

Review Article

Developmental Dynamics of Rett Syndrome

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Rett Syndrome was long considered to be simply a disorder of postnatal development, with phenotypes that manifest only late in development and into adulthood. A variety of recent evidence demonstrates that the phenotypes of Rett Syndrome are present at the earliest stages of brain development, including developmental stages that define neurogenesis, migration, and patterning in addition to stages of synaptic and circuit development and plasticity. These phenotypes arise from the pleotropic effects of MeCP2, which is expressed very early in neuronal progenitors and continues to be expressed into adulthood. The effects of MeCP2 are mediated by diverse signaling, transcriptional, and epigenetic mechanisms. Attempts to reverse the effects of Rett Syndrome need to take into account the developmental dynamics and temporal impact of MeCP2 loss.

1. Introduction

Rett Syndrome (RTT) is a developmental neurological disorder that affects 1 in every 10,000–15,000 live births in the US [1]. The genetic origin of RTT, in ~90% of patients, has been traced to sporadic loss-of-function mutations in the X-linked gene *MECP2* coding for methyl CpG-binding protein 2, mainly localized to methylated pericentric heterochromatin [2]. Clinical features of the disorder involve marked developmental regression, progressive loss of acquired motor and language skills, the acquisition of stereotyped repetitive hand movements, muscle hypotonia, autonomic dysfunctions, and severe cognitive impairment.

MeCP2 is an epigenetic modulator of gene expression. It acts as both a transcriptional activator and repressor [3, 4], in addition to regulating gene expression posttranscriptionally via microRNA- (miRNA-) processing machinery [5] and in an activity-dependent manner to regulate synaptic activity [6]. The binding interaction between MeCP2 and DNA is governed by a variety of genetic and epigenetic factors such as the length of the DNA, nearby sequences, and methylation patterns [3, 7, 8]. MeCP2 is a known binding partner of 5-methylcytosine (5mC) at CpG dinucleotides throughout

the genome, resulting in transcriptional repression in these regions [9]. However, MeCP2 is also the predominant 5-hydroxymethylcytosine- (5hmC-) binding protein in the brain. Enrichment of 5hmC is linked to highly expressed genes [10, 11] in the absence of 5mC, suggesting that, in the context of this binding interaction, MeCP2 facilitates transcription [11]. Of note, MeCP2 is itself subject to methylation-dependent regulation, disruptions which have been linked to autism [12]. Thus, epigenetic modifications can regulate both the expression of MeCP2 and its downstream binding partners.

Alternative splicing of *Mecp2/MECP2* generates two main isoforms that differ exclusively at the N-terminus [13, 14]: MeCP2_e1, the predominant isoform in the brain [13–16], and MeCP2_e2, which displays a later expression onset during mouse brain development [17]. The two isoforms exhibit differential temporal and region-specific differences in their expression profiles in the brain and both contribute to neurological function and gene expression patterns [18–20]. The ratio of splice variants differs in a temporal- and cell type-specific manner, suggesting dynamic regulation of their expression and nonredundant functionality in the distinct stages of neurogenesis and adulthood [15, 17, 18, 21]. Whereas

MeCP2_e1 has been shown to be the isoform most relevant to RTT pathogenesis [20], MeCP2_e2 interacts with forkhead protein FoxG1, which promotes neuronal survival and maturation and in which mutations can also cause RTT [22]. The physiological significance of these two isoforms is not fully understood. Manipulations of independent isoforms in a cell type-specific manner are required in order to reveal their respective contributions to activity-dependent functions of MeCP2.

MeCP2 expression affects successive stages of brain development including prenatal neurogenesis, postnatal development of synaptic connections and function, experience-dependent synaptic plasticity, and maintenance of adult neural function including sensory integration [1, 23, 24]. MeCP2 critically maintains synaptic excitation (E) and inhibition (I), which are fundamental to the function of brain circuits and are often disrupted in neurological disorders including RTT [23, 25]. Additionally, MeCP2 has a remarkably diverse pool of binding partners and downstream targets [26, 27]. This functional and binding complexity, in combination with the domain-specific functionality of the MeCP2 protein [28, 29], confers a pleiotropic effect across age- and cell type-specific backgrounds [7]. Accordingly, different mutations in MeCP2 result in a wide range of phenotypic variability and severity in RTT patients [30], necessitating context-dependent mechanistic insights into MeCP2 function.

Transgenic mouse models that harbor cell type-specific mutations in MeCP2 have shed light on our understanding of RTT pathogenesis in the brain. Expression of MeCP2 under the CamKII or neuron-specific enolase promoter does not prevent the appearance of most RTT phenotypes, suggesting a more complex network of involvement for MeCP2 [31]. Interestingly, mice lacking MeCP2 exclusively in GABAergic neurons recapitulate many RTT features [32], and deletion of MeCP2 in the parvalbumin- (PV-) expressing subset of GABAergic neurons abolishes experience-dependent critical period plasticity in the absence of most RTT phenotypes [33]. The restoration of MeCP2 exclusively in astrocytes results in a non-cell-autonomous ameliorative effect on neurons *in vivo* [34], whereas RTT microglia exhibit adverse non-cell-autonomous effects on WT neurons *in vitro* [35]. In spite of their differing roles and effects on downstream gene regulation [18], transgenic expression of either the MeCP2_e1 or MeCP2_e2 splice variant has been shown to prevent the development of a number of RTT phenotypes in a mouse model lacking MeCP2. However, many abnormalities were only partially prevented, negating the notion that both transcripts are capable of acting independently to fulfill all of the roles of MeCP2 [36]. Accordingly, another study demonstrated that a point mutation in the MeCP2_e1 splice variant is sufficient to recapitulate many RTT phenotypes observed in MeCP2 KO mice [20]. Whereas the complexity that underlies the roles of MeCP2 will not be resolved with a single mouse model, each contributes a piece to the larger puzzle that represents MeCP2 functionality.

Similar to loss-of-function mutations in *MECP2*, the duplication of *MECP2* also results in a progressive neurological disorder that includes stereotypic and repetitive hand or body movements, epilepsy, spasticity, and a severe syndromic

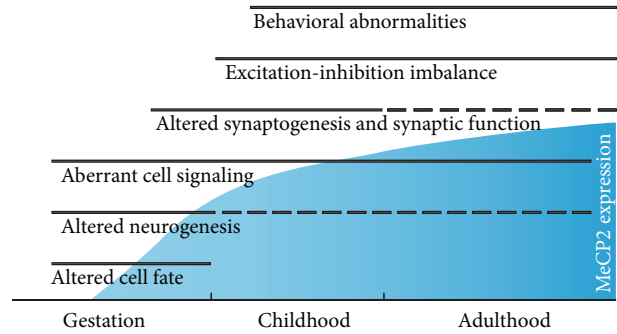


FIGURE 1: MeCP2 influences multiple features of brain development and function, at a variety of time points as its expression increases and is maintained. Thus, prenatal and postnatal brain development, as well as adult function, are all potentially affected in Rett Syndrome.

form of intellectual disability in male patients [37]. Recent studies show that the neurological dysfunctions in *MECP2* duplication syndrome are reversible in adult symptomatic mice and correction of MeCP2 levels genetically or by using antisense oligonucleotides largely restores molecular, electrophysiological, and behavioral deficits [38].

Traditionally, the dynamic time-course of RTT is thought to involve a period of apparently normal early development followed by profound neurological regression—a defining feature of RTT—and subsequent stabilization or partial recovery. However, our understanding of the disease initiation and progression and the ways in which *MECP2* impacts distinct phases of neurodevelopment is gradually evolving. In recent years, there has been a gradual shift in our understanding of atypical regression in RTT patients, with growing evidence of prenatal and early postnatal developmental abnormalities resulting in defects in the establishment and refinement of early neural circuits and, later, cortical plasticity (Figure 1). In this review, we aim to summarize recent findings and argue that *MECP2* serves distinct, discrete functions throughout developmental and adult stages, integrating genomic and environmental signals in a context-dependent manner.

2. Deficits in Early Neurogenesis

Early work in mouse models on the function of MeCP2 reported a pattern of expression limited to the neural lineage, with low expression in neuroblasts and a progressive increase during embryonic and postnatal development. Such findings led to the belief that MeCP2 is predominantly involved in the maturation and maintenance of neuronal function, as opposed to early cell fate decisions, and were further supported by a lack of phenotype observed with respect to differentiation in MeCP2-null neural progenitor cells (NPCs) [39].

Evidence has since demonstrated that, whereas MeCP2 expression increases postmitotically, both mRNA and protein can be detected throughout the majority of the mouse and human lifespan, including embryonic stages during which

neurogenesis occurs [21, 40–44]. MeCP2 protein expression does indeed increase after neuronal differentiation, when the vast majority of RTT phenotypes have been described. Experiments designed to determine isoform-specific expression have detected MeCP2.e1 protein in the mouse hippocampus as early as E14, whereas MeCP2.e2 was first detected at E18 [17]. Samples younger than E14 were not analyzed in this study, and thus these results do not preclude the possibility of expression at earlier embryonic stages. MeCP2.e1 expression increased until it reached a plateau at P7–P21. MeCP2.e2 expression overlapped with MeCP2.e1 after E18, albeit at a decreased level. As the gestational period of synaptogenesis overlaps with that of neuronal migration in human development [45], it stands to reason that MeCP2, known to regulate synaptic development [46–48] and cell guidance and laminar organization in the olfactory system [49], may contribute to the processes of cell fate specification and migration in the developing brain, especially the cortex. Accordingly, the landscape of clinical literature has been shifting to suggest an earlier onset of symptoms in RTT patients [50–54].

3. Cell Fate and Signaling Pathways

Expression of MeCP2 during early neurogenesis suggests a consequent role for the protein during this critical developmental time point. Neurogenic functions of MeCP2 have indeed since been demonstrated in mouse, whereby embryonic NPCs overexpressing MeCP2 exhibited a heightened neural identity *in vitro* [55]. Conversely, embryonic NPCs extracted from mice lacking MeCP2 exhibited a more proliferative—as opposed to late postmitotic—identity and revealed morphological alterations as early as 3 days *in vitro* (DIV) [44]. A human patient-derived induced pluripotent stem cell (iPSC) model of Rett Syndrome expressing a *de novo* frame-shift mutation in exon 4 (c.806delG) illustrated a parallel role for MeCP2 in the promotion of neural identity in which neural stem cells lacking MeCP2 exhibited increased astrocytic differentiation *in vitro* [56]. Mesenchymal stem cells (MSCs) isolated from a Rett patient harboring a different *de novo* mutation (del 1164-1207) also demonstrated impaired neural differentiation *in vitro*, which resulted in a reduced percentage of NeuN-expressing cells and increased senescence [57]. Roles for MeCP2 in determining neurogenic potential have been reported in *Xenopus* [58], zebrafish [59, 60], and chick [61] embryos.

Mechanisms underlying the function of MeCP2 with respect to early cell fate decisions are largely unknown. Neurogenic signaling cascades such as the *Notch-Delta* and PI3K-Akt pathways have been demonstrated to coordinate with MeCP2 throughout various time points including neurogenesis. Phosphorylation of MeCP2 at Serine421 (S421)—known to regulate gene transcription and synaptic development in an activity-dependent manner [62]—has since been shown to modulate the balance between proliferation and differentiation in NPCs isolated from the adult mouse hippocampus. Evidence suggests that the *Notch-Delta* signaling pathway, mediated via MeCP2-S421 phosphorylation, may serve as the hub linking MeCP2 to neural cell fate decisions in adult

NPCs [63]. Experiments performed in *Xenopus* embryos, in which MeCP2 is expressed and is critical for neurogenesis, have demonstrated that the *Notch-Delta* signaling pathway regulates the patterning of primary neuronal differentiation in conjunction with MeCP2 binding. A complete lack of MeCP2 protein resulted in a decrease in the number of neuronal precursors, whereas expression of a truncated form of MeCP2 often found in Rett Syndrome patients—R168X—resulted in an increase in the number of neuronal precursors relative to WT embryos [58]. This phenotypic variety observed as a result of varying dosages and mutations of MeCP2 is echoed throughout the experimental and clinical literature [30, 52, 53, 64].

The PI3K-Akt signaling pathway is implicated in a wide range of cellular functions including cell cycle and transcriptional regulation [65]. The pathway has also been shown to regulate key neurological processes such as synaptic transmission [66] and neurodegeneration [67, 68] and is implicated in a range of neurological diseases and disorders such as spinocerebellar ataxia type 1 [67], Huntington's disease [68], amyotrophic lateral sclerosis (ALS) [69], and RTT [4, 70–72]. The majority of studies performed in RTT models, including those listed above, have examined the contribution of the PI3K-Akt pathway to disease effects and rescue in mature neurons. Whereas PI3K-Akt signaling has been shown to promote adult neurogenesis in the context of exercise enrichment [73], traumatic brain injury recovery [74], and surgical denervation [75], roles for PI3K-Akt signaling have also been demonstrated throughout embryonic neurogenesis in mouse [76], *Xenopus* [77], and zebrafish [78]. However, the precise roles of PI3K-Akt signaling in embryonic neurogenesis in the context of RTT have yet to be elucidated.

4. microRNAs and MeCP2

microRNAs (miRNAs) finely regulate genetic networks throughout the course of brain development and, with astounding complexity, act as critical determinants of early neurogenic activities such as cortical patterning and activity development, cellular subtype specification, and neuronal differentiation [79–81]. They are themselves subject to upstream epigenetic regulation; many are indeed targets of MeCP2 [82] or, as in the case of miR-132, act in a feedback loop as both target and regulator to maintain MeCP2 levels [83]. miR-132 has in turn been shown to promote postnatal neurogenesis and synaptic integration in neurons of the olfactory bulb [84]. Another brain-enriched miRNA target of MeCP2, miR-137, has been shown to regulate neuronal maturation and dendritogenesis in the postnatal hippocampus [85] and to modulate proliferation and differentiation in adult neurogenesis [82]. Moreover, miR-137 has been shown to negatively regulate neural stem cell proliferation and promote differentiation in the embryonic mouse brain [86]. miR-199a has been demonstrated as a link between MeCP2 and the mTOR pathway [87], previously implicated in RTT [72]. MeCP2 facilitates the postprocessing of miR-199a, which positively regulates mTOR signaling. Notably, exogenous miR-199a ameliorates several impairments in RTT neurons

and the genetic deletion of miR-199a-2 results in decreased mTOR activity in the brain and the recapitulation of several RTT phenotypes [87]. MeCP2 is known to influence the production of growth factors such as BDNF and IGF1—the latter via a miRNA-mediated pathway downstream of BDNF [88]. Many pathways and loops that determine the process of neurogenesis are maintained by the concerted regulation of miRNAs and MeCP2. As such, they provide insight into potential avenues by which MeCP2—or the lack thereof—can influence the developing cortex.

5. Deficits in Neuronal Migration and Cortical Patterning

Functions of MeCP2 during early neurogenesis result in immediate and long-term effects on neuronal migration and cortical patterning. Migration begins at gestational week 8 in humans and at E11 in mouse, at which point neural progenitors proliferating within the ventricular zone that lines the cerebral ventricles begin to differentiate to form the cortical laminae [45, 89]. Postmitotic cells migrate over radial glial scaffolds to form the discrete layers of the cerebral cortex in an inside-first, outside-last temporal pattern. Deep-layer cortical neurons are born first and passed by newly born neurons migrating to upper layers. This process is spatiotemporally governed by a variety of signaling, transcriptional, and epigenetic mechanisms [90–92]. Aberrant regulation of the proliferation and differentiation of neural stem cells results in a range of cortical dysplasias and is associated with many neurological and neuropsychiatric disorders including Alzheimer's disease, schizophrenia, and ASDs [93].

Early work demonstrated morphological cortical deficits in 8-week-old MeCP2^{-/-} mice including reduced thickness and increased cell density in neocortical layers; due in part to the belief that MeCP2 was not expressed early on, these alterations were believed to be a result of reduced cell size and complexity as opposed to deficits in corticogenesis [39]. Cerebellar expression profiling performed alongside chromatin immunoprecipitation in MeCP2-deficient mice has since revealed increased expression of *Reln*—encoding the extracellular signaling protein Reelin, known to be essential for proper neuronal lamination [94]. Accordingly, recent evidence has demonstrated that mouse NPCs lacking MeCP2 exhibit delayed corticogenesis with respect to migration from the subventricular and ventricular zones into the cortical plate [44]. These findings suggest a need for a thorough evaluation of the role of MeCP2 in cortical migration and lamination, as layering deficits observed at postnatal time points in RTT may result from combinatorial deficits in cortical development and maintenance.

6. Deficits in Synaptic Transmission and Plasticity during Postnatal Development

Along with deficits in early neurogenesis and cortical patterning, *MECP2* has been shown to play a key role in synaptic maturation and plasticity. Mutant mouse models have been generated with a global deletion of MeCP2 (MeCP2^{-/-}) from

all neurons and selectively from specific cellular subtypes including various neuronal subtypes and astrocytes. These models have served as a robust starting point in which to study the common principles underlying synaptic defects in RTT. They provide unique insight into the genetics that determine cell type-specific contributions to pathogenesis.

Functional defects in synaptic transmission have been investigated in an *Mecp2* global deletion model in which cortical connections were found to have weaker excitatory synaptic transmission and lower levels of basal activity [1, 95–98], reminiscent of an immature circuit. Cellular mechanisms of long-term plasticity, considered the functional basis of learning and memory, have also been found to be impaired in *Mecp2* mutant animals [2, 99, 100]. The majority of these early studies have used brain slice preparations, recording synaptic transmission including miniature synaptic currents and synaptic plasticity deficits. Similar to deficits in excitatory transmission, deletion of *Mecp2* from all forebrain GABAergic interneurons also recapitulates key features of RTT, suggesting that inhibition plays a crucial role in RTT pathophysiology. This includes reduced GABA synthesis, *Gad1* and *Gad2* levels, reduced miniature inhibitory postsynaptic currents (mIPSCs), and an array of behavioral deficits including EEG hyperexcitability and severe respiratory dysrhythmias [3, 4, 32]. Anatomical studies have reported enhanced PV+ neuronal puncta and hyperconnected PV+ circuitry in mouse visual cortex, suggesting that these microcircuits contribute to enhanced inhibition in MeCP2^{-/-} mice [5, 101]. This altered inhibition mediated by PV+ neurons, which regulates the initiation and termination of the critical period, has been proposed to alter the timing of critical period plasticity in RTT [6, 102]. Functional studies, however, have consistently reported decreased inhibitory function including reduced mIPSCs in CA3 pyramidal neurons of MeCP2^{-/-} mice [3, 7, 8, 103]. Although the density and intrinsic membrane properties of PV+ and somatostatin (SST)+ interneurons were not affected in MeCP2^{-/-} mice, miniature excitatory postsynaptic currents (mEPSCs) were found to be smaller and less frequent in fast-spiking PV+ neurons, suggesting impaired glutamatergic drive specifically onto this interneuron population compared to SST+ neurons [103]. Studies in slices have also reported a reduction in mEPSC amplitudes and a deficit in excitatory pathways, in the absence of change in mIPSC amplitude or frequency [95, 104]. These results are consistent with the decreased visually evoked responses found in PV+ interneurons in mouse visual cortex *in vivo* [33]. Interestingly, recent studies have highlighted the differential effects of subtype-specific *Mecp2* deletion on GABAergic inhibition regulating nonoverlapping neurological symptoms: mice lacking MeCP2 in PV+ neurons showed sensory, motor, memory, and social deficits, whereas those lacking in SOM+ neurons exhibited seizures and stereotypies [105], further elucidating the complex regulation of inhibition and their disruption in RTT [23].

Taken together, these features indicate that RTT is a complex disorder that arises from an imbalance of excitation and inhibition and a failure of brain circuitry to attain a mature state [9, 23]. Many of these defects can have a strong early

developmental, even prenatal, component (Figure 1) when the brain fails to attain “phenotypic checkpoint” signatures and in turn provides faulty functional feedback that influences gene expression [106] and network malfunction [107]. A coherent set of physiological measurements using *in vivo* awake animal models of global and neuronal subtype-specific *Mecp2* deletion remains necessary to measure and evaluate functional defects in the synaptic balance of excitation and inhibition. Another important consideration in this regard is to extend findings of cell-specific and synaptic defects in mouse models to identify biomarkers of RTT in human patients. Several recent studies are bridging this gap. Visual evoked potential (VEP) recordings in response to high-contrast oriented gratings have previously revealed loss of visual acuity in adult *Mecp2* mutant mice at the onset of RTT-like symptoms during critical periods of mouse visual cortex development [101], strongly suggesting that vision may serve as a biomarker of altered cortical function in RTT. Recent work has demonstrated that RTT patients exhibit a similar decrease in VEP amplitude and a reduction in visual spatial acuity that is impacted by *MECP2* mutation type [108].

7. Deficits in Adult Maintenance and Function

The onset of symptoms during early life in RTT patients, in conjunction with findings from mouse models suggesting neurodevelopmental abnormalities in RTT, has raised the question whether *Mecp2* function is necessary for integrative function in the adult brain. One study used an inducible knockout approach to delete *Mecp2* by crossing a floxed *Mecp2* allele mice with a tamoxifen-inducible Cre-ER expressing allele in adult mice (P60 or older) following normal development [109]. This late-deletion of *Mecp2* recapitulated key germline knockout phenotypes including abnormal gait, hind-limb clasping, motor abnormalities, impaired nesting ability, and impaired learning and memory, further underscoring the importance of *Mecp2* in adult neurological function [109]. Interestingly, this adult deletion recapitulated an epigenetic memory clock, suggesting a mechanism that extends—or is independent from—its early global genetic regulation [110].

Similar to behavioral deficits, the physiological response features of adult *Mecp2*-deleted neurons have also been characterized *in vivo* [111]. CRISPR-associated endonuclease (Cas) 9 has been used to introduce frame-shifting, insertion/deletion (INDEL) mutations that are targeted to the *Mecp2* locus using specific guide RNAs (gRNAs) via adeno-associated viral (AAV) vectors [112]. *In vivo* genome-editing resulted in ~68% of targeted cells containing INDEL mutations with a >60% reduction in MeCP2 protein levels [111]. Stereotactic injection of AAV-SpCas9 and gRNA targeting *Mecp2* into the superficial layers of mouse primary visual cortex followed by two-photon guided targeted electrophysiological recordings from genome-edited neurons revealed altered integrative visual responses, further emphasizing the maintenance role of *Mecp2* in the adult brain after normal developmental milestones have been achieved.

8. Reversal of Functional and Behavioral Deficits in RTT

One of the key discoveries in RTT has been the recovery of function following reactivation of endogenous *Mecp2* [113, 114]. This striking finding, an important feature not only of RTT but perhaps also of neurodevelopmental disorders in general, suggests that the neurodevelopmental pathology is reversible.

The phenotypic reversibility of advanced neurological phenotypes in both immature and mature adult animals shows that reactivation of the MeCP2 protein even at late stages of the disorder can partially rescue the mutant phenotype [113, 115]. Systemic delivery of MeCP2 cDNA via AAV9, under control of a fragment of its own promoter (scAAV9/MeCP2), has been shown to significantly rescue behavioral and cellular deficits when administered systemically into female RTT mice [116]. Proposed as a model for gene therapy, the retroviral-mediated overexpression of the MeCP2_{e1} isoform in neural stem cells taken from *Mecp2* heterozygous mice was shown to promote dendritic branching *in vitro* [117]. Perhaps more practically, pharmacological manipulations, such as the treatment of *Mecp2* null mice with recombinant human IGF1 (rhIGF1) or a peptide fragment of IGF1, also resulted in a partial rescue of synaptic defects and cortical excitatory synaptic transmission, in addition to restoring activation of signaling pathway proteins [70, 71]. These studies argue that the brain circuits involved in neural processing may not functionally decline but rather remain in a labile, immature state; their subsequent activation by the reintroduction of *Mecp2* [113, 115] or by pharmacological manipulations to activate downstream signaling pathways [70, 71] is an important measure to ameliorate the syndrome's consequences.

9. Conclusions

The fluidity with which MeCP2 regulates the genomic landscape renders a uniquely moving target that has proven difficult to fully understand. Amongst many factors to be taken into account when attempting to attribute mechanistic function to MeCP2 (e.g., cell type, mutation and associated functional domain, and range of downstream targets), it is crucial to consider the time point in question. Deletion of MeCP2 results in a wide and temporally varied range of phenotypes. A complete picture of the MeCP2 protein includes its roles at various life stages, so as to inform our evolving concept of RTT progression in patients and potential phenotypic reversibility.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Danielle Feldman and Abhishek Banerjee contributed equally.

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References

- [1] M. Chahrour and H. Y. Zoghbi, "The story of Rett syndrome: from clinic to neurobiology," *Neuron*, vol. 56, no. 3, pp. 422–437, 2007.
- [2] R. E. Amir, I. B. Van Den Veyver, M. Wan, C. Q. Tran, U. Francke, and H. Y. Zoghbi, "Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2," *Nature Genetics*, vol. 23, no. 2, pp. 185–188, 1999.
- [3] M. Chahrour, Y. J. Sung, C. Shaw et al., "MeCP2, a key contributor to neurological disease, activates and represses transcription," *Science*, vol. 320, no. 5880, pp. 1224–1229, 2008.
- [4] Y. Li, H. Wang, J. Muffat et al., "Global transcriptional and translational repression in human-embryonic-stem-cell-derived Rett syndrome neurons," *Cell Stem Cell*, vol. 13, no. 4, pp. 446–458, 2013.
- [5] T.-L. Cheng, Z. Wang, Q. Liao et al., "MeCP2 suppresses nuclear microRNA processing and dendritic growth by regulating the DGCR8/Drosha complex," *Developmental Cell*, vol. 28, no. 5, pp. 547–560, 2014.
- [6] Z. Qiu, E. L. Sylwestrak, D. N. Lieberman, Y. Zhang, X.-Y. Liu, and A. Ghosh, "The rett syndrome protein MeCP2 regulates synaptic scaling," *Journal of Neuroscience*, vol. 32, no. 3, pp. 989–994, 2012.
- [7] F. R. Zahir and C. J. Brown, "Epigenetic impacts on neurodevelopment: pathophysiological mechanisms and genetic modes of action," *Pediatric Research*, vol. 69, no. 5, pp. 92R–100R, 2011.
- [8] R. P. Ghosh, R. A. Horowitz-Scherer, T. Nikitina, L. S. Shlyakhtenko, and C. L. Woodcock, "MeCP2 binds cooperatively to its substrate and competes with histone H1 for chromatin binding sites," *Molecular and Cellular Biology*, vol. 30, no. 19, pp. 4656–4670, 2010.
- [9] J. Guy, H. Cheval, J. Selfridge, and A. Bird, "The role of MeCP2 in the brain," *Annual Review of Cell and Developmental Biology*, vol. 27, pp. 631–652, 2011.
- [10] C.-X. Song, K. E. Szulwach, Y. Fu et al., "Selective chemical labeling reveals the genome-wide distribution of 5-hydroxymethylcytosine," *Nature Biotechnology*, vol. 29, no. 1, pp. 68–75, 2011.
- [11] M. Mellén, P. Ayata, S. Dewell, S. Kriaucionis, and N. Heintz, "MeCP2 binds to 5hmC enriched within active genes and accessible chromatin in the nervous system," *Cell*, vol. 151, no. 7, pp. 1417–1430, 2012.
- [12] R. P. Nagarajan, K. A. Patzel, M. Martin et al., "MECP2 promoter methylation and X chromosome inactivation in autism," *Autism Research*, vol. 1, no. 3, pp. 169–178, 2008.
- [13] S. Kriaucionis and A. Bird, "The major form of MeCP2 has a novel N-terminus generated by alternative splicing," *Nucleic Acids Research*, vol. 32, no. 5, pp. 1818–1823, 2004.
- [14] G. N. Mnatzakanian, H. Lohi, I. Munteanu et al., "A previously unidentified MECP2 open reading frame defines a new protein isoform relevant to Rett syndrome," *Nature Genetics*, vol. 36, no. 4, pp. 339–341, 2004.
- [15] J. M. Dragich, Y.-H. Kim, A. P. Arnold, and N. C. Schanen, "Differential distribution of the Mecp2 splice variants in the postnatal mouse brain," *Journal of Comparative Neurology*, vol. 501, no. 4, pp. 526–542, 2007.
- [16] L. Kaddoum, N. Panayotis, H. Mazarguil, G. Giglia-Mari, J. C. Roux, and E. Joly, "Isoform-specific anti-MeCP2 antibodies confirm that expression of the e1 isoform strongly predominates in the brain," *FI000Research*, vol. 2, article 204, 2013.
- [17] C. O. Olson, R. M. Zachariah, C. D. Ezeonwuka, V. R. B. Liyanage, and M. Rastegar, "Brain region-specific expression of MeCP2 isoforms correlates with DNA methylation within Mecp2 regulatory elements," *PLoS ONE*, vol. 9, no. 3, Article ID e90645, 2014.
- [18] M. Orlic-Milacic, L. Kaufman, A. Mikhailov et al., "Overexpression of either MECP2-e1 or MECP2-e2 in neuronally differentiated cells results in different patterns of gene expression," *PLoS ONE*, vol. 9, no. 4, Article ID e91742, 2014.
- [19] S. M. Cusack, T. T. Rohn, R. J. Medeck et al., "Suppression of MeCP2 β expression inhibits neurite extension in PC12 cells," *Experimental Cell Research*, vol. 299, no. 2, pp. 442–453, 2004.
- [20] D. H. Yasui, M. L. Gonzales, J. O. Aflatooni et al., "Mice with an isoform-ablating Mecp2 exon 1 mutation recapitulate the neurologic deficits of Rett syndrome," *Human Molecular Genetics*, vol. 23, no. 9, pp. 2447–2458, 2014.
- [21] V. R. B. Liyanage, R. M. Zachariah, and M. Rastegar, "Decitabine alters the expression of Mecp2 isoforms via dynamic DNA methylation at the Mecp2 regulatory elements in neural stem cells," *Molecular Autism*, vol. 4, no. 1, article 46, 2013.
- [22] S. G. Dastidar, F. H. Bardai, C. Ma et al., "Isoform-specific toxicity of MeCP2 in postmitotic neurons: suppression of neurotoxicity by FoxG1," *The Journal of Neuroscience*, vol. 32, no. 8, pp. 2846–2855, 2012.
- [23] A. Banerjee, J. Castro, and M. Sur, "Rett syndrome: genes, synapses, circuits, and therapeutics," *Frontiers in Psychiatry*, vol. 3, article 34, 2012.
- [24] M. J. Lyst and A. Bird, "Rett syndrome: a complex disorder with simple roots," *Nature Reviews Genetics*, vol. 16, no. 5, pp. 261–275, 2015.
- [25] E. M. Boggio, G. Lonetti, T. Pizzorusso, and M. Giustetto, "Synaptic determinants of Rett syndrome," *Frontiers in Synaptic Neuroscience*, vol. 2, article 28, 2010.
- [26] R. G. Urdinguio, L. Lopez-Serra, P. Lopez-Nieva et al., "Mecp2-null mice provide new neuronal targets for rett syndrome," *PLoS ONE*, vol. 3, no. 11, Article ID e3669, 2008.
- [27] D. H. Ebert and M. E. Greenberg, "Activity-dependent neuronal signalling and autism spectrum disorder," *Nature*, vol. 493, no. 7432, pp. 327–337, 2013.
- [28] A. Kumar, S. Kamboj, B. M. Malone et al., "Analysis of protein domains and Rett syndrome mutations indicate that multiple regions influence chromatin-binding dynamics of the chromatin-associated protein MECP2 in vivo," *Journal of Cell Science*, vol. 121, no. 7, pp. 1128–1137, 2008.
- [29] N. L. Adkins and P. T. Georgel, "MeCP2: structure and function," *Biochemistry and Cell Biology*, vol. 89, no. 1, pp. 1–11, 2011.
- [30] V. A. Cuddapah, R. B. Pillai, K. V. Shekar et al., "Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome," *Journal of Medical Genetics*, vol. 51, no. 3, pp. 152–158, 2014.
- [31] M. Alvarez-Saavedra, M. A. Sáez, D. Kang, H. Y. Zoghbi, and J. I. Young, "Cell-specific expression of wild-type MeCP2 in mouse models of Rett syndrome yields insight about pathogenesis," *Human Molecular Genetics*, vol. 16, no. 19, pp. 2315–2325, 2007.
- [32] H.-T. Chao, H. Chen, R. C. Samaco et al., "Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes," *Nature*, vol. 468, no. 7321, pp. 263–269, 2010.

- [33] L.-J. He, N. Liu, T.-L. Cheng et al., "Conditional deletion of *Mecp2* in parvalbumin-expressing GABAergic cells results in the absence of critical period plasticity," *Nature Communications*, vol. 5, article 5036, 2014.
- [34] D. T. Lioy, S. K. Garg, C. E. Monaghan et al., "A role for glia in the progression of Rett's syndrome," *Nature*, vol. 475, no. 7357, pp. 497–500, 2011.
- [35] I. Maezawa and L.-W. Jin, "Rett syndrome microglia damage dendrites and synapses by the elevated release of glutamate," *Journal of Neuroscience*, vol. 30, no. 15, pp. 5346–5356, 2010.
- [36] B. Kerr, J. Soto C, M. Saez, A. Abrams, K. Walz, and J. I. Young, "Transgenic complementation of MeCP2 deficiency: phenotypic rescue of *Mecp2*-null mice by isoform-specific transgenes," *European Journal of Human Genetics*, vol. 20, no. 1, pp. 69–76, 2012.
- [37] H. Van Esch, "MECP2 duplication syndrome," *Molecular Syndromology*, vol. 2, no. 3–5, pp. 128–136, 2012.
- [38] Y. Sztainberg, H.-M. Chen, J. W. Swann et al., "Reversal of phenotypes in *MECP2* duplication mice using genetic rescue or antisense oligonucleotides," *Nature*, vol. 528, no. 7580, pp. 123–126, 2015.
- [39] N. Kishi and J. D. Macklis, "MECP2 is progressively expressed in post-migratory neurons and is involved in neuronal maturation rather than cell fate decisions," *Molecular and Cellular Neuroscience*, vol. 27, no. 3, pp. 306–321, 2004.
- [40] D. Balmer, J. Goldstine, Y. M. Rao, and J. M. LaSalle, "Elevated methyl-CpG-binding protein 2 expression is acquired during postnatal human brain development and is correlated with alternative polyadenylation," *Journal of Molecular Medicine*, vol. 81, no. 1, pp. 61–68, 2003.
- [41] K. Han, V. A. Gennarino, Y. Lee et al., "Human-specific regulation of MeCP2 levels in fetal brains by microRNA miR-483-5p," *Genes & Development*, vol. 27, no. 5, pp. 485–490, 2013.
- [42] A. Kumar and M. K. Thakur, "Epigenetic regulation of prenilin 1 and 2 in the cerebral cortex of mice during development," *Developmental Neurobiology*, vol. 75, no. 11, pp. 1165–1173, 2015.
- [43] M. D. Shahbazian, Y. Sun, and H. Y. Zoghbi, "Balanced X chromosome inactivation patterns in the Rett syndrome brain," *American Journal of Medical Genetics*, vol. 111, no. 2, pp. 164–168, 2002.
- [44] F. Bedogni, C. C. Gigli, D. Pozzi et al., "Defects during *Mecp2* null embryonic cortex development precede the onset of overt neurological symptoms," *Cerebral Cortex*, 2015.
- [45] G. Z. Tau and B. S. Peterson, "Normal development of brain circuits," *Neuropsychopharmacology*, vol. 35, no. 1, pp. 147–168, 2010.
- [46] T. Fukuda, M. Itoh, T. Ichikawa, K. Washiyama, and Y.-I. Goto, "Delayed maturation of neuronal architecture and synaptogenesis in cerebral cortex of *Mecp2*-deficient mice," *Journal of Neuropathology and Experimental Neurology*, vol. 64, no. 6, pp. 537–544, 2005.
- [47] W. E. Kaufmann, M. V. Johnston, and M. E. Blue, "MeCP2 expression and function during brain development: implications for Rett syndrome's pathogenesis and clinical evolution," *Brain and Development*, vol. 27, no. 1, pp. S77–S87, 2005.
- [48] R. D. Smrt, J. Eaves-Egenes, B. Z. Barkho et al., "*Mecp2* deficiency leads to delayed maturation and altered gene expression in hippocampal neurons," *Neurobiology of Disease*, vol. 27, no. 1, pp. 77–89, 2007.
- [49] A. L. Degano, R. J. Pasterkamp, and G. V. Ronnett, "MeCP2 deficiency disrupts axonal guidance, fasciculation, and targeting by altering Semaphorin 3F function," *Molecular and Cellular Neuroscience*, vol. 42, no. 3, pp. 243–254, 2009.
- [50] P. B. Marschik, W. E. Kaufmann, J. Sigafos et al., "Changing the perspective on early development of Rett syndrome," *Research in Developmental Disabilities*, vol. 34, no. 4, pp. 1236–1239, 2013.
- [51] J. L. Neul, J. B. Lane, H.-S. Lee et al., "Developmental delay in Rett syndrome: data from the natural history study," *Journal of Neurodevelopmental Disorders*, vol. 6, no. 1, article 20, 2014.
- [52] S. Fehr, A. Bebbington, C. Ellaway, P. Rowe, H. Leonard, and J. Downs, "Altered attainment of developmental milestones influences the age of diagnosis of Rett syndrome," *Journal of Child Neurology*, vol. 26, no. 8, pp. 980–987, 2011.
- [53] S. Fehr, J. Downs, A. Bebbington, and H. Leonard, "Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome," *American Journal of Medical Genetics Part A*, vol. 152, no. 10, pp. 2535–2542, 2010.
- [54] D. C. Tarquinio, W. Hou, J. L. Neul et al., "Age of diagnosis in Rett syndrome: patterns of recognition among diagnosticians and risk factors for late diagnosis," *Pediatric Neurology*, vol. 52, no. 6, pp. 585–591.e2, 2015.
- [55] K. Tsujimura, M. Abematsu, J. Kohyama, M. Namihira, and K. Nakashima, "Neuronal differentiation of neural precursor cells is promoted by the methyl-CpG-binding protein MeCP2," *Experimental Neurology*, vol. 219, no. 1, pp. 104–111, 2009.
- [56] T. Andoh-Noda, W. Akamatsu, K. Miyake et al., "Differentiation of multipotent neural stem cells derived from Rett syndrome patients is biased toward the astrocytic lineage," *Molecular Brain*, vol. 8, article 31, 2015.
- [57] T. Squillaro, N. Alessio, M. Cipollaro et al., "Reduced expression of MECP2 affects cell commitment and maintenance in neurons by triggering senescence: new perspective for Rett syndrome," *Molecular Biology of the Cell*, vol. 23, no. 8, pp. 1435–1445, 2012.
- [58] I. Stancheva, A. L. Collins, I. B. Van Den Veyver, H. Zoghbi, and R. R. Meehan, "A mutant form of MeCP2 protein associated with human Rett syndrome cannot be displaced from methylated DNA by notch in *Xenopus* embryos," *Molecular Cell*, vol. 12, no. 2, pp. 425–435, 2003.
- [59] L. E. Coverdale, C. J. Martyniuk, V. L. Trudeau, and C. C. Martin, "Differential expression of the methyl-cytosine binding protein 2 gene in embryonic and adult brain of zebrafish," *Developmental Brain Research*, vol. 153, no. 2, pp. 281–287, 2004.
- [60] H. Gao, Y. Bu, Q. Wu et al., "*Mecp2* regulates neural cell differentiation by suppressing the Id1 to Her2 axis in zebrafish," *Journal of Cell Science*, vol. 128, no. 12, pp. 2340–2350, 2015.
- [61] P. Petazzi, N. Akizu, A. Garcia et al., "An increase in MECP2 dosage impairs neural tube formation," *Neurobiology of Disease*, vol. 67, pp. 49–56, 2014.
- [62] Z. Zhou, E. J. Hong, S. Cohen et al., "Brain-specific phosphorylation of MeCP2 regulates activity-dependent *Bdnf* transcription, dendritic growth, and spine maturation," *Neuron*, vol. 52, no. 2, pp. 255–269, 2006.
- [63] H. Li, X. Zhong, K. F. Chau et al., "Cell cycle-linked MeCP2 phosphorylation modulates adult neurogenesis involving the Notch signalling pathway," *Nature Communications*, vol. 5, article 5601, 2014.
- [64] H.-T. Chao and H. Y. Zoghbi, "MeCP2: only 100% will do," *Nature Neuroscience*, vol. 15, no. 2, pp. 176–177, 2012.
- [65] D. P. Brazil, Z.-Z. Yang, and B. A. Hemmings, "Advances in protein kinase B signalling: AKTion on multiple fronts," *Trends in Biochemical Sciences*, vol. 29, no. 5, pp. 233–242, 2004.

- [66] Q. Wang, L. Liu, L. Pei et al., "Control of synaptic strength, a novel function of Akt," *Neuron*, vol. 38, no. 6, pp. 915–928, 2003.
- [67] H.-K. Chen, P. Fernandez-Funez, S. F. Acevedo et al., "Interaction of Akt-phosphorylated ataxin-1 with 14-3-3 mediates neurodegeneration in spinocerebellar ataxia type 1," *Cell*, vol. 113, no. 4, pp. 457–468, 2003.
- [68] S. Humbert, E. A. Bryson, F. P. Cordelières et al., "The IGF-1/Akt pathway is neuroprotective in Huntington's disease and involves huntingtin phosphorylation by Akt," *Developmental Cell*, vol. 2, no. 6, pp. 831–837, 2002.
- [69] B. K. Kaspar, J. Lladó, N. Sherkat, J. D. Rothstein, and F. H. Gage, "Retrograde viral delivery of IGF-1 prolongs survival in a mouse ALS model," *Science*, vol. 301, no. 5634, pp. 839–842, 2003.
- [70] D. Tropea, E. Giacometti, N. R. Wilson et al., "Partial reversal of Rett syndrome-like symptoms in MeCP2 mutant mice," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 6, pp. 2029–2034, 2009.
- [71] J. Castro, R. I. Garcia, S. Kwok et al., "Functional recovery with recombinant human IGF1 treatment in a mouse model of Rett Syndrome," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 27, pp. 9941–9946, 2014.
- [72] S. Ricciardi, E. M. Boggio, S. Grosso et al., "Reduced AKT/mTOR signaling and protein synthesis dysregulation in a Rett syndrome animal model," *Human Molecular Genetics*, vol. 20, no. 6, pp. 1182–1196, 2011.
- [73] E. Bruel-Jungerman, A. Veyrac, F. Dufour, J. Horwood, S. Laroche, and S. Davis, "Inhibition of PI3K-Akt signaling blocks exercise-mediated enhancement of adult neurogenesis and synaptic plasticity in the dentate gyrus," *PLoS ONE*, vol. 4, no. 11, Article ID e7901, 2009.
- [74] H. Wu, D. Lu, H. Jiang et al., "Increase in phosphorylation of Akt and its downstream signaling targets and suppression of apoptosis by simvastatin after traumatic brain injury: laboratory investigation," *Journal of Neurosurgery*, vol. 109, no. 4, pp. 691–698, 2008.
- [75] X. Zhang, L. Zhang, X. Cheng et al., "IGF-1 promotes Brn-4 expression and neuronal differentiation of neural stem cells via the PI3K/Akt pathway," *PLoS ONE*, vol. 9, no. 12, Article ID e113801, 2014.
- [76] C. B. Chan, X. Liu, S. Pradoldej et al., "Phosphoinositide 3-kinase enhancer regulates neuronal dendritogenesis and survival in neocortex," *Journal of Neuroscience*, vol. 31, no. 22, pp. 8083–8092, 2011.
- [77] Y. Peng, B.-H. Jiang, P.-H. Yang et al., "Phosphatidylinositol 3-kinase signaling is involved in neurogenesis during *Xenopus* embryonic development," *The Journal of Biological Chemistry*, vol. 279, no. 27, pp. 28509–28514, 2004.
- [78] Y.-C. Cheng, F.-Y. Hsieh, M.-C. Chiang et al., "Akt1 mediates neuronal differentiation in zebrafish via a reciprocal interaction with notch signaling," *PLoS ONE*, vol. 8, no. 1, Article ID e54262, 2013.
- [79] P. Lau and L. D. Hudson, "MicroRNAs in neural cell differentiation," *Brain Research*, vol. 1338, pp. 14–19, 2010.
- [80] S. K. Fineberg, K. S. Kosik, and B. L. Davidson, "MicroRNAs potentiate neural development," *Neuron*, vol. 64, no. 3, pp. 303–309, 2009.
- [81] M. Coolen and L. Bally-Cuif, "MicroRNAs in brain development and physiology," *Current Opinion in Neurobiology*, vol. 19, no. 5, pp. 461–470, 2009.
- [82] K. E. Szulwach, X. Li, R. D. Smrt et al., "Cross talk between microRNA and epigenetic regulation in adult neurogenesis," *Journal of Cell Biology*, vol. 189, no. 1, pp. 127–141, 2010.
- [83] M. E. Klein, D. T. Lioy, L. Ma, S. Impey, G. Mandel, and R. H. Goodman, "Homeostatic regulation of MeCP2 expression by a CREB-induced microRNA," *Nature Neuroscience*, vol. 10, no. 12, pp. 1513–1514, 2007.
- [84] M. Pathania, J. Torres-Reveron, L. Yan et al., "miR-132 enhances dendritic morphogenesis, spine density, synaptic integration, and survival of newborn olfactory bulb neurons," *PLoS ONE*, vol. 7, no. 5, Article ID e38174, 2012.
- [85] R. D. Smrt, K. E. Szulwach, R. L. Pfeiffer et al., "MicroRNA miR-137 regulates neuronal maturation by targeting ubiquitin ligase mind bomb-1," *STEM CELLS*, vol. 28, no. 6, pp. 1060–1070, 2010.
- [86] G. Sun, P. Ye, K. Murai et al., "MiR-137 forms a regulatory loop with nuclear receptor TLX and LSD1 in neural stem cells," *Nature Communications*, vol. 2, article 529, 2011.
- [87] K. Tsujimura, K. Irie, H. Nakashima et al., "miR-199a links MeCP2 with mTOR signaling and its dysregulation leads to Rett syndrome phenotypes," *Cell Reports*, vol. 12, no. 11, pp. 1887–1901, 2015.
- [88] N. Mellios, J. Woodson, R. I. Garcia et al., " β 2-Adrenergic receptor agonist ameliorates phenotypes and corrects microRNA-mediated IGF1 deficits in a mouse model of Rett syndrome," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 111, no. 27, pp. 9947–9952, 2014.
- [89] K. Y. Kwan, N. Šestan, and E. S. Anton, "Transcriptional co-regulation of neuronal migration and laminar identity in the neocortex," *Development*, vol. 139, no. 9, pp. 1535–1546, 2012.
- [90] S. K. McConnell, "Strategies for the generation of neuronal diversity in the developing central nervous system," *Journal of Neuroscience*, vol. 15, no. 11, pp. 6987–6998, 1995.
- [91] B. Martynoga, D. Drechsel, and F. Guillemot, "Molecular control of neurogenesis: a view from the mammalian cerebral cortex," *Cold Spring Harbor Perspectives in Biology*, vol. 4, no. 10, 2012.
- [92] J. G. Corbin, N. Gaiano, S. L. Juliano, S. Poluch, E. Stancik, and T. F. Haydar, "Regulation of neural progenitor cell development in the nervous system," *Journal of Neurochemistry*, vol. 106, no. 6, pp. 2272–2287, 2008.
- [93] M. Valiente and O. Marín, "Neuronal migration mechanisms in development and disease," *Current Opinion in Neurobiology*, vol. 20, no. 1, pp. 68–78, 2010.
- [94] C. R. Jordan, H. H. Li, H. C. Kwan, and U. Francke, "Cerebellar gene expression profiles of mouse models for Rett syndrome reveal novel MeCP2 targets," *BMC Medical Genetics*, vol. 8, article 36, 2007.
- [95] V. S. Dani, Q. Chang, A. Maffei, G. G. Turrigiano, R. Jaenisch, and S. B. Nelson, "Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett syndrome," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 35, pp. 12560–12565, 2005.
- [96] Q. Chang, G. Khare, V. Dani, S. Nelson, and R. Jaenisch, "The disease progression of Mecp2 mutant mice is affected by the level of BDNF expression," *Neuron*, vol. 49, no. 3, pp. 341–348, 2006.
- [97] E. D. Nelson, E. T. Kavalali, and L. M. Monteggia, "MeCP2-dependent transcriptional repression regulates excitatory neurotransmission," *Current Biology*, vol. 16, no. 7, pp. 710–716, 2006.
- [98] H.-T. Chao, H. Y. Zoghbi, and C. Rosenmund, "MeCP2 controls excitatory synaptic strength by regulating glutamatergic synapse number," *Neuron*, vol. 56, no. 1, pp. 58–65, 2007.

- [99] Y. Asaka, D. G. M. Jugloff, L. Zhang, J. H. Eubanks, and R. M. Fitzsimonds, "Hippocampal synaptic plasticity is impaired in the *Mecp2*-null mouse model of Rett syndrome," *Neurobiology of Disease*, vol. 21, no. 1, pp. 217–227, 2006.
- [100] G. Lonetti, A. Angelucci, L. Morando, E. M. Boggio, M. Giustetto, and T. Pizzorusso, "Early environmental enrichment moderates the behavioral and synaptic phenotype of *MeCP2* null mice," *Biological Psychiatry*, vol. 67, no. 7, pp. 657–665, 2010.
- [101] S. Durand, A. Patrizi, K. B. Quast et al., "NMDA receptor regulation prevents regression of visual cortical function in the absence of *Mecp2*," *Neuron*, vol. 76, no. 6, pp. 1078–1090, 2012.
- [102] K. Krishnan, B. Wang, J. Lu et al., "MeCP2 regulates the timing of critical period plasticity that shapes functional connectivity in primary visual cortex," *Proceedings of the National Academy of Sciences*, vol. 112, no. 34, pp. E4782–E4791, 2015.
- [103] G. Calfa, W. Li, J. M. Rutherford, and L. Pozzo-Miller, "Excitation/inhibition imbalance and impaired synaptic inhibition in hippocampal area CA3 of *Mecp2* knockout mice," *Hippocampus*, vol. 25, no. 2, pp. 159–168, 2015.
- [104] L. Wood, N. W. Gray, Z. Zhou, M. E. Greenberg, and G. M. G. Shepherd, "Synaptic circuit abnormalities of motor-frontal layer 2/3 pyramidal neurons in an RNA interference model of methyl-CpG-binding protein 2 deficiency," *Journal of Neuroscience*, vol. 29, no. 40, pp. 12440–12448, 2009.
- [105] A. Ito-Ishida, K. Ure, H. Chen, J. W. Swann, and H. Y. Zoghbi, "Loss of MeCP2 in parvalbumin- and somatostatin-expressing neurons in mice leads to distinct rett syndrome-like phenotypes," *Neuron*, vol. 88, no. 4, pp. 651–658, 2015.
- [106] Y. Ben-Ari and N. C. Spitzer, "Phenotypic checkpoints regulate neuronal development," *Trends in Neurosciences*, vol. 33, no. 11, pp. 485–492, 2010.
- [107] Y. Ben-Ari, "Is birth a critical period in the pathogenesis of autism spectrum disorders?" *Nature Reviews Neuroscience*, vol. 16, no. 8, pp. 498–505, 2015.
- [108] J. J. LeBlanc, G. DeGregorio, E. Centofante et al., "Visual evoked potentials detect cortical processing deficits in Rett syndrome," *Annals of Neurology*, vol. 78, no. 5, pp. 775–786, 2015.
- [109] C. M. McGraw, R. C. Samaco, and H. Y. Zoghbi, "Adult neural function requires MeCP2," *Science*, vol. 333, article 186, 2011.
- [110] L. Chen, K. Chen, L. A. Lavery et al., "MeCP2 binds to non-CG methylated DNA as neurons mature, influencing transcription and the timing of onset for Rett syndrome," *Proceedings of the National Academy of Sciences*, vol. 112, no. 17, pp. 5509–5514, 2015.
- [111] L. Swiech, M. Heidenreich, A. Banerjee et al., "In vivo interrogation of gene function in the mammalian brain using CRISPR-Cas9," *Nature Biotechnology*, vol. 33, no. 1, pp. 102–106, 2014.
- [112] M. Heidenreich and F. Zhang, "Applications of CRISPR-Cas systems in neuroscience," *Nature Reviews Neuroscience*, vol. 17, no. 1, pp. 36–44, 2015.
- [113] J. Guy, J. Gan, J. Selfridge, S. Cobb, and A. Bird, "Reversal of neurological defects in a mouse model of Rett syndrome," *Science*, vol. 315, no. 5815, pp. 1143–1147, 2007.
- [114] S. Cobb, J. Guy, and A. Bird, "Reversibility of functional deficits in experimental models of Rett syndrome," *Biochemical Society Transactions*, vol. 38, no. 2, pp. 498–506, 2010.
- [115] E. Giacometti, S. Luikenhuis, C. Beard, and R. Jaenisch, "Partial rescue of MeCP2 deficiency by postnatal activation of MeCP2," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 104, no. 6, pp. 1931–1936, 2007.
- [116] S. K. Garg, D. T. Lioy, H. Cheval et al., "Systemic delivery of MeCP2 rescues behavioral and cellular deficits in female mouse models of Rett syndrome," *The Journal of Neuroscience*, vol. 33, no. 34, pp. 13612–13620, 2013.
- [117] M. Rastegar, A. Hotta, P. Pasceri et al., "MECP2 isoform-specific vectors with regulated expression for Rett Syndrome gene therapy," *PLoS ONE*, vol. 4, no. 8, Article ID e6810, 2009.