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Review

Interpreting the rich dialogue between astrocytes and neurons: An overview in Rett syndrome

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ABSTRACT

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting females, with an incidence of 1 in 10,000 live births. It is caused mainly by *de novo* mutations in the X-linked *MECP2* gene, which encodes methyl-CpG binding protein 2 (*Mecp2*), a key epigenetic regulator. *MECP2* mutations have profound impacts on neurons, which exhibit morphological, synaptic and functional impairments. However, more recent evidence highlights a crucial role of astrocytes in RTT pathogenesis. Indeed, RTT astrocytes exhibit structural and functional impairments, failing to support neuronal growth and function through non-cell autonomous mechanisms. Studies reveal that *MECP2* deficient astrocytes secrete abnormal factors that impair neuronal growth and synaptic function. Furthermore, they show dysregulated calcium signalling, disrupted glutamate and potassium homeostasis, and increased inflammatory responses, all of which contribute to neuronal dysfunction. Understanding these neuron-astrocyte interactions may offer novel therapeutic targets for RTT. In the review we aim at presenting the current knowledge of astrocyte-neuron crosstalk in RTT, describing the different mechanisms highlighted so far through which *MECP2* mutant astrocytes impair neurons. Finally, we discuss existing and prospective methodological approaches for investigating cell-to-cell communication in RTT.

1. Rett syndrome

Rett syndrome (RTT, OMIM identifier #312750) is a severe and progressive neurodevelopmental disorder representing a major cause of intellectual disability in girls worldwide, with an incidence of 1 in 10.000 live births (Chahrour and Zoghbi, 2007; Gold et al., 2024). RTT patients typically exhibit a delayed onset of symptoms, whose severity and frequency vary among individuals. Typical neurological hallmarks include loss of purposeful hand skills, loss of spoken language, walking problems, seizures and cognitive impairments. The disease progresses through four distinct stages; however, symptoms may overlap and not all patients necessarily experience every stage (Chahrour and Zoghbi, 2007). After an apparent normal development during the first 6–18 months of life during which signs are subtle and easily overlooked (*Stage 1: early onset*), neurological development halts and patients undergo a rapid regression (*Stage 2: rapid deterioration*), that is usually observed between ages 1 and 4. During this stage, they lose previously acquired abilities such as spoken words, babbling, motor coordination, and purposeful hand use. Also, they display slowed head growth, continuous, distinctive stereotypic hand movements, mobility problems including unsteady gait, and autistic features. As the disorder advances, RTT patients develop a range of additional symptoms during the third stage (*Stage 3: plateau*), that may last for many years. Among the most prevalent and debilitating symptoms are seizures, irregular breathing patterns, and cardiac issues. Conversely, communication skills and autistic behavior might slightly improve. During a late stage (*Stage 4: late motor deterioration*), usually occurring after the age of 10, patients are no longer able to walk. They also show severe scoliosis, muscle rigidity and weakness, sometimes manifesting symptoms resembling Parkinson's disease (Chahrour and Zoghbi, 2007).

Diagnosis in the earliest phases is very challenging because of the variability of symptoms, which are in common with other neurological disorders. Through the years, diagnostic criteria were re-edited many times until 2010, when Dr. Neul and colleagues established main and supportive criteria to distinguish RTT from other neurodevelopmental disorders, and also to discriminate classical forms of RTT from its variants. The main feature for the diagnosis of both classical and variant forms is the presence of the regression phase. In addition, patients affected by classical RTT must manifest other four key features, including loss of acquired spoken language, loss of fine purposeful hand

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skills, the presence of gait abnormalities and hand stereotypic movements. Diagnosis for variant RTT forms requires at least 2 out of the 4 main criteria and other supportive symptoms, such as breathing problems, cardiovascular dysfunctions, growth retardation and scoliosis (Gold et al., 2024).

Mutations in the X-linked *MECP2* gene is the major cause of RTT (Amir et al., 1999). *MECP2* gene encodes for the methyl-CpG binding protein 2 (MeCP2), the founder member of the Methyl Binding Protein (MBP) family, a group of evolutionary conserved nuclear factors involved in the epigenetic regulation of the genome through the binding to methylated DNA (Sharifi and Yasui, 2021). MeCP2 interacts with various cofactors to regulate transcription, acting as both a repressor and an activator of gene expression (Lewis et al., 1992; Jones et al., 1998; Nan et al., 1998; Tillotson et al., 2021; Chahrour et al., 2008; Liu et al., 2024). In addition to its proposed role in modulating gene expression, MeCP2 can also function as an organizer of genome and chromatin architecture (Skene et al., 2010). Over the years, several other functions have been attributed to MeCP2, leading to consider it as a multifunctional protein that manifests different activities depending on its partners and post-translational modifications (Bedogni et al., 2014). Indeed, MeCP2 is involved in protein translation, and functioning of key signalling pathways, including the mammalian target of rapamycin (mTOR) (Sharifi and Yasui, 2021; Ricciardi et al., 2011; Olson et al., 2018). Additionally, it contributes to miRNA maturation (Cheng et al., 2014), RNA splicing (Young et al., 2005), primary cilium formation and functioning (Frasca et al., 2020). *Mecp2* is ubiquitously expressed throughout the body but it is especially abundant in the brain, where its expression begins before birth and gradually increases, reaching its highest levels during synaptic development and plasticity (Shahbazian et al., 2002). Neurons express MeCP2 at levels approximately ten times higher than other cell types, and within neuronal nuclei, its abundance is comparable to that of histone proteins (Skene et al., 2010).

Whereas *MECP2* mutations account for ~95 % of RTT cases, less frequently they have been associated with a wide range of other neurodevelopmental disorders in both males and females, such as X-linked mental retardation, severe neonatal encephalopathy, Angelman syndrome and autism, highlighting the critical role of MeCP2 in brain development (Ezeonwuka and Rastegar, 2014). Complementary, an abnormal overexpression of MeCP2, caused by an extra copy of the gene, causes *MECP2* Duplication Syndrome (MDS), a condition that occurs mostly exclusively in males and characterized by overlapping symptoms with RTT (Van Esch et al., 2005), demonstrating the importance of maintaining physiological levels of MeCP2.

In RTT, the majority of *MECP2* mutations originates spontaneously in the paternal germline, and generally derives from C to T transitions probably due to the deamination of methylated cytosines (Thomas, 1996). Therefore most cases of RTT are females, although boys are also present, showing a very severe symptomatology that develops early in life (Moog et al., 2003). Over 900 unique variants have been identified within the gene, with ~60 % of pathogenic ones mainly represented by frameshift, insertion/deletions and missense mutations. Loss of function mutations in *MECP2* accounts for the vast majority of RTT cases, with a recurrence of 8 variants, among missense (R106W, R133C, T158M, R306C) and nonsense (R168X, R255X, R270X, R294X) mutations, distributed along the different protein domains (Neul et al., 2008). Since *MECP2* is located on the X chromosome, RTT female patients are heterozygous for the mutation, and due to X chromosome inactivation (XCI), they are mosaics for cells expressing either the wild type (WT) or mutant *MECP2* allele. XCI significantly impacts on the onset and severity of the disorder. Individuals with a skewed XCI, favoring the normal *MECP2*, have milder motor and cognitive symptoms, whereas those with a higher proportion of cells expressing the mutated *MECP2* gene typically experience a more severe phenotype (Braunschweig, 2004). Advances in understanding mosaicism could pave the way for more targeted therapies and precision medicine approaches, potentially leading to more effective treatments for RTT in the future.

2. Neuronal and astrocytic defects in RTT

Neurological defects constitute primary symptoms of RTT and extensive research has focused on identifying anatomical, molecular and functional changes within the central nervous system (CNS) (Chen et al., 2001; Gonzales and LaSalle, 2010). Neurons represent the cells mainly affected in the disease, exhibiting prominent morphological and functional abnormalities, consistently observed in human tissues and animal models (Kishi and Macklis, 2004 Nov; Duncan, 2005; Fukuda et al., 2005; Chapleau et al., 2009; Tropea et al., 2009; Belichenko et al., 2009; Jentarra et al., 2010; Dani et al., 2005; Calfa et al., 2015). Neuronal defects arise from a combination of cell autonomous and non-cell autonomous mechanisms, due to the loss of functional MeCP2 in neurons and in other cell types, respectively. *MECP2* mutant neurons show fewer and shorter dendrites compared to healthy ones (Chapleau et al., 2009; Belichenko et al., 2009; Jentarra et al., 2010) and among the cellular components, synapses are particularly impaired, leading to define RTT as a synaptopathy (Boggio et al., 2010). Notably, several synaptic abnormalities have been described, including a decreased number of dendritic spines and synaptic puncta, and impairments of synaptic scaffolding proteins (Chapleau et al., 2009; Zhou et al., 2006), often accompanied by functional alterations (Tropea et al., 2009; Dani et al., 2005; Chang et al., 2006). Specifically, RTT neurons exhibit changes in synaptic function including reduced synaptic plasticity (Moretti et al., 2006; Na et al., 2013; Nelson et al., 2011; Della Sala and Pizzorusso, 2014). Further, an excitatory/inhibitory unbalance is observed in the *Mecp2* deficient brain, showing a heterogeneous pattern in dependence of the developmental stage, the brain region and the cell type (Chao et al., 2007; Dani and Nelson, 2009; Li, 2022).

While the lack of functional MeCP2 in neurons causes cell-autonomous defects in development, maturation, morphology and functions (Belichenko et al., 2009; Kishi and Macklis, 2010; Blackman et al., 2012), growing evidence suggests that these abnormalities are not due to *MECP2* mutations exclusively in neurons. Instead, non-cell autonomous mechanisms, particularly involving astrocytes, significantly contribute to the pathology. Astrocytes, which are essential for providing structural, metabolic and functional support to neurons, play a key role in shaping neuronal maturation, synapse formation and synaptic plasticity (Perea et al., 2014; Allen and Eroglu, 2017; Stogsdill et al., 2023). MeCP2 deficiency in astrocytes has a widespread impact on brain function in RTT, underscoring the importance of including glial contributions in disease progression and the development of therapeutic strategies.

The involvement of astrocytes in RTT pathogenesis was firstly recognized when MeCP2 expression was detected also in astrocytes, albeit at significantly lower levels compared to neurons (Rusconi et al., 2008; Ballas et al., 2009; Maezawa et al., 2009; Olson et al., 2014). It was then demonstrated that *MECP2* mutant astrocytes are defective in supporting neurons through non-cell autonomous mechanisms. In particular, by co-cultures between WT hippocampal neurons and either WT or *Mecp2* KO astrocytes, Ballas and colleagues reported that neurons properly grow in the presence of WT astrocytes, whereas present fewer and shorter dendrites when cultured with KO astrocytes (Ballas et al., 2009). For the first time it thus emerged that *Mecp2* null astrocytes cannot sustain proper neuronal growth, and similar results were obtained by treating neurons with KO astrocyte conditioned medium (ACM), proving that *Mecp2* null astrocytes contribute to altered neuronal morphology through aberrant secretion of soluble factors (Ballas et al., 2009). Five years later these findings were confirmed on human astrocytes differentiated from RTT induced pluripotent stem cells (iPSCs). The negative impact of mutant astrocytes was largely recapitulated by culturing WT neurons with RTT ACM, thus demonstrating again that such non-cell autonomous effects are due to secreted molecules (Williams et al., 2014). Further elements on the topic were

reported by Maezawa's group, which described crucial impaired features of *Mecp2* mutant astrocytes, including delayed growth and constitutive activation of MAPK pathway, associated with a reduced release of cytokines, compared to WT astrocytes. Moreover, they showed that *Mecp2* deficiency spreads to neighboring astrocytes through gap junctions (GJs), also proposing a non-cell autonomous mechanism among astrocytes (Maezawa et al., 2009).

In vivo studies have provided crucial insights into the role of astrocytes in RTT, highlighting how these glial cells contribute to both the development and progression of symptoms. Indeed, the selective re-expression of *Mecp2* in astrocytes in otherwise null mice was sufficient to restore dendritic complexity, and to increase the levels of the vesicular transporter vGlut1. An amelioration of locomotor and anxiety levels and a restoration of respiratory defects were also documented, together with a significant elongation of the lifespan (Lioy et al., 2011). Complementary, in conditional models in which *Mecp2* was specifically deleted in astrocytes, mice developed severe breathing irregularities (Lioy et al., 2011; Garg et al., 2015). This evidence demonstrates that astrocytic dysfunction alone significantly contributes to some RTT features.

As already reported in neurons, and in accordance with the role of MeCP2 as a transcriptional regulator, *MECP2* loss of function causes the deregulation of thousands of molecules in astrocytes (Delépine et al., 2015; Yasui et al., 2013; Pacheco et al., 2017; Sun et al., 2023; Tomasello et al., 2024). Through transcriptomic and proteomic studies, it emerged that the pathways mainly affected include those related to cell maturation, morphology, cell-to-cell communication, cytokine signalling, energy metabolism, and glutamate homeostasis (Delépine et al., 2015; Yasui et al., 2013; Pacheco et al., 2017; Sun et al., 2023). In accordance with molecular results, morphological analyses supported the loss of astrocyte complexity in RTT. Data from cultured astrocytes derived from both *Mecp2* KO and *Mecp2*$^{308/y}$ mouse brain and human RTT iPSCs demonstrated altered morphology and microtubule dynamics, along with impairments in the correct remodeling of cytoskeleton and cellular shape (Sun et al., 2023; Nectoux et al., 2012; Delépine et al., 2016). A reduced branching was observed also in human astrocytes harboring R270X and R133C mutations in co-culture with neurons. As expected, neurons induce astrocytes to shift from a flat and polygonal shape to a stellate morphology. Sholl analysis, quantification of primary branches and analysis of their length in GFP transfected astrocytes reported a significant reduction in structural complexity, branch length and number in mutant astrocytes when co-cultured with WT neurons. Interestingly, these morphological defects are exacerbated when KO neurons are present (Sun et al., 2023). Evidence from the adult brain of animal models documented fewer and poorly branched astrocytic ramifications in the dentate gyrus and corpus callosum of *Mecp2*$^{308/y}$ mouse models (De Filippis et al., 2012), as well as in the hippocampus of a conditional mouse, in which *Mecp2* is postnatally inactivated (Nguyen et al., 2012). We also found that *Mecp2* deficiency induces a reduced astrocyte complexity over disease progression, with region-specific effects, especially in the motor and somatosensory cortex. Accordingly, molecular analysis revealed deregulation of many astrocyte-enriched genes mainly associated with cytoskeletal abnormalities. Notably, in the cortex of heterozygous mice astrocytes with the WT copy of *Mecp2* exhibit comparable alterations to those lacking *Mecp2*, indicating non cell-autonomous effects (Albizzati et al., 2022). Changes in astrocyte structure significantly affect their ability to interact with neurons, compromising essential supportive functions. Furthermore, wide-spectrum alterations of typical astrocytic functions, including the glutamate-glutamine cycle, calcium signalling, lactate-shuttle and potassium (K^+) homeostasis, were reported both in mouse models and human cells (Sun et al., 2023; Tomasello et al., 2024; Okabe et al., 2012; Dong et al., 2018; Rakela et al., 2018; Kahanovitch et al., 2018). Collectively, these alterations in astrocytes impact on neuronal phenotypes through different molecular mechanisms which remain still partly unexplored.

3. The impact of astrocyte alterations on neuronal health: molecular events underpinning the non-cell autonomous mechanisms in RTT

There is considerable evidence indicating a defective communication between astrocytes and neurons in RTT, which probably contributes to neurological dysfunctions. These defects manifest at various levels, including cell-autonomous astrocyte alterations, the dysregulation of signalling molecules crucial for cell communication, and the altered sensitivity of RTT neurons, ultimately leading to the well-known neuronal defects. To better understand astrocyte–neuron communication impairments in RTT, it is useful to have a quick overview of this complex mechanism in physiological conditions, before describing published results on communication defects between astrocytes and neurons in the disease (Fig. 1).

3.1. Astrocyte-neuron communication in physiological conditions

Astrocyte-neuron communication occurs in a dynamic and bidirectional way. The majority of evidence describes the effects exerted by astrocytes on neurons, which mainly rely on ion channels and transporters, as well as adhesion and signalling molecules. Through their perisynaptic astrocyte processes (PAPs), astrocytes enwrap pre- and post-synaptic terminals forming the tripartite synapse, where astrocytes are ideally positioned to finely control the concentration of ions and molecules, regulating synapse activity (Reichenbach et al., 2010; Mederos et al., 2018; Araque et al., 1999). This occurs through multiple mechanisms, which have been extensively reviewed (Chung et al., 2024; Farhy-Tselnicker and Allen, 2018; Semyanov and Verkhratsky, 2021) and for which we here provide only a brief description.

At the synaptic cleft, astrocytes play a crucial role in the regulation of K^+ concentration, which is essential during periods of intense neuronal activity when extracellular K^+ levels rise. Potassium channels, such as Kir4.1, allow rapid uptake of extracellular K^+, preventing hyperexcitability and neuronal circuit damage (Seifert et al., 2009). Moreover, astrocytes control synaptic activity by clearing neurotransmitters from the extracellular space. For instance, astrocytes are responsible for glutamate reuptake through the amino acid transporters GLAST1 (glutamate-aspartate transporter 1) and GLT-1 (glutamate transporter 1), and the human homologous EAAT1 and EAAT2, respectively. By modulating the glutamate transporters' expression and membrane localization, astrocytes influence synaptic activity controlling glutamate spillover beyond synapses (Huang et al., 2004). Astrocytes are also involved in the γ-aminobutyric acid (GABA) removal from the synaptic cleft through GABA transporters, GAT-1 and GAT-3, which show a peculiar cellular distribution in the brain (Jv and A S., 2023). In addition to these roles, astrocytes can release active substances, known as gliotransmitters, including glutamate, GABA, D-serine, adenosine, ATP and cytokines, such as Tumor Necrosis Factor α (TNFα), which target neighboring neurons modulating synaptic function (Allen and Eroglu, 2017; Perea and Araque, 2005, 2007; Harada et al., 2016; Araque et al., 2014). Astrocytes support neuronal activity also through the establishment of the neurovascular unit at level of the blood-brain barrier (BBB), where they respond to local needs, secreting different mediators such as prostaglandins, nitric oxide and arachidonic acid to modify the diameter of blood vessels and regulating the local blood flow to ensure that active brain regions receive sufficient oxygen and nutrients (Lia et al., 2023). Beyond their role in controlling synaptic functions, astrocytes are essential player for synaptogenesis, particularly during brain development. Several data demonstrate that astrocyte-secreted molecules, including proteins, lipids and small molecules, control different aspects of excitatory and inhibitory synapse formation and maturation (Allen and Eroglu, 2017; Fossati et al., 2020). Furthermore, astrocytes supply neurons with energy substrates via the astrocyte-neuron lactate shuttle, providing the substrate for ATP generation (Magistretti and Allaman, 2015). Another mechanism of communication between astrocytes and

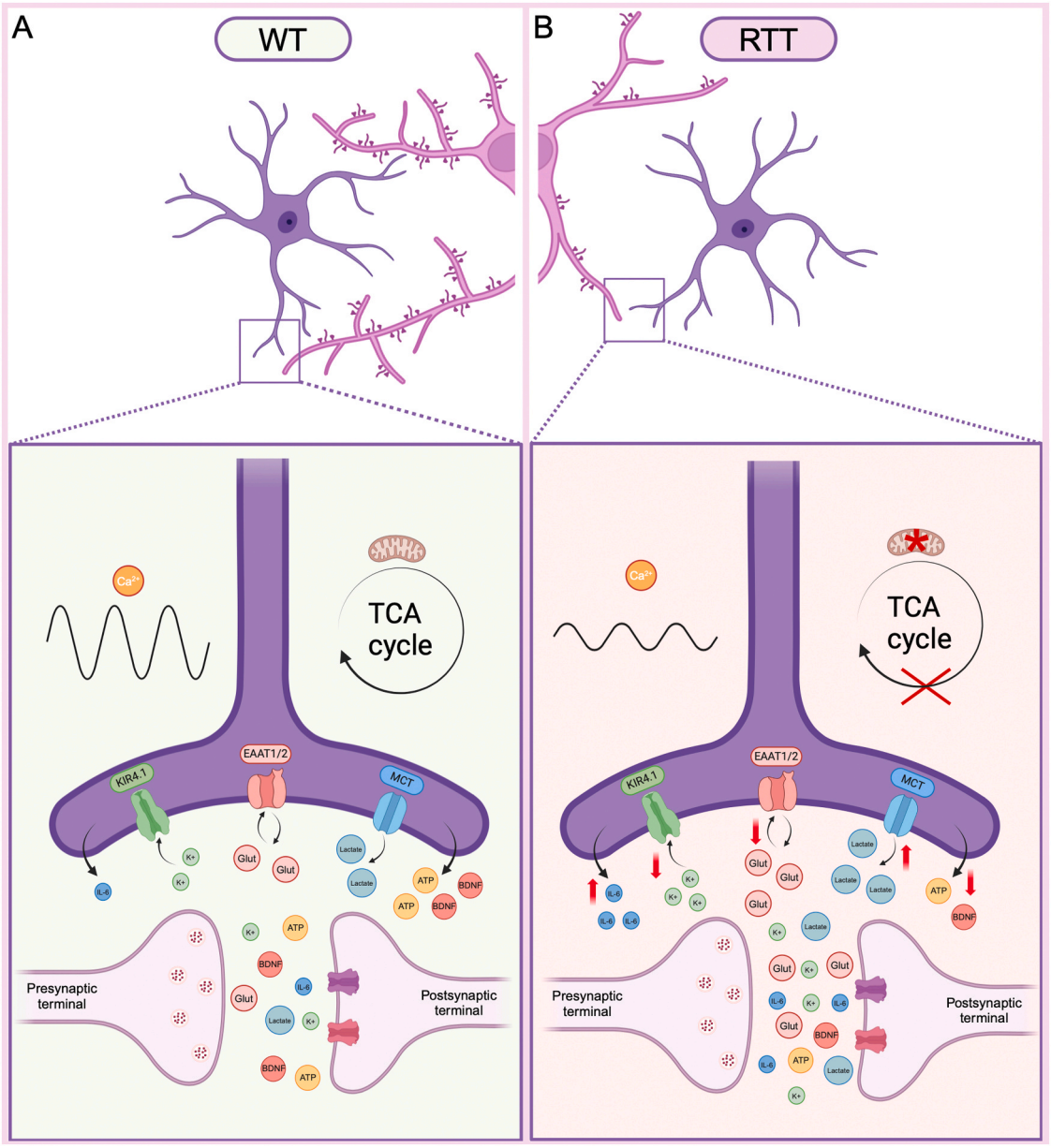

Fig. 1. Disrupted mechanisms underlying astrocyte-neuron communication in Rett syndrome. In physiological conditions (A), astrocytes provide metabolic and functional support to neurons, promoting neuronal maturation and synaptic formation/functioning. In Rett syndrome (B), there is a reduction in potassium (K^+) and glutamate buffering, a disrupted Ca^{2+} signalling, an increased inflammatory response, and an alteration in metabolic and trophic support, which negatively impact the neuronal phenotype.

neuronal synapses involves cell adhesion molecules, including Ephrins, Neuroligin-Neurexin, γ-protocadherins and NrCAM, as elegantly reviewed in (Tan and Eroglu, 2021).

On the other side, molecular, morphological and functional properties of astrocytes are deeply modulated by neurons. For instance, the expression of GLT-1 in astrocytes is induced by neuronal activity (Perego et al., 2000), as well as that of connexins (Ghézali et al., 2020). More extensively, transcriptional changes associated with astrocytic maturation and chromatin re-organization are promoted by neuronal signalling. Similarly, morphological and functional properties of astrocytes depend on neuronal proximity (Schipke and Kettenmann, 2004). Interestingly, single-cell sequencing analyses highlighted different populations of astrocytes among cerebral regions and also within cortical layers, but more relevant is the observation that these differences are abolished when neuronal inputs are altered as occurs in Reeler mouse models, indicating that neuronal proximity is fundamental for dictating astrocyte properties (Lanjakornsiripan et al., 2018). The mechanisms through which neurons promote these changes in astrocytes is not well known, but it might be associated with synaptic activity and the release of neurotransmitters, purines and growth factors (Hasel et al., 2017; Sardar et al., 2021).

3.2. *Astrocyte-neuron communication in RTT*

Many studies indicate a defective astrocyte-neuron communication in RTT. Analyses aimed at characterizing the signalling factors involved in the crosstalk between astrocytes and neurons revealed some deregulated molecules (Sun et al., 2023; Caldwell et al., 2022; Albizzati et al., 2024; Ehinger et al., 2021). Further, alterations of many astrocytic features strictly connected with neuronal functions emerged through *in vitro* and *in vivo* investigations.

Given the rising evidence of the involvement of astrocyte-secreted

factors in RTT, some research groups started to focus on the characterization of *MECP2* mutant astrocyte-conditioned medium (ACM), hypothesizing an increased release of neurotoxic factors or the reduced secretion of beneficial molecules. Indeed, the negative effect exerted by RTT astrocytes on neuronal growth and function could be related either to the presence of growth-inhibiting factors, or the absence of growth-promoting factors, or both. Of interest, the identification of these aberrantly secreted factor(s) could ultimately provide a means of novel pharmacological intervention for RTT. To characterize ACM composition, quantitative mass spectrometry analysis was conducted on ACM from mouse primary cultures of WT and *Mecp2* KO astrocytes. The analysis revealed 29 differentially expressed proteins: up-regulated targets are mostly involved in inflammatory response, complement activation, positive regulation of neuron death and metabolic process, whereas the down-regulated proteins are related to apoptosis, maintenance of protein location, cellular response to Interleukin-1 (Ehinger et al., 2021). Moreover, Caldwell and colleagues recently provided further interesting data by proteomic analysis on the secretome of astrocytes which were immunopanned from the cortex of postnatal day 7 (P7) RTT, Fragile X and Down syndrome mouse models. The study revealed a common aberrant expression of the Insulin-like growth factor binding protein 2 (Igfbp2), that contributes to the stunted dendritic branching of neurons by inhibiting the activity of IGF1, and an alteration in astrocytes of Bone Morphogenetic Protein 6 (BMP6), that impairs astrocyte maturation (Caldwell et al., 2022). Further analysis of secretome collected from hiPSCs differentiated in astrocytes carrying *MECP2* R270X mutation revealed metabolic abnormalities. Untargeted ^{1}H NMR reported a significant increase in lactate and a decreased amount of pyruvate, in association with decreased levels of tricarboxylic acid (TCA) cycle intermediates and ATP. These metabolic alterations are probably mediated by mitochondrial dysfunction (Sun et al., 2023).

Despite the increasing number of findings collected so far, one caveat of the described studies is that the analyses were performed on the secretome of astrocytes cultured alone, without considering the influence of neurons. Indeed, as already mentioned, neuronal inputs exert a strong impact on astrocyte morphology, gene expression and functioning (Hasel et al., 2017), indicating that astrocyte-neuron crosstalk should be considered in the investigation of astrocyte phenotype. In this regard, we recently investigated the effects of *Mecp2* KO astrocytes on WT neurons when cultured in a transwell-based co-culture system, which prevents the contact between the two cell populations but allows the exchange of secreted molecules. We demonstrated that KO astrocytes aberrantly secrete Interleukin-6 (IL-6), impairing synapse formation and functioning. Notably, this excessive secretion of IL-6 only occurs in the presence of WT neurons and is absent when KO astrocytes are cultured alone or with KO neurons, highlighting the critical role of astrocyte-neuron communication in regulating cytokine production (Albizzati et al., 2024). This result is particularly relevant for RTT, characterized by cellular mosaicism involving WT and mutant *Mecp2* expressing cells.

In summary, these results suggest that the negative effect exerted by *Mecp2* mutant astrocytes on neuronal functions and synapses could be caused either by the presence of synaptotoxic factors or the lack of synaptogenic molecules, or both. Probably a concerted action of factors affects neuronal health and identifying these abnormally secreted cue(s) may provide means of pharmacological intervention for RTT.

Regardless of the nature of the molecules, communication mediated by soluble factors might occur through biological vehicles, such as extracellular vesicles (EVs). EVs are lipid-bilayer membrane delimited vesicles which are generated in the cytoplasm or the multivesicular body/endosomal compartments, and contain cargos in the form of RNA, proteins and lipids (Welsh et al., 2024). Astrocyte-EVs (AEVs) might contribute to neuronal dysfunction, by transferring signalling molecules that affect synaptic activity, gene expression, and energy metabolism (Zappulli et al., 2016; Zhao et al., 2021; Patel and Weaver, 2021; Gharbi et al., 2020). As occurred in other neurological diseases, the content and release profile of AEVs could be altered in RTT. Interestingly, analyses of miRNA in EVs isolated from ACM of human astrocytes differentiated from hiPSC revealed an enrichment of miR-483–5p, which specifically suppresses human MeCP2 (Gordillo-Sampedro et al., 2024; Han et al., 2013). Moreover, this small RNA was found to be downregulated in RTT patients, leading the authors to speculate that RTT astrocytes may sense low MeCP2 levels and downregulate miR-483 expression and processing, or reduce its sorting into AEVs. Elucidating the role of AEVs could help explain some of the non-cell autonomous effects induced by RTT astrocytes on neurons.

All these findings indicate the role of astrocytes in supporting neuronal survival and function in RTT. The mechanisms documented so far by which *MECP2* mutant astrocytes affect neuronal health and/or synapses are reviewed below.

3.2.1. *Defective trophic and metabolic support*

Astrocytes support neurons by producing and releasing various neurotrophic factors, which promote neuronal survival, growth and differentiation. These factors include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), glial cell-line derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF). Given the critical role of neurotrophins in RTT and their potential as targets for therapeutic strategies (Nordvall et al., 2022), considerable efforts have been done to investigate how *MECP2* deficiency affects their signalling in astrocytes. Indeed, it is plausible that astrocytes contribute to synaptic dysfunctions in RTT through disrupted signalling of neurotrophic molecules. Most studies have focused on BDNF; however, the findings remain inconclusive, highlighting the complexity of BDNF regulatory pathway. In particular, it has been reported that murine astrocytes lacking *Mecp2* show increased BDNF transcription and secretion (Maezawa et al., 2009), but analysis in rat astrocyte cultures in which Mecp2 is knockdown indicated increased BDNF expression but reduced secretion (Buch et al., 2018). Furthermore, analysis of published RNA-sequencing data from human astrocytes harbouring R270X and R133C mutations reveals a significant increase of BDNF transcriptional expression (Sun et al., 2023). Few evidence are also available for others trophic factors, including NGF and GDNF, reporting an increase in protein and mRNA expression of NGF in Mecp2 knockdown astrocytes, without any alteration in its secretion (Buch et al., 2018) and a strong reduction of GDNF in human mutant astrocytes (Sun et al., 2023).

By supplying essential nutrients and metabolites, astrocytes also provide metabolic support to neurons, contributing to the regulation of glucose and lactate levels in the brain. The first evidence of defective metabolism in RTT astrocytes comes from the study from Sun and colleagues, showing in human RTT astrocytes an impaired energy metabolism, including reduced activity of the tricarboxylic acid (TCA) cycle, lower ATP, and increased lactate and palmitoyl-sn-glycero-3-phosphocholine (LPC) production. These phenotypes are all indicative of anaerobic conditions and enhanced glycolysis in mutant astrocytes. Accordingly, mitochondria, which are the primary energy-producing organelles, exhibit structural and functional changes, characterized by increased ROS production (Sun et al., 2023). Altered mitochondrial morphology was recently described in astrocytes from RTT cerebral organoids (Tomasello et al., 2024). Furthermore, integrating proteomic and metabolomic analyses confirmed the metabolic and energetic dysfunctions in 2D model RTT astrocytes. To extend the knowledge of the non-cell autonomous contribution of astrocytes to the development of neuronal defects, the effect of mitochondria from RTT astrocytes on neuronal functions was assessed by analyzing superoxide production and excitability in neurons. This aspect is particularly relevant given that mitochondria can be transferred from astrocytes to neurons. Interestingly, mitochondria from RTT increase superoxide levels and induce a hyperexcitable state in both control and RTT neurons (Tomasello et al., 2024).

Collectively, RTT astrocyte exhibit an alteration of neurotrophic signalling and energy metabolism, which participate to the occurrence

of neuronal dysfunction.

3.2.2. Calcium signalling dysregulation

Calcium (Ca^{2+}) signalling in astrocytes is crucial for their communication with neurons. Several studies have shown that astrocytes in RTT exhibit altered calcium signalling (Dong et al., 2018; Rakela et al., 2018), which can impair their ability to release gliotransmitters, such as glutamate and ATP, and regulate blood flow, two essential mechanisms for maintaining neuronal health. Ultimately, abnormal Ca^{2+} signalling contributes to the dysfunctional synaptic transmission and neuronal activity observed in the disease.

Specifically, it was reported that the loss of functional *Mecp2* is responsible for defective spontaneous and induced Ca^{2+} signalling in human mutant astrocytes and RTT animal models (Dong et al., 2018; Rakela et al., 2018). In order to analyse the consequences of these alterations on neuronal activity, Dong and colleagues demonstrated that abnormal Ca^{2+} activity in astrocytes leads to increased network excitability, which may underlie RTT symptoms (Dong et al., 2018). Furthermore, a dual patch clamp of astrocytes and neurons in *Mecp2* KO cortical slices revealed a concomitant reduced calcium signalling in cortical astrocytes and a strong impairment in the astrocyte-mediated synaptic transmission in neurons. To determine whether the defective signalling was due to neurons or astrocytes (or both cell types), the authors exploited brain slices collected from the female heterozygous brain, which show the mosaic expression of cells with wild-type or null allele. Obtained results indicated that neuronal transmission proceeds correctly when astrocytes express *Mecp2*, but it is severely affected in the presence of the null gene, extending the knowledge of astrocyte-mediated modulation of synaptic transmission and underlining the importance of non-cell autonomous mechanisms for correct brain functioning (Rakela et al., 2018).

These findings pinpoint the pivotal role of astrocyte Ca^{2+} signalling in maintaining functional synaptic integrity and highlight how Mecp2 deficiency disrupts Ca^{2+} dynamics in astrocytes and their consequences on neuronal transmission.

3.2.3. Alterations in glutamate and potassium homeostasis

Other mechanisms through which RTT astrocytes compromise neuronal health include impaired glutamate uptake and K^+ buffering.

Under physiological conditions, glutamate is taken up by astrocytes through glutamate transporters, including EAAT1 and EAAT2, and then converted into glutamine by glutamine synthetase, and subsequently recycled back to neurons where it is reconverted into active neurotransmitters. This cycle ensures a constant and controlled supply of glutamate. An alteration of this cycle leads to elevated extracellular glutamate concentrations, causing excitotoxicity, a harmful condition for neurons that compromises synaptic and neuronal function (Olsen et al., 2015). Mutations in *MECP2* affect the expression of glutamate transporters and disrupt glutamate homeostasis in astrocytes, thereby contributing to neuronal defects. Increased glutamate clearance was initially observed in cultured astrocytes obtained from *Mecp2* KO mice (Okabe et al., 2012). Conversely, reduced expression of EAAT1 and EAAT2 was found in *MECP2* R270X and R133C human astrocytes, as well as impaired glutamate clearance (Sun et al., 2023). These findings were further corroborated in human astrocytes edited to express the truncated R168X mutation (Tomasello et al., 2024). Accordingly, elevated levels of glutamate have been detected in the brain and cerebrospinal fluid of RTT patients (Hamberger et al., 1992).

Along with their role in glutamate homeostasis, astrocytes are involved in extracellular K^+ buffering, through which they regulate neuronal transmission and excitability (Walz, 2003). One of the key proteins involved in K^+ buffering is Kir4.1, a glia-specific inward rectifying channel, encoded by *Kcnj10* gene, that represents one of the most expressed gene in astrocytes (Nwaobi et al., 2016). Transcriptomic analysis in the cortex of symptomatic *Mecp2* KO mice indicated a significant reduction of *Kcnj10* in astrocytes (Pacheco et al., 2017). Further analysis confirmed its transcriptional and protein decrease in astrocytes isolated from adult *Mecp2* null mice, in association with a deficiency in Kir4.1-mediated currents and altered extracellular K^+ dynamics in the cortex of *Mecp2* KO animals (Kahanovitch et al., 2018).

Collectively, these results underscore molecular and functional deregulations of proteins directly involved in astrocyte-mediated neurotransmitter and ion homeostasis in RTT.

3.2.4. Increased inflammation and immune response

In response to neurological insults, astrocytes undergo a process known as reactive astrogliosis, characterized by the remodeling of biochemical, morphological, and metabolic properties, and the production of a variety of molecular signals, including cytokines, chemokines, amino acids and ions, representing key drivers of neuroinflammation (Sofroniew and Vinters, 2010). Although astrocytes show some common features in response to different pathological stimuli, their heterogeneity is more complex and dynamic than previously thought (Moulson et al., 2021). Increasing evidence highlights that astrocyte-mediated neuroinflammation, together with their complex crosstalk with other glial or immune cells, plays a crucial role in neuronal survival and the maintenance of functional neurocircuits, but in some cases it contributes to the disease progression (Zhao et al., 2024).

Over the past decade, it has become increasingly clear that Mecp2 mutant animal models and RTT patients show immune dysregulation and chronic subclinical inflammation, which cause neuronal stress and damage, possibly exacerbating neuronal dysfunctions (Cortelazzo et al., 2014; Cordone, 2024; Cronk et al., 2015; Pecorelli et al., 2020). To this end, the negative impact of the inflammatory environment on synaptic function and plasticity is well known (Mottahedin et al., 2017). Besides microglia and peripheral immune cells, also astrocytes participate to neuroinflammation in RTT. Without showing the classical features of reactive astrocytes, such as hypertrophy of astrocytic processes and upregulation of glial fibrillary acidic protein (GFAP), *Mecp2* null astrocytes express and release elevated levels of proinflammatory molecules (Albizzati et al., 2024). In particular, MeCP2 deficiency disrupts the activation of signalling pathways, including the MAPK pathway, which plays a key role in regulating cytokine production (Maezawa et al., 2009). Furthermore, we demonstrated the abnormal production and secretion of Interleukin-6 (IL-6) by *Mecp2* KO astrocytes. Notably, the increase in IL-6 was evident only when astrocytes where co-cultured with neurons, highlighting the importance of astrocyte-neuron communication in shaping the molecular and functional properties of astrocytes. We also proved the detrimental effect of the cytokine on synapse formation and functioning, and complementary the efficacy of an antibody against IL-6 to prevent synaptic defects (Albizzati et al., 2024). Additionally, beyond IL-6, proteomic analyses of the secretome of KO astrocytes revealed the up-regulation of other proteins involved in the inflammatory response and activation of the complement cascade, that play an important role for the regulation of immune processes (Ehinger et al., 2021).

In summary, the evidence collected so far indicates the contribution of astrocytes to neuroinflammation in RTT through excessive pro-inflammatory signalling, which in conjunction with oxidative stress and impaired metabolic support, contributes to neuronal and network impairments observed in the disease.

4. Experimental models for studying astrocyte-neuron communication in RTT

All the data collected so far on the non cell-autonomous mechanisms through which astrocytes influence neuronal health and function have been obtained through a combination of methodological approaches, ranging from simplified cell cultured to more complex systems. Whereas *in vitro* systems are essential for uncovering the molecular mechanisms underlying astrocyte-neuron communication, *in vivo* models allow for

the investigation of this crosstalk within the context of an intact organism, where the interactions among multiple components are preserved. Following the increasing in complexity of the experimental models, we here provide a description of the methodological strategies used for studying astrocyte-neuron communication in RTT, highlighting the obtained findings and discussing the associated advantages and limitations (Fig. 2).

The first data in the field were obtained by using primary cell cultures (Ballas et al., 2009; Maezawa et al., 2009; Williams et al., 2014; Yasui et al., 2013; Okabe et al., 2012). Astrocytes, obtained from RTT mouse models or differentiated from human induced pluripotent stem cells (iPSCs), are cultured to study their intrinsic properties in a controlled environment. Whereas studying astrocyte morphology through this system is not informative enough since astrocytes assume a non-physiological flat shape when cultured alone, primary astrocyte cultures were used for studying their molecular features, neurotransmitter and ion homeostasis, metabolic features and protein secretion. Obtained results demonstrated a wide deregulation in gene expression (Yasui et al., 2013; Sun et al., 2023), an alteration in glutamate clearance (Sun et al., 2023; Tomasello et al., 2024; Okabe et al., 2012) and K^+ currents (Kahanovitch et al., 2018), metabolic aberration likely mediated by dysfunctional mitochondria (Sun et al., 2023; Tomasello et al., 2024), and defects in protein secretion, with the increased release of toxic molecules and reduced production of protective ones (Caldwell et al., 2022; Albizzati et al., 2024; Ehinger et al., 2021). To investigate the effect of astrocyte secreted factors on neurons, the treatment of neuronal cells with astrocyte-conditioned medium (ACM) was widely used. The results obtained through the diverse studies in RTT research are concordant, highlighting a non-cell autonomous mechanisms through which RTT astrocytes affect neuronal morphology and synaptic functionality (Ballas et al., 2009; Williams et al., 2014; Sun et al., 2023; Albizzati et al., 2024). A direct characterization of ACM composition through proteomic and metabolomics analyses have provided further information on the signalling molecules involved (Sun et al., 2023; Caldwell et al., 2022; Ehinger et al., 2021).

To study intercellular communication, co-cultures between neurons and astrocytes, obtained from healthy and/or RTT backgrounds, were exploited, with the advantage to maintain a more physiological communication dynamics between cells. With their pioneer work, Ballas and colleagues demonstrated that hippocampal wild-type neurons cultured in contact with Mecp2 KO astrocytes show reduced dendritic branching and stunted dendrites (Ballas et al., 2009). The same results on neuronal morphological defects were observed when human RTT astrocytes harbouring R270X and R133C mutations were cultured with neurons prepared from a wild-type mice and, more recently, with human neurons (Williams et al., 2014; Sun et al., 2023). Furthermore, the work by Sun and colleagues expanded the investigation on the non cell-autonomous effect on neurons, by analysing the influence of RTT astrocytes on synapses, reporting their inability to properly support their formation. They also analysed the expression of neuron-induced astrocytic genes, finding in RTT astrocytes a similar aberration compared to mutant astrocytes cultured alone (Sun et al., 2023).

Since the interaction between astrocytes and neurons is bidirectional, co-cultures are ideal also for studying the effect of neurons on

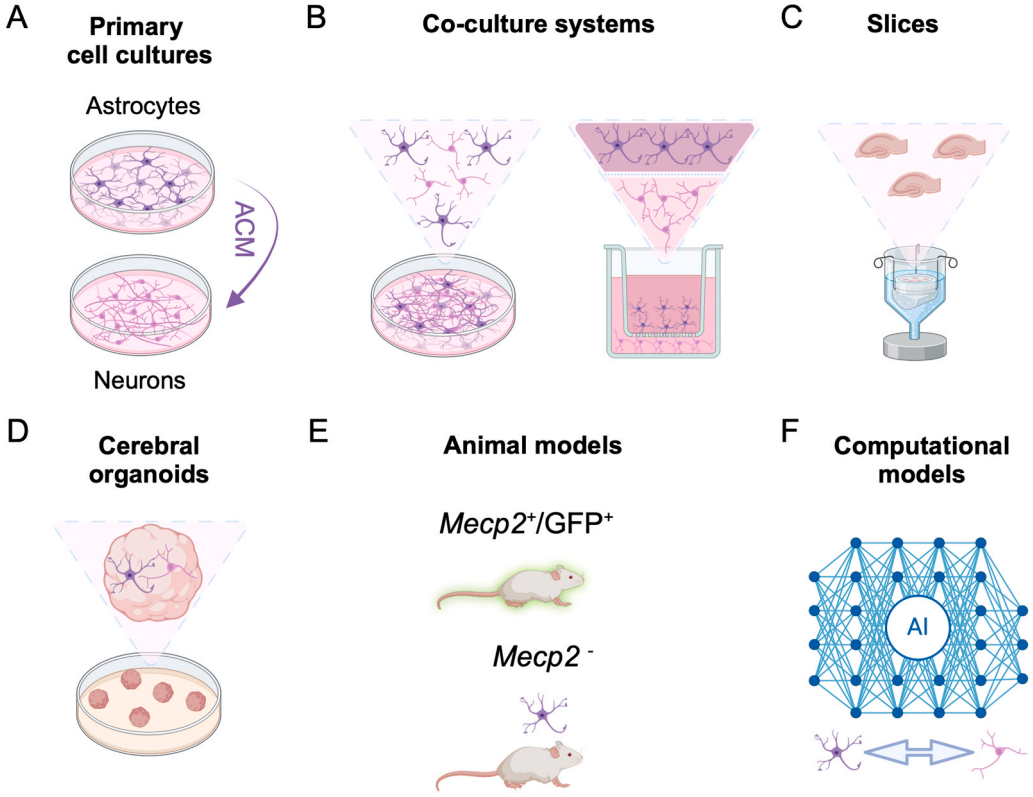

Fig. 2. Experimental models for the study of astrocyte-neuron communications in RTT. (A) Astrocyte conditioned medium (ACM) is collected from *Mecp2* mutant astrocytes, and analysed or used for treating primary neurons. (B) Co-culture systems, in which neurons and astrocytes are cultured in contact (on the left), or through transwell-based systems (on the right). In this case astrocytes are positioned on the top and neurons on the bottom, thus preventing their physical interaction but allowing the exchange of secreted molecules. (C) Acute or organotypic slices are ideal for the analyses of functional properties of astrocyte-neuron network. (D) Cerebral organoids derived from patient-induced pluripotent stem cells (iPSCs) are useful for the study of the cellular and molecular pathophysiology of RTT in a human-like context. (E) RTT transgenic animal models permit to study astrocyte-neuron communication in a complex organism. The mouse model expressing the reporter transgene GFP on the same X chromosome as the wild-type *Mecp2* favors the easy discrimination between *Mecp2*$^+$ and *Mecp2*$^-$ cells. The conditional model in which *Mecp2* is specifically deleted or re-expressed in astrocytes permits to distinguish the astrocyte contribution on neuronal defects in RTT. (F) Mathematical models can simulate the crosstalk between neurons and astrocytes, facilitating the prediction of behaviours and interactions.

astrocytes. To this end, it was demonstrated that morphological complexity of WT astrocytes is reduced in the presence of mutant neurons, whereas human RTT astrocytes co-cultured with WT neurons show a more complex morphology compared to RTT astrocytes cultured with RTT neurons (Sun et al., 2023).

However, although strongly informative, in contact co-cultures combine two different communication components, including the physical interaction and secretion of signalling molecules. To isolate either physical contact or signalling molecule exchange, researchers have employed different methods. One approach is to use transwell systems, where cell types are separated by a permeable membrane, thus preventing their physical interaction but allowing the exchange of secreted factors. Compared to the treatment with ACM, the transwell-based co-cultures ensure a continuous exchange of molecules between neurons and astrocytes, a crucial process for dictating transcriptional, morphological and functional properties of both cell types. To our knowledge, only our research group has used this co-culture system for studying astrocyte-neuron crosstalk in RTT, confirming the detrimental effect of *Mecp2* KO astrocyte-secreted factors on synapse formation and functioning, and reporting the aberrant secretion of IL-6 by KO astrocytes. Intriguingly, IL-6 upregulation was found in *Mecp2* KO astrocytes only when cultured with WT neurons, and not when cultured alone or with KO neurons, demonstrating neuronal inputs and neuronal genotype as critical factors for influencing the molecular traits of astrocytes (Albizzati et al., 2024).

Characterized by a higher complexity compared to 2D cultured cells, acute and organotypic slices, along with cerebral organoids, better mimic *in vivo* tissue architecture and preserve cell-to-cell communication, allowing to analyse in a more physiological context the molecular and functional features of astrocyte-neuron crosstalk. These models were successfully used by some researchers in the field of RTT to dissect the functional communication between astrocytes and neurons in the disease. Dong and colleagues analysed the functional properties of astrocytes and neurons in acute hippocampal slices prepared form KO mice (2–3 weeks old and 6 weeks old) and, through Ca^{2+} imaging analyses, they reported higher amplitude of spontaneous and induced Ca^{2+} oscillation with concomitant activation of the extrasynaptic NMDARs, which was measured in pyramidal neurons by whole cell patch clamp recording. The two events are functionally coupled, as demonstrated by the administration of a Ca^{2+} chelator that, when injected in astrocytes, prevents the excessive activation of extrasynaptic NMDARs on neighboring neurons (Dong et al., 2018). Similarly, dual patch-clamp was successfully applied on cortical slices obtained from younger *Mecp2* KO mice (P10–12), demonstrating that, while depolarization in astrocytes induces activation of neuronal signalling in WT slices, this mechanism is absent in KO slices. Further analyses conducted on *Mecp2* heterozygous slices shed light on the cause of this defective signalling, revealing that astrocytes, and not neurons, require *Mecp2* to have a significant effect on astrocyte-mediated signalling within the local circuit (Rakela et al., 2018). Analysis on acute slices was also pivotal to reveal the dysregulation of K^+ homeostasis in the cortex of Mecp2 KO mice. This functional phenotype, that correlates with decreased expression of Kir4.1 channel, might contribute to neuronal hyperexcitability in symptomatic animals (Kahanovitch et al., 2018).

More recently, brain organoids have emerged as a tool for modeling human diseases, including RTT (Trujillo and Muotri, 2018). “Mini--brains" derived from patient-induced pluripotent stem cells (iPSCs) allow researchers to study RTT’s cellular and molecular pathophysiology, as well as intercellular communication mechanisms, in a human-like context. Recently, using this approach, Tomasello and co-authors highlighted dysfunctional mitochondria in RTT astrocytes and underscored the consequences of their transfer to neurons, such as the induction of hyperexcitability and the alteration of neuronal function (Tomasello et al., 2024). In the future 3D organoid-like spheres, termed asteroids, which combine neuronal and astrocytic cells, could favour the study of astrocyte-neuron interaction also in RTT (Krencik et al., 2017).

Furthermore, transgenic animal models have been instrumental in advancing our understanding of astrocyte-neuron communication in RTT. Importantly, experiments on conditional mice, which selectively express or lack *Mecp2* in astrocytes, confirmed *in vitro* evidence of their non-cell autonomous ability to support neuronal health (Lioy et al., 2011; Garg et al., 2015). Indeed, the selective re-expression of Mecp2 in astrocytes in a null mouse model significantly increases dendritic morphology and the expression of the synaptic marker vGlut1 in mutant neurons. In parallel, Mecp2 restoration in astrocytes improves motor and respiratory defects, reduces anxiety levels and prolongs lifespan (Lioy et al., 2011). Complementary, the selective loss of Mecp2 in astrocytes elicits, at least in part, a RTT-like phenotype, mainly characterized by respiratory abnormalities (Lioy et al., 2011; Garg et al., 2015). In addition, the use of female *Mecp2* heterozygous animals is crucial to shed light on the molecular mechanisms occurring among cells with a different genotype. To this end, the expression of the reporter transgene GFP on the same X chromosome as the wild-type *Mecp2* allowed to easily discriminate *Mecp2*$^+$ from *Mecp2*$^-$ cells in functional studies (Dong et al., 2018; Rakela et al., 2018; Smrt et al., 2011). In the future, the application of optogenetics/chemogenetics, spatial omics or Optical Neuron-Astrocyte Proximity Assay could help in visualizing and studying neuron-astrocyte interactions in animal models in relation to specific behaviours, as has been done in other contexts (Bang et al., 2016; Kastanenka et al., 2020; Octeau et al., 2018).

Finally, we can envisage in the future the use of mathematical models which simulate the cross-talk between neurons and astrocytes, helping to predict behaviours and interactions (Lenk et al., 2020; Nadkarni and Jung, 2007; Amiri et al., 2013; Oschmann and Kruggel-Emden, 2018). These models focus on different scales of increasing complexity, including single cell astrocyte models, tripartite synapse models or neuron-astrocyte network models. In addition, the integration of some important features, such as Ca^{2+} waves dynamics among astrocytes through GJs, gliotransmitters’ release and the formation of multiple tripartite synapses by a single astrocyte, makes the computational models more exhaustive and accurate (Lenk et al., 2020). Computational models provide a more flexible framework to investigate how cells interact together, with the additional advantage to decrease the number of experimental animals in research.

5. Future perspectives and conclusions

Given the importance of astrocytes in pathophysiology of RTT, numerous studies have focused on understanding of astrocyte-neuron communication in the disease, in order to uncover the underlying molecular mechanisms, a fundamental step toward developing novel therapeutic strategies. Considering the defects of Mecp2 mutant astrocytes and their well-accepted non cell-autonomous effects on neurons, efforts to restore proper astrocytic functions, for instance by correcting impaired calcium signalling, modulating the inflammatory response, improving glutamate and ion transport and repairing metabolic pathways, could alleviate some of the neurological RTT symptoms. In the future, the application of advanced techniques and experimental models, along with the development of computational models, which simulate the crosstalk between neurons and astrocytes, could expand our knowledge on neuron-astrocyte interactions in this complex neurodevelopmental disorder.

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Fabio Biella: Writing – review & editing. **Roggero Ottavia Maria:** Writing – review & editing. **Angelisa Frasca:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Postogna Francesca Maddalena:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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