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Role of fragile X messenger ribonucleoprotein 1 in the pathophysiology of brain disorders: a glia perspective

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ABSTRACT

Fragile X messenger ribonucleoprotein 1 (FMRP) is a widely expressed RNA binding protein involved in several steps of mRNA metabolism. Mutations in the *FMR1* gene encoding FMRP are responsible for fragile X syndrome (FXS), a leading genetic cause of intellectual disability and autism spectrum disorder, and fragile X-associated tremor-ataxia syndrome (FXTAS), a neurodegenerative disorder in aging men. Although FMRP is mainly expressed in neurons, it is also present in glial cells and its deficiency or altered expression can affect functions of glial cells with implications for the pathophysiology of brain disorders. The present review focuses on recent advances on the role of glial subtypes, astrocytes, oligodendrocytes and microglia, in the pathophysiology of FXS and FXTAS, and describes how the absence or reduced expression of FMRP in these cells can impact on glial and neuronal functions. We will also briefly address the role of FMRP in radial glial cells and its effects on neural development, and gliomas and will speculate on the role of glial FMRP in other brain disorders.

1. Introduction

Fragile X messenger ribonucleoprotein 1 (FMRP) is an RNA binding protein, is encoded by the fragile X messenger ribonucleoprotein 1 gene (*FMR1*) located on Xq27.3, and plays a key role in several steps of RNA metabolism, i.e. mRNA transport, alternative splicing, editing, and translation (Maurin et al., 2014; Richter and Coller, 2015). FMRP binds hundreds of mRNAs in the mouse brain, including transcripts that codify for synaptic proteins or proteins linked to autism spectrum disorder (ASD) (Darnell et al., 2011); for many of these mRNAs, e.g. those encoding CAMKIIα (Liu et al., 2018), MAP1B (Lu et al., 2004), MBP (Li et al., 2001), PDE2A and NR2B (Maurin et al., 2018), FMRP functions as an inhibitor of translation, but it can also promote translation of other FMRP-target transcripts, e.g. mRNAs encoding SOD1 (Bechara et al., 2009), potassium channel Kv4.2 (Gross et al., 2011), DGKk (Tabet et al., 2016) (see Maurin and Bardoni, 2018 for a review). FMRP can inhibit the translation of specific mRNAs through the association with stalled polyribosomes (Feng et al., 1997a; Stefani et al., 2004; Darnell et al., 2011) and the interaction with microRNAs and components of the RNA-induced silencing complex (Jin et al., 2004; Muddashetty et al., 2011; Li et al., 2014). Importantly, FMRP regulates local translation at synapses (reviewed in Banerjee et al., 2018). Alongside its canonical function as a translation regulator, growing evidence indicates that FMRP plays key roles in the nucleus (Dockendorff and Labrador, 2019). In addition to regulating RNA editing, splicing and nuclear export of target mRNAs, FMRP contributes to the maintenance of genome stability, by limiting the expression of transposable elements (Jiang et al., 2016) and the formation of double strand breaks during replicative stress (Dockendorff and Labrador, 2019; Chakraborty et al., 2020), and by modulating DNA damage response (Alpatov et al., 2014) and repair pathways (Alpatov et al., 2014; Ledoux et al., 2023; Chakraborty et al., 2022). FMRP can also interact with several proteins, including regulatory proteins and channels, modulating their function (Deng et al., 2013; Ferron, 2016; Castagnola et al., 2018) and is recruited in stress granules (SGs) during stress, suggesting that it participates in the integrated stress response (Di Marco et al., 2021).

FMRP expression has been studied in different species, although most studies have been performed in mice (see Table 1). FMRP is ubiquitously expressed in the body, with the highest levels observed in the brain and testes in both humans (Devys et al., 1993; Tamanini et al., 1997) and mice (Khandjian et al., 1995). Western blot experiments performed in different brain regions of young mice revealed that FMRP is expressed highly in the cortex and olfactory bulb, moderately in the hippocampus, cerebellum and striatum, while brain stem and spinal

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Table 1
Brain FMRP expression and cellular distribution in humans and rodents.

SPECIES	AGE	SAMPLE		TECHNIQUE	EVIDENCE	CITATION
		BRAIN REGION	CELL CULTURE TYPE			
HUMAN	Not indicated	Whole brain		IHC (hybridoma cultures supernatant)	FMRP is highly expressed in neurons; low levels are detected in glia. Strong staining in the ctx and crb. Low levels in the white matter.	Devys et al., (1993)
	Adult	Ctx, crb,brain stem		IHC (Ab1C3)	FMRP is expressed in the cytoplasm of neurons. Strong expression in Pj cells.	Tamanini et al., (1997)
	Fetus (18 weeks)	Brain		IHC (Ab1C3)	FMRP is present in the cytoplasm of neurons.	Tamanini et al., (1997)
	Embryos (3–7 weeks) Fetus (16–25 weeks)	Whole embryo and fetal brain		IHC (Ab1C3)	FMRP is present in embryos. Intense staining in the neuron rich regions of the fetal brain. Expression in dendrites and the most proximal part of axons. Low levels in astrocytes, OLGs and axons.	Agulhon et al., (1999)
	Fetus (22 weeks)	Brain		IHC (Abcam, 17722)	FMRP is expressed in mature OLGs.	Giampetruzzi et al., (2013)
	Adult (57–96 years)	Brain stem		IHC (Abcam, 17722)	FMRP is widely expressed, but not ubiquitous in the human brain stem. The pontine nuclei, the abducens nucleus and the principle nucleus of the inferior olive had fewer FMRP positive neurons.	Beebe et al., (2014)
RAT	Young adult	Whole brain		IHC (mAb1a, Devys et al., 1993)	FMRP is highly expressed in neurons; glial labeling is minimal.	Feng et al., (1997b)
		Whole brain		Immunogold labeling and EM analysis (mAb1a, Devys et al., 1993)	FMRP is present in the nucleus and cytoplasm of neurons and dendrites. Few immunogold particles are found in the nuclei or cytoplasm of astrocytes or OLGs.	
	P12-P15	Ctx, hipp, crb		IHC, EM analysis (Ab1C3)	FMRP is present in spines, dendrites and somata, but not in axons, neuronal nuclei, or glia.	Weiler et al., (1997)
	Neonate	Brain	Primary cultures of OLGs	ICC FMRP-A2B5; FMRP-O1 (Ab1C3)	FMRP is present in the cytoplasm, soma and developing processes. High levels in OPCs, low levels in differentiated OLGs. No detection in mature OLGs.	Wang et al., (2004)
			OLGs cell lines (CG4, C6)	ICC (Ab1C3)	FMRP is detected in the soma and extending processes.	
				WB (Ab1C3)	FMRP expression declines upon differentiation.	
	P1-P3	Brain	Cultured OLGs	WB performed at 1–3–5 DIV (Abcam, 17722)	FMRP is expressed in cultured OLGs and its expression does not decline as cells progress from immature OLGs to mature OLGs.	Giampetruzzi et al., (2013)
		Brain	Cultured OLGs	ICC FMRP-MBP (Abcam, 17722)	FMRP is expressed in mature OLGs.	
	4 M and 22 M	Dentate girus		WB (Millipore, MAB2160) IHC (Merck, MAB2016)	FMRP expression declines in dentate girus of aged rats.	Smidak et al., (2017)
MOUSE	P10-P12 and adult	Brain and crb		WB (hybridoma culture supernatant or ascites fluid)	FMRP is strongly expressed in brain and crb. Young mice express higher FMRP levels than adult mice.	Khandjian et al., (1995)
	Not indicated	Brain		WB (Ab1C3, Ab734)	FMRP is expressed in the brain.	Bakker et al., (2000)
		Ctx, crb, brain stem		IHC (Ab1C3)	FMRP is highly expressed in the cytoplasm of most neurons. Glial cells are not labeled.	
		Hipp		Immunogold labeling and EM analysis (Ab734)	FMRP is present in the cytoplasm in association with polyribosomes and ribosomes attached to the endoplasmatic reticulum, in the nucleus and the nucleolus.	
	P4, P7, P14, P28	Hipp, crb		WB (Ab1C3)	FMRP expression reachs a peak at the end of the first postnatal week, gradually decreases and remains at a moderate level.	Lu et al., (2004)
	P4, P7, P14, P21, P28	Brain stem		WB (Ab1C3)	FMRP is highly expressed at P7. After the first week, FMRP expression declines and stays at low levels.	Wang et al., (2004)
	P2	Brain	Cultured OLGs	ICC FMRP-NG2, FMRP-MBP (Ab1C3)	FMRP is detected in the soma, cytoplasm and nucleus and it is expressed in progenitors and immature	

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Table 1 (*continued*)

SPECIES	AGE	SAMPLE		TECHNIQUE	EVIDENCE	CITATION
		BRAIN REGION	CELL CULTURE TYPE			
					OLGs. It is not detected in cells expressing high levels of MBP.	
	2–7 days	Brain (exluding crb)	Neurospheres	ICC FMRP-GFAP, FMRP-NG2, FMRP-betaIII tubulin, FMRP-GFAP-vimentin (clone 2F5–1 Ab)	FMRP and glial markers are coexpressed in differentiated neurospheres. FMRP is expressed by betaIII tubulin-positive cells, NG2-positive cells, GFAP-positive cells, betaIII tubulin/GFAP-positive cells and GFAP/vimentin-positive cells.	Pacey and Doering, (2007)
	Embryos (E17), P1, P7, 2 M	Hipp, ependyma of the third ventricle		IHC FMRP-GFAP, FMRP-NG2, FMRP-betaIIItubulin, FMRP-GFAP- vimentin (clone 2F5–1 Ab)	FMRP is expressed by GFAP -positive cells in the hipp of embryos and mice at P1 and P7 but not 2 M. FMRP and GFAP are coexpressed in the ependyma of the third ventricle in the postnatal brain. High coexpression at P7, absence in adult mice.	
	P1	Hipp, corpus callosum		IHC FMRP-Olig 1, FMRP-NG2 (clone 2F5–1 Ab)	FMRP is expressed in OPCs.	
	1–2 M, 4–6 M, 14–16 M	Brain		WB, IHC (Ab1C3)	FMRP expression decreases during development.	Singh et al., (2007); Singh and Prasad, (2008)
	3 M	Brain	Cultured primary hippocampal neurons, primary astrocytes, primary microglia, and primary neuronal precursor cells	WB (the antibody used is not indicated)	FMRP is expressed in all analyzed cells. FMRP levels in astrocytes are lower than in primary hippocampal neurons. Microglia and neural precursor cells express FMRP at comparable levels than neurons.	Yuskaitis et al., (2010)
			BV-2 microglial cells (immortalized cells derived from C57BL6 mice)	ICC (the antibody used is not indicated)	FMRP is expressed in BV-2 microglial cells.	
	P0, P3, P5, P7, P10, P12, P14, P21, P28, adult	Total brain		WB (Ab1C3)	FMRP is strongly expressed during the first two post-natal weeks, then its expression decreases and reaches lower levels during adulthood.	Davidovic et al., (2011)
	P12	Total brain		IHC (Ab1C3)	FMRP is strongly expressed in the brain. High levels in ctx, hipp, str and crb	
	P0-P2		Cultured cortical OLGs	ICC (Abcam, 17722)	FMRP is present in mature OLGs.	Giampetruzzi et al., (2013)
	P10, P24, Adult	Corpus callosum		IHC FMRP-MBP, FMRP-CNP (Abcam, 17722)	FMRP is present in mature OLGs.	
	P0-P3		Cultured cortical astrocytes	WB (2F5 Ab, 7G1 Ab)	FMRP is expressed in cortical astrocytes.	Higashimori et al., (2013)
	P7, P40	Ctx of BAC ALDH1L1 TRAP transgenic mice and CaMKIIα TRAP transgenic mice		TRAP and QRT–PCR approach (7G1 Ab)	FMRP is present in developing and in mature cortical astrocytes. Translating FMRP mRNA levels in astrocytes are 15–20% of those in neurons.	
	P26 Bac Glt1 eGFP mice	Ctx		IHC FMRP-MAP2 (2F5 Ab)	FMRP is expressed in the soma of cortical astrocytes.	
	P1, P3, P7, P14, P21, P28, P35, P42, 2 M	Cxt, crb, brain stem		WB	FMRP expression is highest during the first two postnatal weeks, it decreases around P28 and remains constant through adulthood.	Pacey et al., (2013)
	Adult	ctx		IHC (clone 2F5–1 Ab)	FMRP is expressed in all major neuronal populations.	
	P7	Ctx, crb, brain stem		IHC FMRP-NG2, FMRP-PDGFRα, FMRP-MBP (clone 2F5–1 Ab)	FMRP is highly expressed in neurons, but is also present in OPCs and mature OLGs.	
	P3, P7, P14, P23, P45, adult (3 M-1Y)	Ctx, crb, hipp, str, olfactory bulb, brain stem, spinal cord		WB (Ab1C3)	FMRP is strongly expressed during the first week and gradually decreases thereafter. High expression in the ctx and olfactory bulbs; moderate expression in hipp, crb, str; low expression in brain stem and spinal cord.	Bonaccorso et al., (2015)
	P0-P1		Hippocampal cultured neurons	ICC FMRP-MAP2 (R1 Ab; Adinolfi et al., 1999)	Strong expression in neurons at 3 DIV; high expression at 7 and 13 DIV, decrease at 20 DIV.	
	P0, P10, P20, Young adult (2–3 M)	Cingulate ctx, hipp, crb, str, corpus callosum		IHC FMRP-Neu N, FMRP-S100, FMRP-Iba1, FMRP-NG2 (5C2 Ab; LaFauci et al., 2013)	FMRP/NeuN co-expression in the different brain areas at all ages analyzed. Decline in FMRP/S100 co-expression in str and hipp during development.	Gholizadeh et al., (2015)

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cord exhibit low amount of protein (Bonaccorso et al., 2015). FMRP is abundantly expressed during the first two weeks of post-natal life, peaking at 7–14 days and declines in adulthood (Khandjian et al., 1995; Lu et al., 2004; Wang et al., 2004; Singh et al., 2007; Singh and Prasad, 2008; Davidovic et al., 2011; Pacey et al., 2013; Bonaccorso et al., 2015; Wallingford et al., 2017). High levels of FMRP expression in this temporal window of brain development suggest that the function of FMRP is fundamental during a period of intense synaptogenesis and circuit formation. Early studies investigating the cell-specific expression of FMRP in mammalian brain highlighted a major expression of this protein in neurons, while the expression of FMRP in non-neuronal cells was found negligible in both humans (Devys et al., 1993; Tamanini et al., 1997; Agulhon et al., 1999) and rodents (Feng et al., 1997b; Weiler et al., 1997; Bakker et al., 2000). However, emerging evidence suggests that although glial cells express FMRP at lower extent than neurons, their function can be regulated by FMRP and can be substantially affected by altered levels of FMRP, particularly during development. While the expression of FMRP in neurons persists in the adult, although at a lower level than in infant or juvenile mice, it declines between the first and the second postnatal week to almost undetectable levels in astrocytes, oligodendrocytes, and microglia (Wang et al., 2004; Pacey and Doering, 2007; Gholizadeh et al., 2015).

Expansions of the CGG-repeats at the 5′-UTR of the *FMR1* gene over 200 repeats lead to silencing of *FMR1* gene and cause fragile X syndrome (FXS), which is a neurodevelopmental disorder, while premutation CGG-repeat expansions (55−200) are associated with the neurodegenerative disorder fragile X-associated tremor-ataxia syndrome (FXTAS) that affects mainly men in the seventh decade. Considering that every aspect of brain functioning involves a glia-neuron partnership, we speculate that changes of FMRP expression in both neurons and glial cells under pathological condition could have a substantial impact on the pathophysiology of brain disorders in which levels of FMRP are modified.

Here, we review the evidence regarding dysfunction of glial cells in both FXS and FXTAS, with a focus on the possible underlying mechanisms involving FMRP. We highlight that these diseases are not exclusively caused by neuronal dysfunctions and that lack/deficiency of FMRP in glial cells can significantly contribute to the pathophysiology of both FXS and FXTAS. We will also discuss the role of FMRP in gliomas and radial glial cells, which are neural progenitor cells, and the consequences of the absence of FMRP in radial glial cells for neural differentiation. While the link between the lack of FMRP and FXS pathophysiology has been extensively investigated, the role of FMRP in the pathophysiology of other brain disorders is much less explored. Thus, we will also touch on neuropsychiatric and neurodevelopmental disorders in which FMRP levels have been found altered, suggesting that changes of FMRP in glial cells might also have a role in their pathophysiology.

2. Fragile X syndrome and glial cells

FXS is the most frequent cause of inherited intellectual disability (ID) and a leading genetic form of ASD. In FXS a moderate to severe ID is often associated with symptoms of autism, epilepsy, and other behavioral disturbances such as social anxiety, hyperactivity, hypersensitivity to sensory stimuli and attention deficits (Cowley et al., 2016; Hagerman et al., 2017). Dysmorphic features such as long face, large and protruded ears and macroorchidism are also observed in individuals with FXS (reviewed in Saldarriaga et al., 2014). The disorder is diagnosed on average around 35–39 months of age, but a diagnosis could also be possible earlier (Bailey et al., 2009). A review of epidemiological studies indicates that FXS affects about 1 in 7,000 males and 1 in 11,000 females worldwide (Hunter et al., 2014). In most cases, FXS is caused by a CGG repeat expansion in the promoter of the *FMR1* gene, which leads to methylation and ensuing transcriptional silencing of the gene and lack/reduction of FMRP (Verkerk et al., 1991; Pieretti et al., 1991). In rare cases, the disease can be caused by point mutations or deletions in the *FMR1* gene (De Boulle et al., 1993; Hammond et al., 1997; Myrick et al., 2014, 2015; reviewed by Suhl and Warren, 2015). Females with FXS typically display milder symptoms than males probably due to compensation by the second not-affected X chromosome or by sex hormones regulating *FMR1* gene expression (see Romano et al., 2016 for a review on sex difference in neurodevelopmental disorders).

One of the earliest anatomical findings in the FXS human brain was the observation that the dendritic spines of cortical neurons have an immature elongated appearance (Rudelli et al., 1985; Hinton et al., 1991; Irwin et al., 2001). This observation has been subsequently confirmed in the *Fmr1* knockout (KO) mouse model (reviewed in He and Portera-Cailliau, 2013), which also exhibits seizure susceptibility and behavioral and cognitive traits resembling those observed in FXS patients (Musumeci et al., 2000; Bernardet and Crusio, 2006; Ding et al., 2014; Kazdoba et al., 2014). Due to the high expression of FMRP in neurons, distinctive features of the FXS mouse model, such as protein synthesis-dependent synaptic plasticity (Huber et al., 2002) and abnormal maturation of dendritic spines (Cruz-Martín et al., 2010) were considered cell-autonomously dependent on the lack of FMRP in neurons. In contrast, the contribution of glia in the pathophysiology of FXS

Table 1 (*continued*)

SPECIES	AGE	SAMPLE		TECHNIQUE	EVIDENCE	CITATION
		BRAIN REGION	CELL CULTURE TYPE			
					Decline in FMRP/Iba1 co-expression and in FMRP/NG2 co-expression during development in all brain areas analyzed except for cingulate ctx.	
	P7, P14, P21	Hipp		WB (Cell Signaling, 4317)	FMRP expression is greatest at P7 and declines during development.	Wallingford et al., (2017)
		Ctx		WB (Cell Signaling, 4317)	FMRP expression is greatest at P14, and then, by P21, declines to a lower level than that expressed at P7.	
	P40-P45	Whole brain		IHC (7G1 Ab, 2F5 Ab)	Widespread distribution of FMRP-rich cells throughout the brain. High expression in the olfactory bulbs, isocortex, hipp, thalamus, and crb. It is extensively localized in the cytoplasm. Low levels are detected in glia.	Zorio et al., (2017)

The anti-FMRP antibodies used in different articles are indicated in the table. Crb: cerebellum; ctx: cortex; DIV: day in vitro; EM: electron microscopy; hipp: hippocampus; ICC: immunocitochemistry; IHC: immunohistochemistry; M: months; P: postnatal days; Pj: Purkinje; str: striatum; WB: Western blot; TRAP: Translating Ribosome Affinity Purification; QRT-PCR: Quantitative Real Time PCR; OLGs: oligodendrocytes; OPCs: OLGs precursor cells; A2B5, NG2, Olig1, PDGFR2α: markers of OPCs; betaIII tubulin: marker of neuronal differentiation; CNP, MBP: markers of mature OLGs; GFAP, S100: markers of astrocytes; Iba1: marker of microglia; MAP2, NeuN: markers of neurons; O1: marker of immature OLGs.

has been considered irrelevant until recently.

Glial cells are about half of all neural cells in the central nervous system (CNS) of mammals (von Bartheld et al., 2016) and include astrocytes, microglia and oligodendrocytes. Astrocytes, the star-shaped brain cells, are the most abundant glial cell type in the CNS and play a key role in regulating synaptic function during development and adulthood. They provide metabolic and trophic support to neurons (Banker, 1980), control synapse formation, maturation, elimination and function, modulate synaptic transmission (Paixão and Klein, 2010; Chung et al., 2015; Allen and Eroglu, 2017) and, together with microglia, are regulators of inflammatory response. Microglia act as the resident immune cells in the brain and are the main actor in neuroinflammation (Kwon and Koh, 2020; Borst et al., 2021). Microglia also provide support through secretion of pro-survival molecules, refine synaptic connections and are involved in neuroprotection and regulation of neuronal activity, synaptic plasticity and learning and memory (Cornell et al., 2022). Oligodendrocytes, the myelin-forming cells of the CNS, maintain nerve impulse conduction and provide nutrition for axons (for a review see Bergles and Richardson, 2016).

Glial cells have emerged to play an active role in the formation and functioning of neuronal circuits participating in information processing and storage. Indeed, emerging evidence suggests that glial cells are important for higher cognitive functions and for setting normal behavioral responses to environmental stimuli. Interestingly, a recent study suggests that protein synthesis in astrocytes is crucial for synaptic plasticity and consolidation of long-term memory (Sharma et al., 2023). Abnormalities of glial cells are common in neurological and psychiatric disorders and are believed to participate in their pathophysiology (see Elsayed and Magistretti, 2015 for a review).

Several studies now demonstrate that lack of expression of FMRP in astrocytes, oligodendrocytes or microglia has a prominent role in causing different aspects of FXS pathological phenotype (see below). The contribution of glial cells in determining FXS phenotypes has also been suggested by *indirect* evidence obtained combining viral and mouse genetic approaches to delete or re-express FMRP in neurons. Indeed, the re-expression of FMRP in neurons of *Fmr1* KO mice was able to correct abnormal repetitive behaviors and social dominance, but it did not revert other pathological behaviors such as motor hyperactivity, ultrasonic vocalizations, and audiogenic seizures (Gholizadeh et al., 2014). The contribution of glial cells in the spine phenotype of FXS has also been proposed, with interesting differences between development and adult life that suggest a cell-autonomous function of FMRP in spine dynamics during development and the contribution of factors extrinsic to neurons in adult life (Gredell et al., 2023). The contribution of altered mechanisms of glia/neuron communication in mediating defective glial phagocytic clearance of developmentally transient neurons has been highlighted in the Drosophila model of FXS (Vita et al., 2021; Song and Broadie, 2023). These authors demonstrated that FMRP is required in neurons to regulate neuron/glia communication and to drive glial phagocytic clearance, which is important to establish the correct brain circuit connectivity during development. Similarly, a defect of microglia engulfment of synaptic proteins during synaptogenesis has been detected in the mouse model of FXS (Jawaid et al., 2018).

2.1. FXS and Astrocytes

2.1.1. FMRP expression in astrocytes and dysregulated gene expression in Fmr1 KO astrocytes

The expression of FMRP in developing glial cells/astrocytes was observed both in cultured cells and brain slices. Pacey and Doering first showed that FMRP was present in cells of the astrocytic lineage in neurospheres isolated from postnatal mouse brains and differentiated into glial cells *in vitro* (Pacey and Doering, 2007). They detected FMRP in both differentiated astrocytes expressing glial fibrillar acidic protein (GFAP) and progenitors expressing both vimentin and GFAP. The presence of FMRP in GFAP-positive cells was also detected by immunohistochemistry in the hippocampus and ependyma of third ventricle of fetal (E17) and neonatal mice up to post-natal day (PND) 20, but not in young 2 month old adult mice (Pacey and Doering, 2007). The presence of FMRP in developing, but not in mature astrocytes was subsequently confirmed in the hippocampus by Gholizadeh and collaborators (2015), who also reported a decline of FMRP expression in astrocytes in the striatum, but not in the cingulate cortex, cerebellum and corpus callosum. By using a mouse in which the enhanced green fluorescent protein (EGFP) reporter is highly expressed in the soma of most mature cortical astrocytes, Higashimori and colleagues detected the presence of FMRP in mature astrocytes; furthermore, they also provided evidence, by using a translation ribosome affinity purification (TRAP)-quantitative RT-PCR approach, that FMRP is actively translated not only in developing (PND7), but also in mature cortical astrocytes (PND40), although at lower extent than in neurons (15–20%) (Higashimori et al., 2013). The absence of FMRP in astrocytes, particularly during brain development, may alter the expression of key proteins whose mRNAs are FMRP direct targets, but may also cause changes in astrocytic gene expression as a consequence of genomic instability; dysregulation of astrocytic gene expression may also indirectly result from the FMRP loss of function in other cell types. These direct and adaptive changes of proteins expression may in turn influence synaptic development of adjacent neurons and may account for synaptic dysfunctions observed in FXS (Fig. 1). Indeed, several mRNAs that are highly enriched in astrocytes such as *SLC1A2* (*GLT1,* encoding glutamate transporter 1), *GLUL* (encoding glutamine synthetase), *APOE* (encoding apolipoprotein E), *SPARCL1* (encoding Hevin) mRNAs are targets of FMRP (Darnell et al., 2011; Ascano et al., 2012; Maurin et al., 2018) and levels of proteins encoded by some of these mRNAs are abnormal in *Fmr1* KO mice and brain tissue from FXS patients (Higashimori et al., 2016; Wallingford et al., 2017; see below). In addition, a single cell transcriptomic study, performed in the cortex of wild type (WT) and *Fmr1* KO mice at PND5 revealed that changes in the mRNAs levels are cell type specific: while neurons were mostly affected by the absence of FMRP with FMRP-bound transcripts being mainly down-regulated (e.g. *Camkk2, Camk2b, Vamp2, Slc1a4, Nrxn1)*, in astrocytes, oligodendrocytes and endothelial cells major changes occurred in the expression of genes that are not target of FMRP (e.g. *Mt1*, *Mt2, Ephb3, Slc6a1, Slc6a, Slc30a10* in astrocytes, *Slc7a5* in endothelial cells). Interestingly, the same groups of genes encoding synaptic, plasma membrane and adhesion proteins that were down regulated in neurons, were up-regulated in astrocytes. In contrast, other groups of genes, such as those related to translational processes, were equally up-regulated in neurons and astrocytes. As an example, genes dysregulated in astrocytes included *Mt1* and *Mt2*, which were downregulated, and *Ephb3*, *Epha4*, *Gabbr1*, *Gabbr2*, which were up-regulated. Overall, the analysis of cell-specific changes in gene expression suggested that *Fmr1* KO astrocytes can contribute to FXS pathogenesis by favoring an environment of increased excitability (Donnard et al., 2022).

In line with this finding, single-cell RNAseq analyses performed on satellite glial cells of 28–30 day old WT and *Fmr1* KO mice showed that 111 genes were upregulated and 19 genes downregulated in *Fmr1* KO cells. Satellite glial cells are specialized glial cells that envelope the soma of neurons of dorsal root ganglia and share several properties with astrocytes (Hanani and Verkhratsky, 2021). Upregulated genes are involved in calcium signaling (such as *Trpc3, Syt1, Dpep1, Kcnh1*), vesicle organization (such as *Rph3a, Syt1, Vamp1, D*nm1) and chemical synaptic transmission (such as *Gabbr2, S*yt1, *Plp1, Slc17a6, Slc17a7, Gabrg2*), whereas downregulated genes are implicated in response to cytokine stimulus (*Myc, Lcn2, Ccl2, Irf8, Cxcl1*) and inflammatory response (such as *CybB, Ccl2, Cxcl1*). These dysregulations are associated with a disruption of sensory neuron-satellite glial cells association. Considering the role of these cells in regulating sensory neuron function, impaired neuron-glia association may contribute to sensory deficits observed in FXS (Avraham et al., 2022).

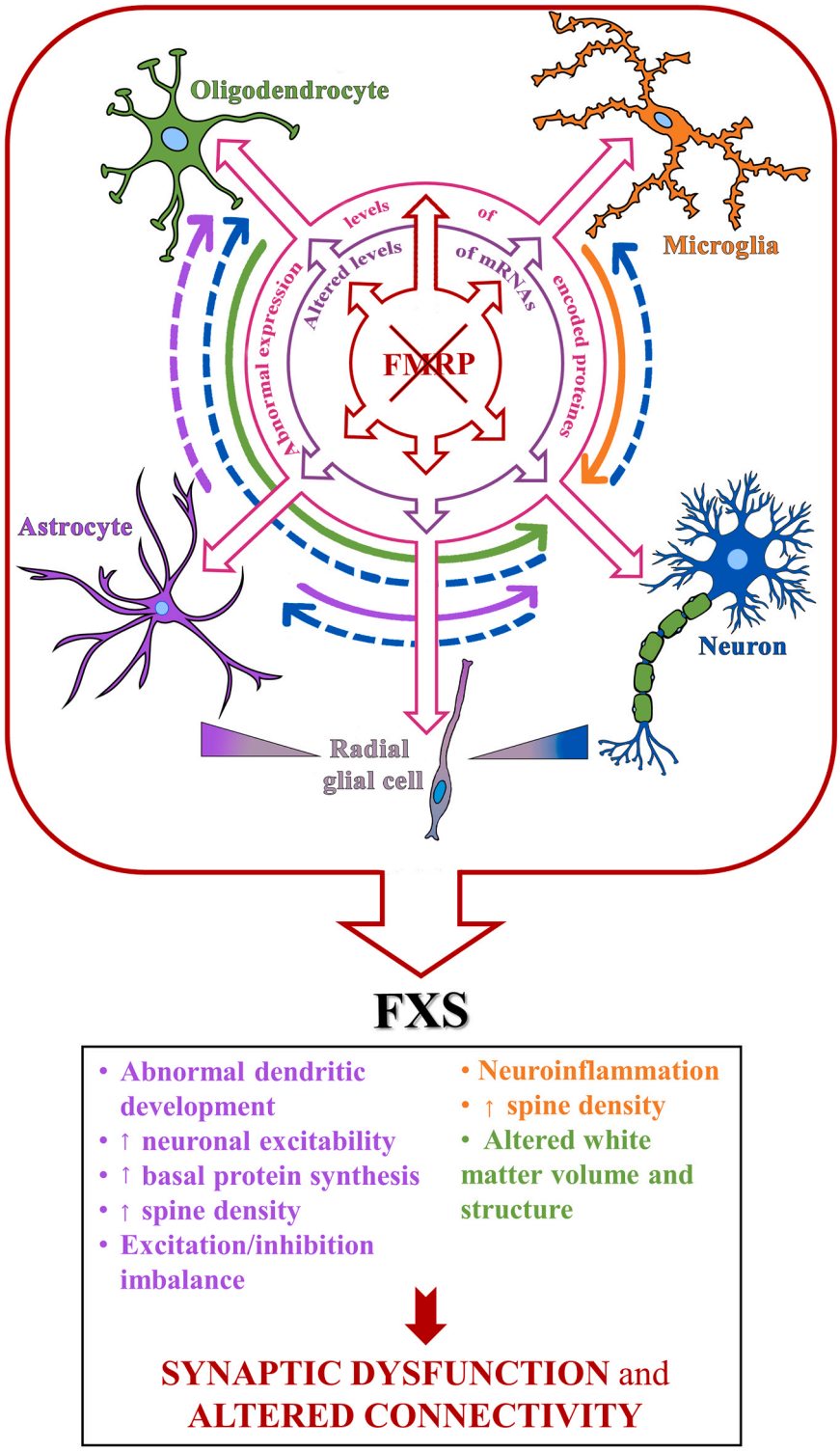

Fig. 1. Schematic representation that illustrates how the absence of FMRP can cause changes in neurons and glial cells responsible for the pathological phenotype observed in Fragile X syndrome. The absence of FMRP alters the expression of key proteins whose mRNAs are FMRP targets in glial cells and neurons, but may also cause changes of gene expression in all cell subtypes as an indirect consequence of its loss of function in other cell types. Changes in the encoded proteins lead to dysfunctions in glial and neuronal cells and affect the fate of neural precursors. All these alterations are responsible for the pathological phenotypes observed in FXS. A detailed description of changes in glial cells is reported in the text. The effects of FMRP deficiency in astrocytes, microglia and oligodendrocytes are indicated in purple, orange and green respectively. Continuous arrows indicate a direct involvement of one cell subtype in alterations found in another subtype; dashed arrows indicate an indirect or hypothesized role. The heat maps show the possible changes of cell fate specification in the absence of FMRP from radial glial cells (mauve) towards astrocytic (purple, on the left) or neuronal lineage (blue, on the right), as described in the paragraph "FMRP, radial glial cells and neurogenesis".

2.1.2. Abnormal astrocyte-neuron crosstalk and synaptic dysfunction in FXS

2.1.2.1. In vitro and ex-vivo studies in FXS mouse models: role of astrocytes in neuronal development. The possible contribution of astrocytes to the abnormal neuronal development occurring in FXS was first suggested by co-culture studies showing that WT hippocampal neurons grown in the presence of *Fmr1* KO astrocytes exhibited abnormal dendritic morphology, with increased dendritic branching, shorter neurites, and overall reduced arbor area at 7 days *in vitro* (DIV), but not at later developmental stages (Jacobs and Doering, 2010; Jacobs et al., 2010). Interestingly, these dendritic defects were significantly rescued when neurons were grown on a monolayer of WT astrocytes. *Fmr1*-deficient astrocytes also affected synapse formation at 7 and 14 DIV, but not at 21 DIV, with neurons grown on *Fmr1* KO astrocytes having more excitatory synapses than neurons grown on WT astrocytes (Jacobs et al., 2010). Interestingly, both excitatory and inhibitory hippocampal neurons were affected (Jacobs et al., 2016). On the same line, another paper confirmed that *Fmr1* KO astrocytes can induce an abnormal neuronal dendritic development of cultured cortical neurons and showed that this occurs through an excessive astrocytic production and release of neurotrophin-3, whose mRNA is a target of FMRP (Yang et al., 2012a). The same group showed an imbalanced release of glutamate and GABA in cultured astrocytes that was associated with increased levels of glutaminase and GABA transaminase expression (Wang et al., 2016). In line with the above-described *in vitro* studies showing increased levels of glutamate, western blot analysis revealed a reduction of the astroglial glutamate transporter (GLT1) in *Fmr1* KO mice and in human FXS cortical tissues (Higashimori et al., 2013, 2016). By using inducible astrocyte-specific *Fmr1* conditional KO and restoration mouse models these authors confirmed the reduction of GLT1 in *Fmr1* KO cultured astrocytes (immunoblot results) and demonstrated that the ensuing impairment of glutamate uptake contributes to increased neuronal excitability, increased spine density and increased protein synthesis, which are hallmarks of FXS pathology (Higashimori et al., 2016). The reduction of GLT1 expression in *Fmr1* KO astrocytes was related to the reduced levels of metabotropic glutamate receptor subtype 5 (mGlu5) (immunoblot results) (Higashimori et al., 2013), which mediates the neuron-mediated increase of glutamate transporters in astrocytes (Aronica et al., 2003). Mechanistically, the reduction of mGlu5 receptor protein levels in astrocytes was related to the up-regulation of miR-128–3p, a miRNA involved in neurogenesis, memory formation and neuronal excitability (Men et al., 2020). Notably, both GLT1 and mGlu5 mRNAs are target of FMRP (Darnell et al., 2011; Ascano et al., 2012; Maurin et al., 2018). Thus, the downregulation of both proteins may also be a direct consequence of the absence of FMRP in astrocytes. The downregulation of mGlu5 receptors in glial cells was more robust in early post-natal stages, suggesting again that the impact of FMRP loss in astrocytes may be more pronounced during early development. Consistent with GLT1 and mGlu5 reduction, a significant decrease of GLT1 and mGlu5 receptor mRNA levels have been found in cortical astrocytes isolated by an immunopanning procedure from cortex of 7 days old *Fmr1* KO mice (Caldwell et al., 2022). Interestingly, the lack of FMRP caused changes in the expression levels and in the localization of several mRNAs enriched at cortical astroglial processes, supporting the possible involvement of protein dysregulation occurring in the astroglial processes in the pathogenesis of FXS (Men et al., 2022). In line with a reduction of mGlu5 expression in *Fmr1* KO astrocytes, we have recently found that mGlu5 receptor mediated-phosphoinositide hydrolysis is reduced in both the cortex and hippocampus of *Fmr1* KO mice (Di Menna et al., 2023). It would be interesting to test the hypothesis that this blunted response is caused by reduction of mGlu5 receptor-mediated signaling in astrocytes.

2.1.2.2. In vitro and in vivo studies in FXS mouse models: alteration of astrocytic secretome. Astrocytes can influence both synaptogenesis and synapse maturation through secretion of astrocytic soluble factors, including matricellular proteins, such as thrombospondins (TSPs-1–4), SPARC, SPARC-like 1 (Hevin), and Tenascin C (TNC). The expression of these proteins has been found to be altered in FXS mouse, possibly contributing to abnormal neuronal dendritic development and altered connectivity observed in FXS (Wallingford et al., 2017; Krasovska and Doering, 2018; Reynolds et al., 2021a).

Hevin and SPARC regulate excitatory synaptogenesis *in vitro* and *in vivo* (Kucukdereli et al., 2011; Jones and Bouvier, 2014). Levels of these proteins were found to be down- or up-regulated in *Fmr1* KO mice in a region and age-specific manner. In detail, Hevin exhibited increased protein levels in the cortex of PND14 F*mr1* KO mice and decreased levels in the hippocampus of PND7 *Fmr1* KO mice compared to WT, whereas SPARC levels were found reduced in the cortex of *Fmr1* KO mice at PND7 and PND14. Western blotting analysis confirmed increased levels of Hevin in astrocytes isolated with magnetic-activated cell sorting from cortices of PND14 *Fmr1* KO mice (Wallingford et al., 2017). Furthermore, in line with the role of Hevin in the establishment and maintenance of excitatory thalamocortical synapses, an increased density of thalamocortical synapses was observed in WT cortical and thalamic co-cultured neurons grown in the presence of *Fmr1* KO cortical astrocytes (Wallingford et al., 2017).

TSP-1 is secreted from astrocytes and promotes the formation of excitatory synapses (Christopherson et al., 2005; Eroglu et al., 2009). An *in vitro* study detected a small yet significant decrease of TSP-1 levels in *Fmr1* KO cultured cortical astrocytes and their conditioned media; interestingly, addition of TSP-1 reverted spine and synaptic alterations in *Fmr1* KO cultured neurons (Cheng et al., 2016). In another study, *Fmr1* KO cultured cortical astrocytes exhibited an increased expression of $P2Y_2$ and $P2Y_6$ purinergic receptors and ensuing production/secretion of TSP-1 upon activation of purinergic receptors (Reynolds et al., 2021a). These authors also detected an increased TSP-1 expression in the cortex of *Fmr1* KO mice at PND7-PND14, but no changes at PND1 and PND21 (Reynolds et al., 2021a). This increase in a specific temporal window could be related to a transient function of TSP-1 during the critical period of synaptogenesis. The different results obtained by Cheng (2016) and Reynolds (2021a) could be reconciled considering that the two studies were performed in cultures and tissues, respectively. The increased expression of purinergic receptors might be a compensatory mechanism to counteract the basal reduced expression of TSP-1 in *Fmr1* KO astrocytes.

TNC is an extracellular matrix glycoprotein secreted by astrocytes and is involved in extracellular matrix re-modeling during tissue repair and synapse development, neuronal migration and plasticity (Jones and Bouvier, 2014; Stamenkovic et al., 2017). Interestingly, TNC induces the production of IL-6 from astrocytes and both TNC and IL-6 have been found to be up-regulated in *Fmr1* KO cortical tissue and astrocytes (Krasovska and Doering, 2018; Reynolds et al., 2021b).

Overall, these data indicate that the imbalance of many secreted factors may contribute to the abnormal formation of synapses and the consequent impaired development of neuronal circuitries observed in FXS.

Indication that extracellular factors secreted by *Fmr1* KO astrocytes can affect neurogenesis came from studies investigating the *in vitro* proliferative capacity of neurospheres originating from stem cells or progenitor cells of newborn hippocampus. Indeed, the presence of *Fmr1* KO astrocytes conditioned medium (ACM) causes increased proliferation of stem cells-derived-neuropheres and decreased proliferation of WT neural progenitor-derived-neurospheres, suggesting a modification of the differentiation program induced by *Fmr1* KO astrocytes secreted factors; on the other hand, *Fmr1* KO progenitor-derived neurospheres showed a decreased proliferation in the presence of both WT and *Fmr1* KO ACM, probably due to their inability to respond to environmental cues (Sourial and Doering, 2016).

Importantly, WT and *Fmr1* KO neurons showed an increased number of excitatory synaptic connections when they were supplemented and maintained for 12 days *in vitro* with ACM from *Fmr1* KO astrocytes (Krasovska and Doering, 2018).

Interestingly, 131 upregulated and 108 downregulated proteins were found in the ACM of cortical astrocytes FXS (PND7) isolated by immunopanning procedure compared to WT. Several of these altered proteins were also detected in cortical astrocytes obtained from mouse models of Rett and Down syndrome (88 proteins upregulated and 32 proteins downregulated). Importantly, two of the detected upregulated proteins (Igfbp2 and BMP6) exert negative effects on neuronal development (Caldwell et al., 2022). These results suggest that alterations in astrocytic secreted factors can be similar in different neurodevelopmental disorders and can affect neuronal development.

All these results support the idea that the identification of factors secreted by astrocytes may be useful for understanding the impact of the extracellular environment on neurons in neurodevelopmental disorders.

2.1.2.3. In vivo imaging and behavioral studies in FXS mouse models. Using transgenic mice in which deletion of FMRP occurs exclusively in astrocytes, Hodges and collaborators found that adult mice lacking FMRP in astrocytes exhibit impaired motor skill acquisition and increased density of immature thin dendritic spines in the motor cortex. This feature is possibly acquired during development because in adolescent mice the astrocytes-specific deletion of *Fmr1* led to an overproduction of spines, which was not compensated by spine pruning (Hodges et al., 2017). However, in contrast to what reported by Higashimori and collaborators (2016), restoration of FMRP in astrocytes failed to completely rescue the abnormal spine morphology and motor skill learning deficits associated with the *Fmr1* KO phenotype, indicating that the presence of FMRP in both astrocytes and neurons is necessary for brain healthy functioning (Hodges et al., 2017). More recently, astroglial *Fmr1* conditional KO mice were also shown to exhibit increased locomotion and hyperactivity and reduced social novelty preference and memory acquisition/extinction deficits. The selective loss of astroglial FMRP also contributes to cortical hyperexcitability by elongating cortical UP state duration and by enhancing NMDA receptor-mediated evoked EPSCs. Interestingly, re-expression of FMRP in astrocytes rescued cortical hyperexcitability, motor hyperactivity and social novelty phenotypes, but had no effects on memory acquisition/extinction deficits (Jin et al., 2021).

Another recent work shows that a reduction of Kir4.1 channel in *Fmr1* KO astrocytes is responsible for impaired extracellular K^+ homeostasis in the hippocampus of *Fmr1* KO mice which in turn contributes to altered behavioral phenotype of *Fmr1* KO mice. Indeed, astroglial Kir4.1 mRNA is a target of FMRP and restoring *Kir4.1* expression selectively in astrocytes corrects neuronal hyperexcitability, cognitive and social interaction deficits in *Fmr1* KO mice (Bataveljic et al., 2024).

Overall, a growing body of evidence is indicative of an altered crosstalk between astrocytes and neurons in the abnormal behavior in FXS, although a better dissection of the impact that loss of FMRP in astrocytes has on different behavioral aspects of FXS phenotype is needed; the underlying mechanisms are beginning to be elucidated and should be deepened in the future, since their identification can lead to the discovery of molecules able to rescue a balanced astrocyte-neuron interaction in FXS.

2.1.2.4. Studies in human-derived astrocytes. The use of patient-derived induced pluripotent stem cells (iPSCs) and human embryonic stem cells (hESCs) makes it possible to assess whether the astrocytic impairments observed in animal models are also present in FXS human cells and provides the possibility to better understand the effect of FMRP deficiency in astrocytes and their contribution to FXS.

Patient iPSCs-derived FXS astrocytes show an alteration of cell cycle dynamics, an increase of ATP-induced Ca^{2+} signaling, an increase of GFAP expression, altered proteomic profiles and dysregulated metabolic and signaling pathways, including altered sterol biosynthesis, but no difference in glutamate uptake (Ren et al., 2023). In agreement with these findings, an altered cholesterol homeostasis in human iPSC derived FXS astrocytes and *Fmr1* KO mouse astrocytes has been found. This alteration was associated with a reduction of expression of the main cholesterol efflux transporter in astrocytes ATP-binding cassette transporter A1, accumulation of cholesterol and desmosterol in astrocytes, changes in membrane lipids composition and a dysregulation of the cytokine/chemokine secretome profile (Talvio et al., 2023). Cholesterol is produced by astrocytes and neurons, is an essential component of synapses and is involved in synapse development (Pfrieger, 2003). Thus, alterations of cholesterol levels in astrocytes can contribute to synaptic dysfunctions detected in FXS. Interestingly, decreased serum levels of cholesterol were detected in FXS patients and in a rat model of FXS (Berry-Kravis et al., 2015; Çaku et al., 2017; Parente et al., 2022), suggesting that impaired cholesterol homeostasis is a common feature of brain and peripheral tissues in FXS.

Another study using human FXS and control astrocytes generated from human iPSCs revealed an increased expression and secretion of urokinase plasminogen activator (uPA) in FXS astrocytes (Peteri et al., 2021). Upon binding of uPA with uPA receptors, the zymogen plaminogen is converted into the proteinase plasmin which contributes to remodeling extracellular matrix; however, uPA/uPAR can also activates intracellular signalling pathways involved in regulating several astrocytic and neuronal function (Blasi and Carmeliet, 2002).

Recent results reported that human FXS cortical neurons co-cultured with FXS astrocytes, derived from an iPSC line generated from an FXS patient, exhibit an aberrant electric activity that is related to changes in the persistent sodium currents. The same effect was observed in control neurons grown in the presence of FXS astrocytes or with ACM. Interestingly, these effects were linked to the reduced concentration of the calcium-binding protein S100β in the secretome of FXS astrocytes and the addition of S100β to co-cultures of either control or FXS neurons with FXS astrocytes restores normal electric activity (Das Sharma et al., 2023).

These findings confirm the involvement of astrocytes in FXS and their impact on neuronal functions which had emerged from research on animal models, suggest that astrocyte modulation can restore altered phenotypes in FXS, and underscore the importance of performing more studies in humans to reveal novel dysregulated biochemical pathways in FXS astrocytes.

2.1.3. Morpho-functional properties of astrocytes are abnormal in FXS

2.1.3.1. Astrocyte-neuron/synapse association. Compared to WT mice, *Fmr1* KO mice show a decrease of astrocytic processes at the synaptic cleft in both the hippocampus (Jawaid et al., 2018) and somatosensory cortex (Simhal et al., 2019). This reduced association together with reduced levels and functioning of GLT1 can explain the impaired glutamate uptake observed in the inducible astrocyte-specific *Fmr1* conditional KO mice (Higashimori et al., 2016). These results further highlight the contribution played by astrocytes in synaptic dysfunctions and hyperexcitability observed in FXS.

2.1.3.2. GFAP overexpression and reactive gliosis. Several studies report an increased expression of GFAP in FXS, which is a hallmark of reactive gliosis. Astrogliosis or reactive gliosis has long been considered a secondary nonspecific reaction to pathological conditions and is characterized by morphological, molecular, and functional changes in astrocytes. Yuskaitis and collaborators first detected an increased GFAP expression in the striatum, hippocampus and cerebral cortex of adult *Fmr1* KO mice (immunoblot results); interestingly, this GFAP overexpression was reduced after a treatment with lithium, which inhibits glycogen synthase kinase-3, a serine threonine protein kinase involved

in the regulation of several functions such as gene expression, apoptosis and inflammation (Yuskaitis et al., 2010). Complementary to these data, Lee and collaborators observed a prominent GFAP expression in *Fmr1* KO mice and increased GFAP levels and hypertrophy in cortical astrocytic cultures (immunoblot and immunohistochemistry results) (Lee et al., 2019). Similarly, astrocyte activation was also detected in the cerebella of *Fmr1* KO mice; this increased expression begins in the second postnatal week, persists into adulthood and it is not related to microglia activation (Pacey et al., 2015). However, others failed to reveal astrogliosis in both global and astrocytic selective *Fmr1* KO mice (Higashimori et al., 2013; Hodges et al., 2020).

The meaning of reactive gliosis in FXS is not clear. The up regulation of GFAP might be indicative of a chronic stress response and is in line with the increased oxidative stress found in FXS. On the other side, an increased expression of GFAP has been related to an increased number of astrocytes as result of an unbalanced glia-neuron differentiation (see paragraph on radial glial cells). In addition, considering the importance of astrocytes in the regulation of myelination (Domingues et al., 2016), the increased expression of GFAP could also be a mechanism to compensate for the reduced myelination observed in *Fmr1* KO mice (Pacey et al., 2013) (see paragraph myelination in FXS). Given the role of glia-glia crosstalk in brain function during development and disease, glia-glia interaction is another issue to be better investigated in FXS (see below).

2.1.3.3. Oxidative homeostasis and mitochondrial dysfunction. Astrocytes play a role as regulators of oxidative homeostasis, acting as a source of antioxidant enzymes and reactive oxygen species (Hart and Karimi-Abdolrezaee, 2021). In the brain of *Fmr1* KO mice, increased levels of reactive oxygen species (ROS), increased lipid peroxidation and protein oxidation have been detected at different ages (el Bekay et al. 2007; Davidovic et al., 2011; D'Antoni et al., 2020). Increased ROS levels in FXS are associated with mitochondrial dysfunction (D'Antoni et al., 2020) and are possibly exacerbated by reduced levels of SOD1 (Bechara et al., 2009), a well-known enzyme with antioxidant properties involved in several functions including activation of nuclear gene transcription following exposure to oxidative stress (for a review on SOD1 see Eleutherio et al., 2021). *Fmr1* KO cortical cultured astrocytes showed increased ROS production, whereas mitochondrial respiration was comparable to that of WT astrocytes (Vandenberg et al., 2021). A subsequent study from the same group revealed that the increased ROS production was present only in male *Fmr1* KO cortical astrocytes when grown in high O_2 tension (21%, normoxic), but not in low tension (3%, physiological hypoxia). In contrast, both male and female *Fmr1* KO astrocytes grown in hypoxia showed an increased oxygen consumption (Vandenberg et al., 2022), in line with the increased activity of mitochondrial chain complexes found in the cortex of *Fmr1* KO mice (D'Antoni et al., 2020). The difference between the two sexes may depend on the effect of estrogens on the expression of antioxidants (Borrás et al., 2003).

Mitochondrial fractions and extracellular vesicles of *Fmr1* KO astrocytes show a decreased expression of mitochondrial proteins (such as MT-CO1, ATP5A, ATPB, and VDAC1), which result in a reduction of mitochondrial membrane potential in *Fmr1* KO cortical astrocytes (Ha et al., 2021). These findings support the idea that not only mitochondrial dysfunction may contribute to the pathogenesis of FXS (Shen et al., 2019; D'Antoni et al. 2020), but also that mitochondrial dysfunction in astrocytes may play an important role in the disease. We believe that this aspect needs to be better investigated.

2.1.3.4. Stress granule formation. SGs are membrane-less structures composed of stalled preinitiation complexes, RNAs and proteins, including initiation factors and RNA-binding proteins that scaffold untranslated mRNAs and interact with each other (Anderson and Kedersha, 2002; Buchan and Parker, 2009; Protter and Parker, 2016). These cytoplasmic aggregates are formed only under stress conditions and their composition varies according to the type of cellular stress, cell type and disease. They are dynamic structures, and their assembling and disassembling are influenced by several factors including post-translational modification which alter protein-protein interactions (reviewed in Protter and Parker, 2016). These aggregates are involved in neurodegenerative disease, myopathies and cancer (Li et al., 2013; Ramaswami et al., 2013; Zhou et al., 2023). FMRP is present in SGs, and its absence affects their formation (Didiot et al., 2009). We have found that cortical astrocytes obtained from *Fmr1* KO mice exhibit a reduced number of SGs in response to oxidative insults (Di Marco et al., 2021). The reduced formation of these granules supports an additional vulnerability of FXS phenotype to cope with several stressors and may be associated with an increased susceptibility to apoptosis (Arimoto et al., 2008).

Dysfunctions observed in astrocytes are summarized in Table 2 and the consequences of astroglial alterations on neurons are reported in the Fig. 1.

2.2. FXS and microglia

2.2.1. FMRP deficiency and microglia dysfunctions

FMRP expression was detected in cultured microglia (Yuskaitis et al., 2010) and in resident microglia in different mouse brain regions such as corpus callosus, cingulate cortex, striatum, hippocampus and cerebellum, with a strong expression in the first 2–3 postnatal weeks (Gholizadeh et al., 2015). A slight reduction in the number of microglial cells was observed in the neocortex of adolescent (4 weeks) *Fmr1* KO mice (Lee et al., 2019). In addition, a reduced ability of microglia to exert synaptic pruning has also been reported in *Fmr1* KO mice at three weeks of age (Jawaid et al., 2018). Overall, these observations are in line with the increase of dendritic spine density detected in *Fmr1* KO mice at different ages. In contrast, no difference in the number of microglial cells was detected in the auditory brainstem nuclei between infant WT and *Fmr1* KO mice (PND6 and PND14) (Rotschafer and Cramer, 2017).

FMRP-deficient microglia exhibit an exaggerated pro-inflammatory response and a mitochondrial vulnerability to inflammation. An *in vitro* study using cultured cortical microglia isolated from WT and *Fmr1* KO neonate mice, reports that upon LPS challenge microglia from *Fmr1* KO mice exhibit an increased gene expression of *IL-6, IL-1β, iNOS and TNFα*, an increased secretion of IL-6 and TNFα and an increased microglia phagocytic activity. In addition, a high mitochondrial membrane potential, and a reduced mitochondrial population and mitochondria area were also observed in *Fmr1* KO microglia under basal condition. LPS stimulation caused a significant decrease in mitochondria perimeter in *Fmr1* KO microglia versus WT microglia and amplified basal differences in mitochondrial function and content suggesting that mitochondria of *Fmr1* KO microglia are vulnerable to inflammation (Parrott et al., 2021). In contrast, Yuskaitis and collaborators (2010) found no differences in the production of TNFα and IL-6 between WT and *Fmr1* KO cultured microglia challenged with LPS, although using slightly different concentration and time lengths of exposure (Yuskaitis et al., 2010).

2.2.2. FXS and immune dysfunction

An important yet unresolved issue is the link between FXS and autism, and particularly the identification of key factors determining the presence of autistic symptoms in FXS. The factors that influence the emergence of different clinical signs and that account for the variability of phenotypic expression in FXS patients are not known. It has been proposed that an altered immune response driven in the brain by microglia and astrocytes may be linked to the pathogenesis of autism (reviewed in Di Marco et al., 2016). Patients with autism exhibit a dysregulated expression of genes involved in immune and inflammatory response, an increased production of cytokines and interleukins (such as IL-1β, IL-6) and microglia activation (reviewed in Erbescu et al., 2022).

Table 2
Alterations in glial cells in the absence of FMRP.

	EVIDENCE	CITATION
ASTROCYTES	Dysregulated gene expression	Avraham et al., (2022); Caldwell et al., (2022); Donnard et al., (2022); Men et al., (2022)
	↑ GFAP expression	Yuskaitis et al., (2010); Pacey et al., (2015); Rotschafer and Cramer, (2017); Sunamura et al., (2018); Lee et al., (2019); Brighi et al., (2021); Ren et al., (2023)
	Altered levels/production of astrocytic secreted factors:	
	↑ neurotrophin 3 release	Yang et al., (2012a)
	↓ TSP-1 intracellular and extracellular expression levels in cortical astrocytes	Cheng et al., (2016)
	↑ production/secretion of TSP-1 after purinergic stimulation in cortical astrocytes	Reynolds et al., (2021a)
	↓ proteins involved in neural progenitor cell proliferation and brain development in the ACM (e.g. MRP1β, MTIF, FEZ2)	Sourial and Doering, (2016)
	↑ Hevin levels in cortical astrocytes	Wallingford et al., (2017)
	↑ TNC and IL-6 levels in cortical astrocytes	Krasovska and Doering, (2018); Reynolds et al., (2021b)
	altered levels of proteins involved in neuronal development and neurite outgrowth in the ACM (e.g. ↑ Igfbp2; BMP6, class 3 semaphorin; ↓ Sulf2, Hdgfrp3, Ptn)	Caldwell et al., (2022)
	Mitochondrial dysfunctions:	
	↑ ROS production in cultured astrocytes	Vandenberg et al., (2021)
	↓ expression of mitochondrial proteins (e.g. MT-CO1, ATP5A, ATB and VDAC1) and ↓ MMP in cultured astrocytes	Ha et al., (2021)
	↑ NOX2 and catalase levels in cortical astrocytes	Vandenberg et al., (2021)
	Altered glutamatergic system:	
	↓ GLT1 expression	Higashimori et al., (2013), (2016); Caldwell et al., (2022); Men et al., (2022)
	↓ mGlu5 receptor expression	Higashimori et al., (2013); Men et al., (2020); Caldwell et al. (2022)
	↑ release of glutamate in the ACM; ↑ glutaminase expression in cultured astrocytes	Wang et al., (2016)
	↓ astrocytic processes in excitatory synapses	Simhal et al., (2019)
	↑ GABA transaminase expression and ↓ monoamine oxidase beta levels in cultured astrocytes; ↓ GABA levels in the ACM	Wang et al., (2016)
	↓ Number of stress granules	Di Marco et al., (2021)
	Altered calcium response:	
	↓ DHPG stimulated calcium response	Higashimori et al., (2013)
	↓ amplitude of $[Ca^{2+}]i$ responses to elevated $[K^+]e$ in human astrocytes	Peteri et al., (2021)
	↑ ATP induced Ca^{2+} signaling in FXS hiPSC-astrocytes and *Fmr1* KO cortical astrocytes	Reynolds et al., (2021a); Ren et al., (2023)
	↓ concentration of the Ca^{2+} binding protein S100β in the secretome of FXS astrocytes	Das Sharma et al., (2023)
	Altered lipid metabolism:	
	↑ lanosterol levels, ↓ cholesterol levels, ↓ levels of enzymes involved in cholesterol synthesis (e.g. CYP51A1, MSM01) in astrocytes derived from FXS patient stem cells	Ren et al., (2023);
	↓ ABCA1 and changes in membrane lipid composition in hiPSC derived FXS astrocytes and *Fmr1* KO astrocytes; accumulation of cholesterol, ↑ desmosterol and polyunsaturated phospholipids in the lipidome of FXS mouse astrocytes	Talvio et al., (2023)
	↓ Kir4.1 channel	Bataveljic et al., (2024)
MICROGLIA	↓ Number in the cortex of *Fmr1* KO mice	Lee et al., (2019)
	Altered phagocytic activity:	
	↓ ability to exert synaptic pruning	Jawaid et al., (2018)
	↑ phagocytic activity after LPS exposure	Parrott et al., (2021)
	Mitochondrial dysfunctions:	
	mitochondrial vulnerability to inflammation; ↑ MMP, ↓ mitochondrial population and mitochondria area under basal condition and LPS exposure, ↓ mitochondria perimeter after LPS exposure in cultured microglia	Parrott et al., (2021)
	Exaggerated pro-inflammatory response: ↑ *IL-6*, *IL-1β*, *iNOS* and *TNFα* gene expression and ↑ IL-6 and TNFα secretion after LPS exposure in cultured microglia	Parrott et al., (2021)
OLIGODENDROCYTES	Downregulation of genes	Donnard et al., (2022)
	Altered myelination:	
	↓ MBP expression, ↓ myelination, ↓ OPCs cells in cerebellum of *Fmr1* KO mice at P7	Pacey et al., (2013)
	↑ Olig2-positive pre-myelinating OLGs in the neocortex of *Fmr1* KO mice	Lee et al., (2019)
	↓ growth of myelin sheaths and ↓ Mbp expression in *fmr1*−/− mutant zebrafish	Doll et al., (2020)
	↑ number of mature and precursors oligodendrocytes in the auditory brain stem of adult (P72-P167) *Fmr1* KO mice	Lucas et al., (2021)

ABCA1: ATP-binding cassette transporter A1; ACM: astrocyte-conditioned medium; hiPSCs: human-induced pluripotent stem cells; LPS: lipopolisaccaride; MMP: mitochondrial membrane potential; OLGs: oligodendrocytes; OPCs: oligodendrocytes precursors cells; P: postnatal days.

Interleukins regulate synaptic functions and are also involved in learning and memory processes (reviewed in Yirmiya and Goshen, 2011 and Gruol, 2015) and elevated levels of IL-1β can have detrimental effects on these processes (reviewed in Huang and Sheng., 2010). Furthermore, a link between IL-1 gene family and X-linked intellectual disability has been suggested (Nawara et al., 2008; Youngs et al., 2012).

An immune response during pregnancy has been proposed to be causally related to autism in the child. Recently, a relation between maternal immune activation (MIA) and autism has been reported. MIA induces microglia activation, mitochondrial dysfunctions and oxidative stress, which cause neuroinflammation and neurodevelopmental disorders in the offspring (reviewed in Zawadzka et al., 2021). The involvement of the immune system in FXS is supported by data obtained with minocycline. A treatment with this antibiotic, which exerts anti-inflammatory effects, rescued dendritic spine and synaptic abnormalities, reduced anxiety in *Fmr1* KO mice (Bilousova et al., 2009) and normalized reduced ultrasonic vocalizations of *Fmr1* KO mice during mating (Rotschafer et al., 2012). Furthermore, minocycline is a well-tolerated drug and exerts positive effects on behavioural symptoms, including social interaction deficits and repetitive behavior, in FXS patients (Paribello et al., 2010; Leigh et al., 2013; for a review on FXS proposed treatments and clinical trials see Johnson et al., 2023). Another evidence of altered immune function in FXS comes from a study showing a higher prevalence of various infectious diseases and an underrepresentation of autoimmune disorders in FXS patients (Yu et al., 2020). Interestingly, an altered profile of cytokines and chemokines has been detected in the plasma of FXS patients and FXS individuals with ASD (Ashwood et al., 2010; Van Dijck et al., 2020). Furthermore, a defect in the peripheral and brain immune system has also been confirmed in Drosophila melanogaster *Fmr1* mutants. In these flies, a decreased phagocytosis of bacteria by systemic immune cells has been found. In addition, *Fmr1* mutant flies show defects in the recruitment of activated glia causing a delay in neuronal clearance after axotomy in adults and exhibit a developmental defect in the clearance of gamma-neurons in mushroom body, a brain structure important for learning and memory (O'Connor et al., 2017). Young adult *Fmr1* KO mice did not exhibit a different pattern of cytokines (IL-1β, IL-6, TNFα, MCP-1, IL-10) expression in the hippocampus compared to WT mice; however, when challenged with LPS they showed a significantly upregulated expression of IL-6 and IL-1β in the hippocampus (Hodges et al., 2020). In contrast, Pietropaolo and colleagues found region-specific changes of cytokines in the brain of *Fmr1* KO mice, with a reduction of IL-10 and IL-1β in the CA1 region of the hippocampus and prefrontal cortex, respectively, and an increase of IL-1β in the CA3 region of the hippocampus (Pietropaolo et al., 2014). Discrepancies could be related to the strain of the mice (C57BL6 versus FVB strain) and region-specific differences. Other authors observed no changes in serum levels of TNFα and IFNγ between WT and *Fmr1* KO mice (Yuskaitis et al., 2010).

More studies are needed to better characterize the brain immune dysfunctions found in FXS and the mechanisms by which lack of FMRP leads to an altered neuroimmune response, taking into consideration sex, age and brain regions. Clarifying these aspects can be of paramount importance to exploit new therapeutic avenues in this disorder.

Dysfunctions observed in microglia are summarized in Table 2 and the consequences of microglia alterations on neurons are reported in the Fig. 1.

2.3. FXS and oligodendrocytes

2.3.1. FMRP and oligodendrocytes

The first evidence that FMRP is expressed in cells of the oligodendroglia lineage was provided by Wang and collaborators, who reported that FMRP is expressed in the brain stem of mice in the first two weeks of post-natal development to decline thereafter (Wang et al., 2004). FMRP was expressed in progenitors and immature oligodendrocytes in cultures from neonatal brain, in oligodendrocytic cell lines and immature oligodendrocytes *in vivo*, but was not detected in mature oligodendrocytes expressing myelin basic protein (MBP), a major myelination protein, suggesting a role for FMRP in the development and maturation of oligodendrocyte precursor cells (OPCs) (Wang et al., 2004). Double labeling experiments in mouse brains confirmed FMRP expression in OPCs and revealed a decline in the co-expression of FMRP with NG2, a marker of OPCs, during development in the hippocampus, cerebellum, striatum and corpus callosum, but not in the cingulate cortex (Gholizadeh et al., 2015). Pacey and colleagues confirmed FMRP expression in cells of the oligodendrocyte lineage in the developing cerebellum of mice, but they detected FMRP expression not only in OPCs cells, but also in mature oligodendrocytes (Pacey et al., 2013). In line with these findings, Giampetruzzi and collaborators showed that FMRP is expressed in mature cells expressing MBP in cultures of rat and mouse oligodendrocytes and detected FMRP in MBP-positive oligodendrocytes in human tissue (Giampetruzzi et al., 2013). The different results can be related to the method and the antibody used to detect FMRP and overall suggest higher expression in OPCs than mature adult oligodendrocytes (see Table 1). RNA-Seq studies, performed in zebrafish and mouse brain, confirmed that both OPCs and myelinating oligodendrocytes express *Fmr1* (Doll et al., 2020). Furthermore, FMRP is subcellularly located within myelin sheaths in zebrafish during early myelination, and oligodendrocytes in *fmr1*−/− mutant zebrafish develop diminished growth of myelin sheaths, suggesting a role for FMRP in myelination (Doll et al., 2020) (see next paragraph).

2.3.2. Myelination in FXS

Very little is known about oligodendrocytes in FXS, nevertheless recent findings point to a possible contribution of these cells in FXS pathophysiology. FMRP binds mRNA encoding MBP (Darnell et al., 2011; Ascano et al., 2012; Maurin et al., 2018), it is associated to polyribosomes in oligodendrocytic cell lines, inhibits MBP RNA translation *in vitro* (Li et al., 2001; Wang et al., 2004), promotes differentiation of oligodendrocytes in the embryonic spinal cord of zebrafish and regulates the timing of differentiation of oligodendrocytes and the conversion of OPCs to oligodendrocytes (Doll et al., 2021). Single-cell RNA sequencing performed in cerebral cortex of WT and *Fmr1* KO mice at PND5 revealed that the lack of FMRP in oligodendrocytes causes a downregulation of the expression of genes implicated in glutamate regulation, such as *Slc1a2* (Donnard et al., 2022). Several transcription factors involved in the regulation of myelination and many micro RNAs (miRNA) which regulate gene expression in oligodendrocytes are target of FMRP (Darnell et al., 2011; Ascano et al., 2012; Giampetruzzi et al., 2013; Maurin et al., 2018, see Jeon et al., 2017 for a review). In line with a possible involvement of FMRP in myelination, Pacey and collaborators (2013) observed a reduction of MBP expression, a reduction in the number of OPCs, a reduced myelination in *Fmr1* KO cerebellum of mice at PND7 and a smaller cerebellar volume. These alterations were not associated with changes in axonal structure (Pacey et al., 2013). A reduction of Mbp expression has also been detected in *fmr1* -/- mutant larvae of zebrafish, particularly in the ventral myelin tract, whereas the number of oligodendrocytes and *mbp* mRNA abundance in myelin tracts were not affected (Doll et al., 2020). On the other hand, a recent paper reports an increased number of mature and precursors oligodendrocytes, associated with a reduction in myelin thickness and axon diameter and an increase in g-ratio, an indicator of structural and functional myelination, in the region of the medial nucleus of trapezoid body in adult *Fmr1* KO mice (PND72-167) (Lucas et al., 2021), suggesting that aberrant myelination is not caused by a reduced number of oligodendrocytes. An increase in Olig2-positive pre-myelinating OLGs was also observed in the neocortex, but not in the corpus callosum of *Fmr1* KO mice and may be responsible for the enhanced myelination detected in the medial part of the corpus callosum (Lee et al., 2019). The authors suggest that the increase in mature oligodendrocytes and precursors could be an overcompensation for the reduction in the number of oligodendrocytes observed at a young age by other researchers (Pacey

et al., 2013). Low levels of myelin in the critical early postnatal period (Pacey et al., 2013) could lead to deficits even if myelin levels normalize thereafter. Moreover, FMRP could exert a distinct role in the oligodendrocyte development and myelination in specific brain regions at different ages. This idea is also supported by results obtained using brain imaging methods which revealed alterations in white matter volume and structure in caudate nucleus, cerebellar vermis, amygdala, thalamus and defective myelination in medial corpus callosum and cerebellum in mice (Pacey et al., 2013; Lee et a., 2019) and patients (Haas et al., 2009; Hoeft et al., 2010; Hall et al., 2016; Swanson et al., 2018, for a review on patients and mice see Razak et al., 2020). Some structural abnormalities are present in very young children, while other abnormalities evolve over time; thus, it is important to identify critical windows in which therapies can be most effective (reviewed in Razak et al., 2020).

Impaired myelination could be a potential mechanism responsible for some deficits observed in FXS, so future research should aim to identify the factors that underlie this process. Defective myelination can result from a direct alteration in the number of oligodendrocytes or the ability to produce myelin, or can be indirectly caused by a dysfunction of neuronal activity that occurs in the affected circuit (Fig. 1). Future studies should be performed to understand if these changes in myelin gene expression or white matter structure directly result from the lack of FMRP in oligodendrocytes or are a consequence of brain dysfunction on white matter. Furthermore, it would be interesting to understand whether defects in myelination are cell-autonomously caused by the loss of FMRP in oligodendrocytes or can also be indirectly ascribed to the absence of FMRP in neurons and astrocytes interacting with oligodendrocytes. The role of FMRP in oligodendrocytes and how FMRP regulates apoptosis or development of oligodendrocytes, e.g. differentiation of OPCs to mature oligodendrocytes, should be clarified.

Alterations observed in oligodendrocytes in the absence of FMRP and the consequences of oligodendrocytic dysfunctions on neurons are described in Table 2 and depicted in Fig. 1 respectively.

3. FMRP, radial glial cells and neurogenesis

Many pieces of evidence suggest the involvement of FMRP in neurogenesis during development and in adults. FMRP has been shown to regulate neural stem and progenitor cell proliferation, differentiation, and survival, therefore controlling the balance between neurons and glia production (Luo et al., 2010; Bardoni et al., 2017; Liu et al., 2018) (Fig. 1). However, the underlying mechanisms are beninning to be elucidated.

FMRP is present in neural stem cells and in glial lineages in the developing larval brain of Drosophila and in both these cells is necessary for neuroblast reactivation through intrinsic and extrinsic signaling (Callan et al., 2012). FMRP is also present at high levels in radial glial cells (RGCs) of the embryonic mouse neocortex, where it controls mRNAs transport and localization (Pilaz et al., 2016). RGCs function as neural stem cells and give rise to neurons directly or indirectly through intermediate progenitor cells (IPCs) (Kriegstein and Alvarez-Buylla, 2009); RGCs also provide a scaffold for cell migration during corticogenesis, and later in embryonic development can also produce glial cells including astrocytes. FMRP in RGCs controls the transition from RGCs to IPCs, which is important to determine the overall neuronal production. Indeed, the knock-down of FMRP through electroporation of FMRP small hairping RNA at an early stage of mouse neocortical development causes a marked depletion of RGCs and an increase of IPCs production at the expenses of RGCs (Saffary and Xie, 2011). However, these changes were more limited in *Fmr1* KO embryos compared to electroporated embryos and cytoarchitecture of the cortex is not drastically affected in *Fmr1* KO mice, possibly because of compensatory mechanisms occurring during development. The number of neurons is reduced in certain regions (cingulate cortex), but not in others (motor and somatosensory cortex), whereas the number of oligodendrocytes and GFAP expressing cells is increased in the cortex of young adult *Fmr1* KO mice (Lee et al., 2019). Similarly, an increased number of astrocytes and reduced size of neurons was also detected in the auditory brainstem nuclei of *Fmr1* KO mice (Rotschafer and Cramer, 2017). Interestingly, an increased number of astrocytes has been detected in the cortex of FXS patients compared to age-matched controls (Ren et al., 2023). It remains to be established whether the increased number of astrocytes in FXS models and patients results from differentiation abnormalities or increased reactivity and subsequent gliosis or both (see above).

Castren and collaborators reported that neuroprogenitors isolated from *Fmr1* KO embryonic day 13 mouse embryos and PND6 mouse brains differentiate *in vitro* into a higher number of immature neurons compared with the respective WT cells; on the other hand, they observed a reduction in the number of GFAP-expressing cells, possibly caused by an increased apoptotic death. A similar altered differentiation was also observed in neural progenitor cells (NPCs) derived from a Fragile X human embryo (18 weeks) (Castrén et al., 2005). However, similar experiments performed using human NPCs (hNPCs) isolated from a 14-week-old fetal cortex carrying the *FMR1* mutation did not show differences in neurogenesis whilst identified changes in gene expression (Bhattacharyya et al., 2008). Using Fragile X hESCs that recapitulate the early expression of FMRP occurring during human embryogenesis, Telias found that FXS cell lines produce more glial cells than neurons as opposite to non FXS cell lines (Telias et al., 2013). Similarly, FXS cell lines obtained from iPSCs also exhibited an increased glial differentiation (Sheridan et al., 2011) and more recently, an increased expression of GFAP was found in FMRP-deficient NPCs (Sunamura et al., 2018). Brighi and collaborators also reported an increased expression of GFAP and concomitant reduction of the neuronal precursor marker TBR2 in iPSC-derived differentiated 2D cell cultures and an increased number of GFAP-expressing astrocytes in 3D organoids, suggesting the involvement of FMRP in the development and balance of neuronal and glial component (Brighi et al., 2021).

The lack of FMRP has also been shown to be associated with an alteration of adult neurogenesis, which plays a role in learning and memory (Luo et al., 2010). FMRP-deficient adult NPCs from mouse brain exhibited increased proliferation and decreased neuronal differentiation accompanied by increased astrocytic differentiation, while no differences were found in oligodendrocytes differentiation (Luo et al., 2010). Similarly, another study reports that the selective ablation of FMRP in adult mice causes an increased production of glia, stem and progenitors cells and a reduction of neuronal production; furthermore, the ablation of FMRP specifically in adult-born new neurons causes impaired learning in mice that is rescued by restoration of FMRP expression specifically in adult neural stem cells and NPCs (Guo et al., 2011).

Overall, the above-described studies using mouse and human progenitor cells obtained from different sources and different methods highlighted a role of FMRP in the early and late events of neuro- and gliogenesis. However, the resulting mixed and sometimes contradicting data make it difficult to precisely indicate which role FMRP plays as molecular switch dictating the cellular fate during neurogenesis.

4. Fragile X-associated tremor-ataxia syndrome and glial cells dysfunctions

FXTAS is a rare late-onset neurodegenerative disorder caused by CGG trinucleotide repeat expansions (55–200 CGG repeats) in *FMR1* gene. Premutation occurs in 1 in 150–300 women and 1 in 400–850 men. Clinical features begin in individuals older than 50 years. Patients exhibit tremor and cerebellar ataxia, cognitive impairment, autonomic dysfunction, and peripheral neuropathy. Tremor and ataxia progress faster in males than in females (reviewed in Amiri et al., 2008; Hagerman and Hagerman, 2021). FXTAS patients and FXTAS mouse models [CGG knock-in (KI) mice carrying an expanded trinucleotide CGG repeat] exhibit elevated levels of *FMR1* mRNA expression and reduced FMRP levels (Hessl et al., 2005). Excessive *FMR1* mRNA is hypothesized to be toxic to neurons and glia (Jacquemont et al., 2004;

Arocena et al., 2005).

The pathology of FXTAS is complex and involves both glia and neurons. The neuropathological hallmark of this disorder is the presence of ubiquitin-positive intranuclear inclusions in neurons and astroglia (astrocytes and cerebellar Bergmann glia) of FXTAS patients and FXTAS mice (Greco et al., 2002, 2006; Tassone et al., 2004; Wenzel et al., 2010; Schluter et al., 2012). Notably, intranuclear inclusions are common characteristics of trinucleotide repeat neurodegenerative disorders (Den Dunnen, 2017). *FMR1* mRNA is also present in these inclusions (Tassone et al., 2004). The number and size of inclusions increase with advancing age and increasing length of CGG repeats (Greco et al., 2002; 2006; Willemsen et al., 2003). Interestingly, in human cortical gray matter there are more inclusions in astrocytes than in neurons (Greco et al., 2002, 2006; Tassone et al., 2004), suggesting that *FMR1* CGG expansion repeats might trigger abnormalities in astrocytes that promote neuropathology. Accordingly, a transgenic mouse model of FXTAS that selectively expresses a 99-CGG repeat expansion fused to eGFP in astrocytes and Bergmann glia show features of FXTAS pathology, including intranuclear inclusions, translation of FMRpolyG (a polyglycine-containing protein critical for the formation of the inclusions) and deficits in motor function. Interestingly, intranuclear inclusions are present not only in astrocytes, but also in neurons in different brain regions suggesting a spread of pathology from astrocytes to neurons by a yet unknown mechanism (Wenzel et al., 2019). These results highlight the role played by neuron-glia interaction in this disorder.

Another hallmark of FXTAS brain is the presence of high levels of iron accumulation in the putamen. Iron is essential for cell metabolism; nevertheless, uncomplexed iron can lead to oxidative stress and inflammation present in FXTAS (Ross-Inta et al., 2010; Giulivi et al., 2016). Iron depositions are more present in neurons and oligodendrocytes of FXTAS patients compared to control cases, and this accumulation may be linked to a reduction in the levels of ceruloplasmin iron-binding protein (Ariza et al., 2017). These depositions in oligodendrocytes have been related to white matter degeneration observed in FXTAS (Greco et al., 2002; Filley et al., 2015). In contrast, the number of microglial cells containing iron, and levels of transferrin and ceruloplasmin in microglia are increased, suggesting that microglia attempt to remove iron accumulation (Ariza et al., 2017). Interestingly, in the putamen the presence of dystrophic senescent microglia was also detected, and this presence was correlated with the number of CGG repeats and high levels of iron accumulation (Martínez Cerdeño et al., 2018). The involvement of microglia in this disease is also confirmed by the increase in the number and status of activation of these cells found in FXTAS patients (Martínez Cerdeño et al., 2018; Robinson et al., 2020). It is unclear whether microglial activation initiates neurodegeneration or whether microglial activation is a consequence of neurodegeneration.

In line with microglia activation, astrocytes show a reactive phenotype (Robinson et al., 2020). The activation of both these cells is indicative of neuroinflammation, a common neuropathological alteration across most neurodegenerative disorders and it is in line with an increase of TNFα and IL-12 levels in the brain of FXTAS patients (Dufour et al., 2021). It was also observed that cortical astrocytes isolated from KI mice with premutation CGG expansions (~ 170 repeats) have elevated *Fmr1* mRNA levels and a moderate decrease of FMRP. They also exhibit an increase of spontaneous Ca^{2+} oscillations, a reduced expression of glutamate transporters GLAST and GLT1 and a deficit in glutamate uptake (Cao et al., 2013). As mentioned above, a reduction of glutamate transporter has also been detected in *Fmr1* KO mice (Higashimori et al., 2013, 2016), suggesting that these two different disorders present some common alterations. These findings are in line with impaired glutamate uptake detected in preCGG hippocampal astrocytes and alterations in Ca^{2+} dynamics observed in *Fmr1* preCGG mouse neuronal cultures (Cao et al., 2012) and premutation human neurons derived from induced pluripotent stem cells (Liu et al., 2012), and support the view that impaired glutamate uptake and the increased frequency of spontaneous Ca^{2+} oscillations observed in preCGG astrocytes may contribute to the etiology of FXTAS. Elevated Ca^{2+} levels in astrocytes can influence neuronal excitability (Liu et al., 2021).

An important advance in elucidating the contribution of glia to the pathophysiology of FXTAS has been made with a cell type–specific transcriptomic analysis. Single-nucleus RNA sequencing performed on postmortem frontal cortex and cerebellum of FXTAS and control individuals revealed a modest upregulation of *FMR1* mRNA in cerebellar Bergmann glia and cortical microglia of individuals with premutation expansions. Interestingly, a significant positive correlation between cortical microglia *FMR1* expression and repeat size was found suggesting that this increase may have clinical relevance. Gene ontology analysis revealed that biological processes such as synaptic functioning, axon guidance, and neurotransmitters were perturbed in glial cells. Interestingly, a decreased number of astrocytes in the cortex, a dysregulation of FMRP network in the cortical oligodendrocyte lineage and differences in early gene expression in oligodendrocyte developmental trajectories in FXTAS cases were also detected (Dias et al., 2023). A recent anatomo-pathological study in the striatum and cerebellum of FXTAS patients confirms widespread reactive gliosis and shows massive degeneration of astrocytes (Dufour et al., 2024). These findings underline that glial dysregulation is critical in FXTAS molecular neuropathology and suggest that glial cells could be therapeutic targets in this disorder.

Alterations of glial cells observed in FXTAS are summarized in Table 3.

5. FMRP and glioma

Clinical and epidemiological data suggest that the absence of FMRP can exert a protective effect against tumor growth. A decreased cancer risk has been observed in FXS patients (Schultz-Pedersen et al., 2001) and a reduced glioblastoma invasiveness has been detected in a FXS patient (Kalkunte et al., 2007).

Several evidence suggest the direct or indirect involvement of FMRP in cancer: i) FMR1 acts as an oncogene, ii) FMRP is implicated in the progression of several malignant tumors, iii) a subset of mRNA targets of FMRP and several FMRP interactors play a role or are mutated in cancer (Bagni and Klann, 2012; Lucá et al., (2013); Pasciuto and Bagni, 2014; Di Grazia et al., 2021). Overexpression of FMRP in non-brain tumors (such as breast cancer) is related to a more aggressive metastatic phenotype (Lucá et al., 2013; Di Grazia et al., 2021). The biological mechanisms underlying the reduced risk of cancer in FXS patients are unclear and difficult to reconcile with the evidence that lack of FMRP is associated with increased DNA damage and chromosomal instability (Chakraborty et al., 2020; Ledoux et al., 2023). Chromosomal instability is a hallmark of malignancies (Negrini et al., 2010) and a driver of tumorigenesis, malignancy progression and a promoter of metastasis formation (Bakhoum et al., 2018). On the other hand, chromosomal instability may also lead to the expression of genetic programs that halt progression of tumors and triggers mechanisms inducing cell cycle arrest in a p53-dependent manner; furthermore, it may promote proteotoxic stress, which can be amplified by the increased protein translation occurring in the absence of FMRP (Hosea et al., 2024). It is possible that, in the absence of FMRP, additional mechanisms occur that counteract the formation and progression of tumors. Indeed, a recent paper provides evidence that FMRP promotes tumor immune escape in the tumor microenvironment, thus facilitating tumor progression and metastasis (Zeng et al., 2022).

The involvement of FMRP in brain tumors has also been shown (Xing et al., 2016; Jiang et al., 2021; Pedini et al., 2022). Gliomas are the most common primary malignant brain tumors and can be astrocytic, oligodendrocytic, or a mix of these two cell types (Ostrom et al., 2014). Glioblastoma or astrocytoma grade IV is the most aggressive and common of all primary brain tumors. In astrocytoma tissue samples from patients, FMRP expression is associated with increasing tumor grade,

Table 3
Abnormalities of glial cells in FXTAS.

	EVIDENCE	CITATION
ASTROCYTES	Presence of ubiquitin-positive intranuclear inclusions in astrocytes of FXTAS patients and FXTAS mice	Greco et al., (2002), (2006); Tassone et al., (2004); Wenzel et al. (2010); Schluter et al., (2012); Wenzel et al., (2019)
	Altered glutamatergic system: ↓ glutamate clearance in hippocampal astrocytes of FXTAS mouse	Cao et al., (2012)
	↑ spontaneous Ca^{2+} oscillations, ↓GLAST and GLT1 expression, deficit in glutamate uptake in cortical astocytes of FXTAS mouse	Cao et al., (2013)
	↓ Number of cortical astrocytes in FXTAS patients	Dias et al., (2023)
	↑ *Fmr1* mRNA, ↓ FMRP levels in FXTAS mouse and in FXTAS patients	Cao et al., (2013); Dias et al., (2023)
	Degeneration of astrocytes in striatum and cerebellum of FXTAS patients	Dufour et al., (2024)
	Reactive astrocytes in FXTAS patients	Robinson et al. (2020); Dufour et al., (2024)
MICROGLIA	Presence of dystrophic senescent microglia in FXTAS patients	Martínez Cerdeño et al., (2018)
	↑ Number and ↑ activation status in FXTAS patients	Martínez Cerdeño et al., (2018); Robinson et al., (2020)
	Upregulation of *FMR1* mRNA in cortical microglia of FXTAS patients	Dias et al., (2023)
	↑ Number of microglial cells containing iron; ↑ microglial levels of transferrin and ceruloplasmin in FXTAS patients	Ariza et al. (2017)
OLIGODENDROCYTES	Presence of iron depositions, ↓ number of cells containing ceruloplasmin in oligodendrocytes of FXTAS patients	Ariza et al. (2017)
	Abnormal oligodendrocyte development and dysregulation of FMRP network in the cortical oligodendrocyte lineage of FXTAS patients	Dias et al., (2023)

Ki67 expression and poor prognosis (Xing et al., 2016). Furthermore, FMRP promotes proliferation and tumorigenesis of TP53-wild-type gliomas (Jiang et al., 2021). In line with these findings, FMRP levels have been found to be upregulated in glioblastoma and high levels of FMRP are linked to low survival rates. In contrast, patients with high levels of *FMR1* mRNA expression show a better prognosis than those with low levels of expression. It is possible that cells with low levels of *FMR1* mRNA have a high efficiency of translation. Interestingly, in stem-like cells derived from glioblastoma patients, the reduction of FMRP causes a considerable inhibition of proliferation capability (Pedini et al., 2022). All these findings suggest that FMRP regulates common pathological pathways in gliomas and may be a potential therapeutic target for these tumors.

6. FMRP and other neurological disorders

Although the function of FMRP has been mainly studied in the context of FXS pathophysiology, recent evidence suggests an involvement of this protein in other neurological diseases. An altered expression of FMRP has been detected in a variety of neurodevelopmental disorders and neurodegenerative diseases including Tuberous Sclerosis Complex (TSC), Rett syndrome, Alzheimer disease (AD) and Parkinson disease (PD). Furthermore, several mRNA targets of FMRP are dysregulated in different neurological disorders, suggesting an indirect implication of FMRP.

A reduction of FMRP levels has been detected in different brain regions of individuals with autism (Fatemi and Folsom, 2011; Fatemi et al., 2011), in the cortex of MeCP2 KO mice (Arsenault et al., 2021) and in human iPSCs derived Purkinje cells from patients with TSC2 mutations (Sundberg et al., 2018). The expression of FMRP targets (such as SHANK2, DLG3, KIF3C) is dysregulated in TSC (Dalal et al., 2021). Furthermore, in TSC2-deficient neurons an increased ubiquitination and degradation of FMRP has been linked to increased spontaneous activity, this being corrected by the overexpression of FMRP (Winden et al., 2023). Interestingly, FMRP deficit/loss in neurons and associated reduced size of the neuron somata and nuclei, and infiltration of FMRP positive astrocytes in different brain regions have been detected in individuals with idiopathic and syndromic autism (duplication 15q11.2-q13) (Wegiel et al., 2018). This is the only direct evidence of a possible involvement of glial FMRP in ASDs other than FXS.

Importantly, a reduction of FMRP levels has also been found in the lateral cerebella and Broadmann area 9 of subjects with schizophrenia, bipolar disorder, and major depression (Fatemi et al., 2010, 2013). Interestingly, FMRP levels were also decreased in the peripheral blood of patients with schizophrenia (Kelemen et al., 2013; Kovács et al., 2013) and this reduction is related to lower IQ and earlier onset of the disease (Kovács et al., 2013).

The mRNA encoding amyloid precursor protein (APP) is a target of FMRP (Darnell et al., 2011; Ascano et al., 2012) and APP synthesis is constitutively increased in the absence of FMRP, with a concomitant accumulation of amyloid plaques (Westmark and Malter, 2007). Furthermore, a reduction in FMRP levels, correlated with an increase of APP levels, was observed in the hippocampus of mice overexpressing the APP695 fragment with the Swedish mutation (Tg2576 mutant mice) at young ages (Borreca et al., 2016). In contrast, an increase of FMRP levels was detected in the coronal brain slices of 12 month-old APPswe/PS1ΔE9 mice (a double transgenic AD mouse model) (Hamilton et al., 2014) whilst no changes were found in the cortex and cerebellum of these double mutant mice at 18 months of age (Renoux et al., 2014). The different findings could be related to different genotypes, age, and brain region examined. As suggested by Borreca and colleagues, a reduction of FMRP in presymptomatic young mutants may contribute to the development of the disease while an increase of FMRP in symptomatic aged mutants may reflect a compensatory mechanism. Interestingly, a reduction of FMRP levels was observed in hippocampal synaptosomes of one sporadic AD patient (Borreca et al., 2016); in contrast, no changes in FMRP levels were detected in the cortex and cerebellum of ten AD patients (Renoux et al., 2014). Given the results obtained in AD mice, FMRP levels should be evaluated in a greater number of AD patients to better establish the role of the protein in different stages of disease.

Premutations in the *FMR1* gene may be linked to parkinsonism (Toft et al., 2005). Reduced FMRP levels have been observed *in vitro* and *in vivo* models overexpressing α-synuclein and in post-mortem brain tissue from PD patients and individuals in the early stages of incidental Lewy bodies diseases, which is considered a precursor of PD (Tan et al., 2020). Results obtained in AD mice and in PD mice/patients suggest that the reduction of FMRP may precede the formation of the aggregates and may be related to early pathogenic events. This hypothesis could also be valid for Amyotrophic Lateral Sclerosis (ALS). Although FMRP levels have not been extensively examined in ALS, a direct or indirect contribution of FMRP has been shown in the pathogenetic mechanisms of the disease. Proteins involved in ALS pathology, such as FUS, Ataxin-2, SOD1, TDP-43 interacts with FMRP; FMRP and FUS are also components of stress granules; FMRP may contribute to TDP-43 aggregation

and, in association with TDP-43, regulates transport and translation of selected mRNAs (Bechara et al., 2009; Coyne et al., 2015; Yu et al., 2012; reviewed in Mueller et al., 2023). In FUS zebrafish mutants FMRP levels were comparable to control, but an increased expression of the FMRP target MAP1B, a microtubule stabilizing protein involved in axonal development and regeneration or axonal guidance and neuronal migration (reviewed in Yang et al., 2012b), has been detected, with possible consequences on motor neuron morphology and survival (Blokhuis et al., 2016). Furthermore, FMRP overexpression rescued/mitigated the altered phenotype in ALS animal model (Blokhuis et al., 2016; Coyne et al., 2015); FMRP interacts with ALS-related miRNAs and it is also involved in their biogenesis or degradation (Freischmidt et al., 2021).

All these findings suggest that FMRP deficit and its consequences are not exclusively present in FXS and FXTAS. This may explain why FXS patients exhibit some synaptic dysfunctions, cognitive impairments, genomic and molecular features like those seen in patients with other neurological diseases such as AD, Down and Rett patients (reviewed in Bach et al., 2021; Bleuzé et al., 2021; Chang et al., 2013). It is known that glial cells play a role in the neurodegenerative and neurodevelopmental diseases mentioned above. These cells exhibit changes in gene expression, in phenotype, in their homeostatic function at the synapse and contribute to create an inflammatory environment detrimental for neurons (reviewed in Liu et al., 2021; Lukens and Eyo, 2022; Brandebura et al., 2023; Gao et al., 2023). As mentioned before, glial FMRP is implicated in many of these dysfunctions and can therefore participate in the pathophysiology of these different diseases. Thus, the effect of the deficiency of glial FMRP in neuropathological processes should be examined because it can disclose additional pathogenic pathways. Glial FMRP could be a hub protein which regulates biological processes common to several diseases. Thus, it would be of interest to evaluate whether manipulating FMRP expression in glial cells is able to change the severity or the development of neurological disorders.

7. Concluding remarks and future perspectives

FMRP is expressed in glial cells where it regulates the expression of proteins implicated in key biological functions. Although FMRP is expressed at lower levels than neurons, its absence in astrocytes plays a key role in synaptic dysfunctions and behavioral abnormalities of FXS. Furthermore, lack of FMRP in oligodendrocytes and microglia may also contribute to establish the FXS phenotype. It is now clear that the pathological phenotype observed in FXS is not a consequence of an exclusive role exerted by neurons or glial cells, but the mutual interaction between different neural cells, particularly neuron-astrocyte crosstalk, fundamentally contributes to disease pathogenesis. It is important to clarify whether changes observed in glial cells are causally related to the lack or reduced expression of FMRP or if these cells are atypical because they develop and function in a diseased microenvironment.

Data on FMRP-deficient microglia have been collected using cultured microglia, thus more molecular and *in vivo* studies using microglia-selective *Fmr1* KO mice are needed for a better understanding of the contribution of microglia to FXS phenotype.

Another aspect that requires more investigation is the link between lack of FMRP in astrocytes, hyperexcitability and seizure susceptibility. Epilepsy occurs in 10–40% of FXS patients (Musumeci et al., 1999; Berry-Kravis, 2002; Hagerman and Stafstrom, 2009; Albizua et al., 2022), more frequently during childhood, and *Fmr1* KO mice exhibit an elevated seizure susceptibility (Musumeci et al., 2000). Although glial cells are deeply involved in pathophysiological mechanisms of epilepsy (reviewed in Vezzani et al., 2022; Shen et al., 2023; Yu et al., 2023), the role of glia and consequences of the lack of glial FMRP on this altered phenotype in FXS is not clear. By crossing mice with conditional deletion or expression of *Fmr1* with *Emx1*$^{Cre/+}$ mouse, which expresses Cre mainly in excitatory neurons and glia in cortical structures, Gonzalez et al. (2019) excluded that lack of FMRP in glial cells in cortical structures is involved in audiogenic seizures (Gonzalez et al., 2019). However, the re-expression of FMRP in neurons of *Fmr1* KO mice did not revert audiogenic seizures (Gholizadeh et al., 2014), but direct evidence that the absence of FMRP in astrocytes contributes to AGS is lacking.

FXS phenotype is heterogeneous and varies between males and females. Considering that glial cells produce steroids (e.g. progesterone) and express sex hormone receptors (reviewed in Garcia-Ovejero et al., 2005), and that several glial function (such as myelination, inflammatory response to brain injury) are regulated by estrogens (reviewed in Arevalo et al., 2010), it would be interesting to investigate whether there are sex differences in biological mechanisms mediated by FMRP in glial cells.

Glial cells are also affected in FXTAS and their dysfunction may precede neuronal degeneration. Levels of FMRP are decreased in FXTAS and have also been found reduced in other neurological disorders, including ASD, AD and PD. Further studies in human model systems are needed to confirm whether glial abnormalities causally contribute to FXTAS or represent a secondary response to neuronal dysfunction. Furthermore, the role played by the reduction of glial FMRP expression and the relationship between *FMR1* expression levels and the degeneration or activation of glial cells in FXTAS should be investigated. Deficit of FMRP may be a common marker for different neurological diseases and can represent a key determinant for dysregulation of a common set of genes in different disorders. However, the specific role of glial FMRP in various neurological diseases awaits further investigation, which may greatly benefit from the use of recently developed human models. The use of single-cell sequencing, glia depleting drugs, cell type-specific isolation and gene silencing, human derived iPSCs, organoids and *in vivo* imaging may help to better understand the functional role of each specific cell type and the effect of their interactions in brain diseases. In the near future, research on glial FMRP might offer new therapeutic strategies for different neurological diseases.

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Conflicts of Interest

The authors declare no conflict of interest.

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