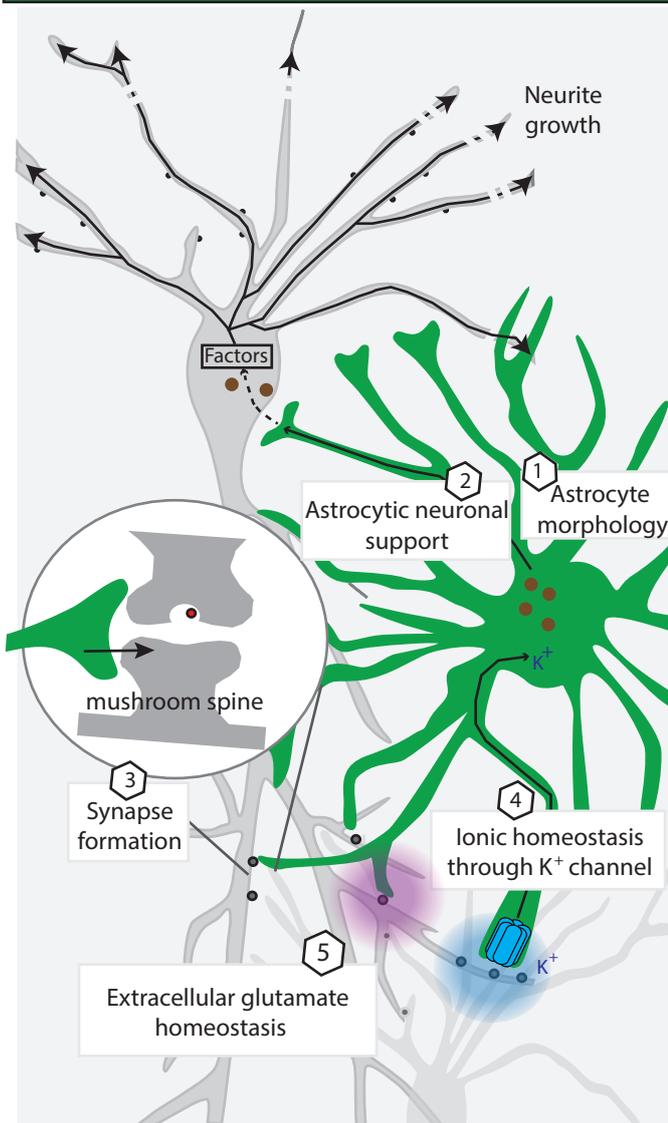
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Normal Physiology



Intellectual Disability

