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**Review**

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# Role of MeCP2 in oligodendrocyte lineage cells in Rett syndrome: review and inference

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## Abstract

Rett syndrome (RTT) is a neurodevelopmental disorder primarily caused by mutations in the *MECP2* gene. Neuronal damage is the main factor contributing to RTT, and the loss of MeCP2 function can result in reduced neuronal somas size, decreased dendritic abundance, and impaired neuronal function. While specific restoration of MeCP2 expression in neurons has been reported to partially rescue the behavioral phenotype and prolong the lifespan of mice, it cannot provide a complete cure. Therefore, other cells may be involved in the development of RTT. Although imaging and autopsy findings have revealed decreased white matter volume and corpus callosum thickness in RTT patients, the mechanisms underlying the development of white matter abnormalities remain unclear. These abnormalities are predominantly caused by damage to mature oligodendrocytes. This review provides an overview of the proliferation, differentiation, and function of oligodendrocyte lineage cells and elucidates the role of MeCP2 in these cells.

**Keywords:** Rett syndrome, MeCP2, oligodendrocyte lineage cells, white matter

## INTRODUCTION

Rett syndrome (RTT) is a severe and rare neurodevelopmental disorder with no effective treatment for its complex pathogenesis[1]. It has a female preponderance (rarely occurs among men), with the incidence rate ranging from 1/10000 to 1/15000 among female patients[2]. RTT is caused by gene mutations and can be classified as classic and non-classic RTT based on the specific mutation involved. Classic RTT results from a loss-of-function mutation in the X-linked methyl CpG-binding protein 2 (*MECP2*) gene, which encodes the MeCP2 protein. Clinical studies have reported that 90%-95% of cases are attributed to classic RTT[3]. In contrast, non-classic RTT is primarily caused by mutations in the cyclin-dependent kinase-like 5 (*CDKL5)* and forkhead box G1(*FOXG1)* genes[4,5]. It exhibits clinical features similar to those of classic RTT, including early-onset epilepsy and developmental delay[6]. Therefore, MeCP2 has become the focus of research on RTT. Hundreds of *MECP2* mutation sites that can cause classic RTT have been identified[7,8]. It is noteworthy that large segment deletions and eight hotspot mutations account for approximately 80% of the reported cases[7]. The mutations of *MECP2* have been validated in relevant mouse models.

Research on RTT has been primarily focused on the process and function of neurons. Autopsy reports of patients have shown reduced brain volume, neuronal soma size, dendritic arborization, and dendritic spine abundance[7]. Therefore, neurons have become the core of research into the pathological mechanisms of RTT. The abovementioned pathological features commonly observed in neurons have been validated in different mouse models with various mutations[9,10]. In addition, specific restoration of MeCP2 expression in neurons has been shown to restore relevant behaviors and prolong the lifespan of mice[11,12]. However, some phenotypes cannot be restored through this approach, suggesting that MeCP2 in the central nervous system (CNS) may be involved in RTT development through the regulation of other cells[13,14]. In the CNS, MeCP2 can be detected not only in neurons but also in astrocytes, oligodendrocytes (OLs), and microglia. Relevant studies have demonstrated that restoring the expression of MeCP2 in astrocytes, OLs, and microglia can alleviate some symptoms in knockout mouse models, indicating that glial cells also play an indispensable role in RTT[15]. With a deeper understanding of the function and structure of glial cells, novel mechanisms have been proposed to elucidate the development of RTT.

The application of Magnetic Resonance Imaging (MRI) in biological research has facilitated dynamic observation of abnormal brain development in patients. Brain imaging has revealed significant abnormalities in the total volume of white matter (WM) in RTT patients, in addition to gray matter (GM) abnormalities commonly observed on pathological examination[16,17]. WM is primarily connected through WM fiber bundles across the left and right hemispheres and various brain regions, forming a complex WM signal network[18]. WM fiber bundles are primarily composed of axons of neurons and myelin sheaths wrapped around them.

Given that neuronal bodies are not found in WM and only mature OLs can form myelin sheaths in the CNS, we have proposed that MeCP2 leads to WM abnormalities by regulating the abnormal development of OL lineage cells and myelin formation. The OL lineage cells include oligodendrocyte precursor cells (OPCs) and OLs. OPCs undergo a series of biological regulations and eventually differentiate into functionally specific mature OLs at specific locations[19]. In the CNS of mammals, myelin sheaths are exclusively formed by mature OLs[19]. This review summarizes the mechanisms underlying the development of WM abnormalities resulting from MeCP2 dysfunction and explores the role of MeCP2 in regulating cell proliferation, differentiation, and myelin sheath formation in OLs, thereby providing a rational basis for the study of MeCP2 in OLs.

## STRUCTURE AND FUNCTION OF MECP2

MeCP2, a member of the methyl-CpG-binding protein family, has two subtypes, *MECP2-E1* and *MECP2-E2*, each containing four exons that encode four structural domains, including the N-terminal domain (NTD), methyl-CpG-binding domain (MBD), transcription repression domain (TRD), and C-terminal domain (CTD)[7]. Analysis of the expression of the two subtypes revealed that the expression levels of E1 in the human and mouse brains were about 10 times higher than E2, but there was no difference in their expression levels in the liver and testes of mice[20,21]. MeCP2 was initially identified as a nuclear protein that binds to methylated DNA, which led to its characterization as a transcriptional repressor[22] [Figure 1] However, recent studies have demonstrated that MeCP2 is involved in various functions, including activation and inhibition of transcription, RNA splicing, and miRNA regulation within the nucleus[23,24].

### Mutations in MeCP2

The majority of RTT cases (over 95%) are due to de novo mutations in the *MECP2* gene, mainly occurring on the paternal X chromosome[25]. Because the X chromosome of spermatozoa is hypermethylated, the methylated cytosine residue can undergo spontaneous deamination to form thymine[7,26]. Familial inheritance of RTT is rare and is due to X-chromosomal inheritance from a carrier mother[27]. To date, over 500 *MECP2* mutations have been identified, including missense mutations, nonsense mutations, insertion mutations, and small or large deletions[28]. Point mutations are the most common mutation types, with C > T being the most frequently observed[29]. Eight single-point mutations, R106W, R133C, T158M, R168X, R255X, R270X, R294X, and R306C, account for about 70% of the reported cases[6] [Figure 1]. R106W, R133C, and T158M are located in the MBD domain of *MeCP2*, which can affect the methyl binding capacity of MeCP2[30]. Patients with R106W or T158M mutation exhibit severe pathological phenotypes[31,32]. R306C is located in the TRD domain, preventing MeCP2 from binding to the NCoR/SMRT complex, thus affecting transcriptional activation or inhibition[30,33]. Four nonsense mutations, R168X, R255X, R270X, and R294X, give rise to premature stop codons, resulting in truncated MeCP2. R255X, R270X, and R294X are located in the TRD domain[6]. R168X is located in the intervention outcome domain (ID), which can cause the MeCP2 to lose the entire TRD domain[30]. Patients with T168X exhibited the most severe clinical phenotypes, with the majority losing their walking ability[7,34,35]. In addition, the large segment deletion and C-terminal domain deletion of MeCP2 account for about 13% of RTT cases[25]. Large segment deletion often causes more severe clinical phenotypes, whereas the C-terminal domain deletion is relatively mild[25]. Researchers have established various RTT animal models based on different mutation types, which have greatly assisted in understanding the pathogenesis of RTT.

### MeCP2 and transcription

MeCP2 was originally known as a methyl-binding protein that regulates transcription [Figure 1]. The MBD of MeCP2 has a strong affinity for CpG-methylated DNA, and the affinity of MeCP2 for chromatin is significantly reduced in MeCP2-deficient cells. Mellén *et al.* revealed that MeCP2 could bind to 5-hydroxymethylcytosine (5hmc) with an affinity similar to that for 5-methylcytosine (5mc) in actively transcribed genes[36]. However, the biological significance of the binding between MeCP2 and 5hmc remains unclear. In addition to binding to CpG, MeCP2 can bind to methylation sites such as CpA, CpC, and CpH[37,38]. But the implications of this binding warrant further investigation. Lyst *et al.* demonstrated that MeCP2 acted as a junction protein between DNA and the NCoR/SMRT complex to repress the transcription of target genes[33]. Continuous investigation of the structure and function of MeCP2 has improved the understanding of mechanisms through which MeCP2 regulates transcription.

### MeCP2 and RNA splicing

Although MeCP2 can directly regulate gene transcription, recent studies have shown that MeCP2 can regulate gene expression by splicing mRNA [Figure 1]. Young *et al.* found that truncated MeCP2 can lead to

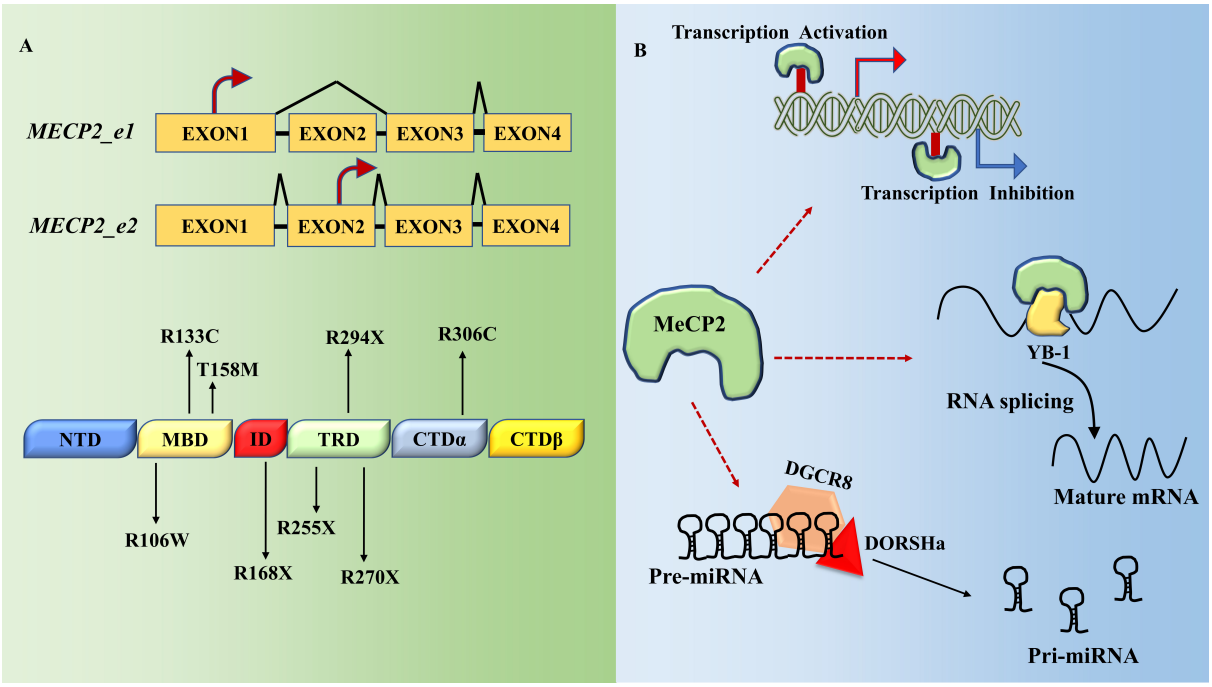


**Figure 1.** Characteristics of *MECP2* gene and its protein function. Note: (A) *MECP2* gene subtypes, functional domains, and common mutation types (eight hotspot mutations). Two isoforms of the MECP2: MECP2-E1 (encoded by exons 1, 3, 4) and MECP2-E2 (encoded by exons 1, 3, 4). Red arrows indicate the transcription start sites (ATG) of the two isoforms. MeCP2 protein structure is composed of five major domains, N-terminal Domain (NTD), Methyl Binding Domain (MBD), Inter-Domain (ID), Transcription Repression Domain (TRD), and C-terminal Domain (CTD). The AT-Hook domain is located in the CTD, which allows binding to adenine-thymine (AT) rich DNA. Eight Hotspot Mutations: R106W (Arginine to Tryptophan), R133C (Arginine to Cystine), T158M (Threonine to Methionine), R168X (Arginine to termination codon), R255X (Arginine to termination codon), R294X (Arginine to termination codon), R270X (Arginine to termination codon), R306C (Arginine to Cystine); (B) Mechanisms through which MeCP2 regulates transcription, RNA splicing, and mRNA cleavage. The MBD and CTD domains of MeCP2 can activate or inhibit transcriptional regulation by binding to DNA. MeCP2 can regulate the alternative splicing of RNA by combining it with YB-1 and other proteins. MeCP2 can also regulate the expression of miRNAs through the interaction with the Dorsha complex. AT: adenine-thymine; CTD: C-terminal Domain; ID: Inter-Domain; MBD: Methyl Binding Domain; NTD: N-terminal Domain; TRD: Transcription Repression Domain.

abnormal RNA splicing in Mecp2$^{308/y}$ male mice[39]. They reported that MeCP2 directly interacts with Y box-binding protein 1 (YB-1) mediated by RNA and regulates the splicing of genes such as CD44 molecule (*CD44*), nuclear receptor 1(*NR1*), and homeobox gene distal-less homeobox 5(*Dlx5*)[39]. Brito *et al.* also reported that MeCP2 can regulate mRNA splicing through intron retention or exon skipping[40]. LaSalle laboratories reported that MeCP2 can regulate RNA splicing by binding to YB-1 to promote the formation of neurons and regulate the plasticity of synapses in neuronal cells cultured *in vitro*[41]. In addition to binding to YB-1, MeCP2 can interact with RNA splicing factors such as martin 3 (MATR3), splicing factor proline and glutamine-rich (SFPQ), and serine and arginine-rich splicing factor 1 (SFRS1) to regulate RNA splicing[42]. The loss of MeCP2 function can lead to intron retention in blood cells as well as intron retention and exon skipping in some genes in neurons[41,43].

## MeCP2 and miRNA

Recent studies have demonstrated that MeCP2 can regulate the expression of miRNAs [Figure 1]. MeCP2 represses the transcription of primary miRNAs (pri-miRNAs), including miR-137[44], miR-15a[45], miR-184[46], and miR-7b[47], by binding to mCG sites in gene promoter regions. Consequently, the loss of MeCP2 enhances the transcription of pri-RNAs, resulting in the expression of mature miRNAs[48]. Furthermore, MeCP2 can alter the differentiation fate of cells by affecting the expression level of miRNAs. For example, MeCP2 can lead to the upregulation of miR-199, which could inhibit the ERK signaling pathway by

targeting PAK4, thus hindering early neuron development[49]. In MeCP2 knockout male mice, Mellios *et al.* observed that the absence of MeCP2 resulted in the upregulation of Let-7f miRNA by suppressing BDNF expression. Subsequently, the elevated Let-7f miRNA levels exerted a direct inhibitory effect on IGF-1 synthesis, consequently leading to perturbed neuronal and astrocytic morphology as well as compromised functional integrity[50]. The deficiency of MeCP2 is associated with the downregulation of miR-146a and miR-146b, leading to the concomitant upregulation of their target gene, IL-1 receptor-associated kinase 1 (Irak1). As a consequence, this dysregulation instigates inflammatory responses, specifically within neurons[51]. Horvath *et al.* conducted a study on the hippocampus, revealing that MeCP2 exerts regulatory control over synaptic function through its interaction with miR-101a[52]. However, the specific molecular mechanisms underlying this phenomenon have yet to be elucidated. Altogether, the abovementioned studies suggest that RTT-associated mutations can alter multiple miRNA pathways downstream of MeCP2 and lead to impaired brain development and maturation. An in-depth understanding of MeCP2 function may help to elucidate the pathogenesis of RTT and develop effective therapeutic strategies.

## CLINICAL CHARACTERISTICS OF RTT

The clinical presentation of RTT is closely related to the age of female patients and can be divided into four stages accordingly[53]. Patients develop normally during the first 6 - 18 months of life, and then experience four sequential stages of onset: stagnation (age 6-18 months), rapid regression (age 1-4 years), pseudo stationary (age 2-potentially life) and late motor deterioration (age 10-life)[7]. Despite their poor physical conditions, patients with RTT can typically survive until adulthood and even up to 70 years of age (70% of patients survive until 45 years of age)[22]. Cardiopulmonary problems are the main cause of death in patients with RTT[54]. Compared with female patients, male patients present with more severe phenotypes that are typically accompanied by severe congenital brain disease. *MECP2* mutations have been detected in male fetal tissues and are considered lethal[55]. Owing to its typical sex preference and a sex ratio opposite to that of autism spectrum disorder (ASD) (male: female = 4:1), RTT is no longer classified as ASD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).

## RTT AND WM ABNORMALITIES

The pathogenesis of RTT remains largely unclear due to the limited research available, which is primarily based on autopsy reports. However, the rapid development of imaging technology, particularly MRI, and its application in the medical field have improved the understanding of brain developmental abnormalities in RTT patients, providing valuable guidance for further research. MRI scans conducted on patients of varying ages and with different mutation types have revealed that abnormal brain regions in patients with RTT are primarily localized in the frontal lobe, caudate nucleus, putamen, thalamus, parietal lobe, and hippocampus[56]. In addition to the commonly observed GM abnormalities, a decrease in the overall volume of WM and thickness abnormalities in the genu and splenium of the corpus callosum (CC) suggest that functional defects in MeCP2 can lead to WM abnormalities[57]. MRI has been used to image mouse and monkey models to examine the potential association between abnormal brain structure development and behavioral phenotypes in RTT. Grand *et al.* used MRI and detected overall brain shrinkage and significantly decreased motor cortex and CC thickness in *MECP2*-knockout mouse models[58]. The presence of CC abnormalities indicates the occurrence of WM abnormalities in mouse models[59]. Similarly, we have observed abnormalities in WM development, particularly in brain regions such as the prefrontal lobe and motor cortex, through brain imaging of monkey models established using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9) technology[55]. Both mouse and monkey models exhibit WM development abnormalities similar to those found in patients. As shown in Table 1, the results of MRI detection of brain dysplasia in patients with RTT (including atypical RTT) and RTT models (mouse and monkey) show that WM abnormalities (especially in the CC) are common in RTT. Owing to the absence of

**Table 1. Differences in brain imaging findings between patients with RTT and animal models of RTT**

| Gene | Species | Sex | Mutation | Cerebral Atrophy | The total volume of WM | Abnormal brain regions in GM | Abnormal brain regions in WM | Ref. |
|---|---|---|---|---|---|---|---|---|
| *MECP2* | Human | Female Male | -- | √ | √ | Frontal lobe, parietal Lobe, and cerebellum | Superior longitudinal fasciculus, CC, and middle cerebellar peduncle | Mahmood[57] |
| *MECP2* | Human | Female | -- | √ | -- | The parietal lobe, prefrontal lobe, and white matter fiber bundles | -- | Carter[65] |
| *MECP2* | Human | Female | -- | √ | -- | -- | All | Tani[66] |
| *MECP2* | Human | Female | R190H | √ | -- | -- | All (delayed myelination) | Zhou[67] |
| *MECP2* | Human | Female | -- | √ | -- | Frontal lobe | CC | Ryo[60] |
| *MECP2* | Human | Male | -- | √ | -- | -- | -- | Takaji[68] |
| *CDKL5* | Human | Female | -5bp | √ | -- | Frontal lobe | CC | Saitsu[69] |
| *FOXG1* | Human | Female | -- | × | × | Frontal lobe | | Kumakura[70] |
| *Mecp2* | Mouse | Male | 308 | √ | -- | X | CC | De[71] |
| *Mecp2* | Mouse | Male | KO | √ | √ | All | All | Akaba[59] |
| *MECP2* | Monkey | Female | KO | √ | √ | occipital gyri, inferior temporal gyrus, and annectant gyrus | cingulate WM CC | Chen[55] |

neuronal bodies in WM, it can be inferred that WM abnormalities are closely associated with glial cells. With the rapid development of imaging technology and improved understanding of glial cells, the role of WM in the brain is gradually receiving substantial attention from scholars.

The clinical symptoms of RTT are similar to those of ASD, and the imaging results of ASD patients also found that the abnormalities of CC are also similar to those of RTT patients[60,61]. Given that the WM abnormalities of RTT and ASD are similar, this finding suggests that WM abnormalities have common features among neurodevelopmental disorders[16,61,62]. The main cell group in WM is OL lineage cells, and OLs are one of the most important components of nerve fiber bundles[63,64]. OPCs differentiate into mature OLs through a series of complex and precise processes[19]. Therefore, we speculate that inhibition of oligodendrocyte precursor cells (OPCs) differentiation is the primary cause of WM abnormalities in patients with RTT. The following sections describe the developmental process of OPCs, which may help to understand the cause of WM abnormalities.

## Generation of OPCs

OPCs are widely distributed throughout the CNS and account for approximately 5% of the total cells in the CNS[72]. They can continuously proliferate and differentiate, with their primary function being the differentiation into mature OLs. Additionally, OPCs have the capacity to differentiate into astrocytes and neurons[73]. They play a crucial role in the CNS by participating in immune regulation, neurogenesis regulation, and the formation of synapses with neurons[73]. It is important to note that OPCs are heterogeneous, meaning that their functions vary across different brain regions. Despite originating from the neural tube epithelium, OPCs exhibit functional heterogeneity throughout the CNS, which can be attributed to variations in their time of generation[74,75]. Studies have demonstrated that the developmental process of OPCs and the timing of their development are different between humans and mice. In mice, OPCs are generated in different brain regions at three distinct time points during development. Initially, OPCs emerge in the embryonic cerebellum at E11.5d[74]. OPCs in the cerebral cortex are produced in the medial ganglionic eminence and the medial prefrontal region at E12.5d; these OPCs migrate dorsally and

ventrally, eventually reaching the developing cortex at E16.5d[76]. The second phase of OPC proliferation mainly originates from the striatum at E15.5d; these cells migrate to the cortex and eventually become distributed throughout the brain[76]. The third stage of OPC production occurs in the subventricular zone (SVZ) at birth; these cells migrate to the CC and neighboring cortex[76]. Notably, the earliest OPCs that migrate to the cortex are gradually replaced by OPCs produced during the third stage of development, with complete replacement occurring approximately 10 days after birth[77]. At present, the understanding of OPCs in the human brain is not as clear as that in the mouse brain. Studies have suggested that OPCs in the human brain are generated during two concentrated periods. The first peak appears around week 10 of pregnancy. During this stage, OPCs can be observed in the frontal brain, lasting until approximately week 15[77,78]. The second peak occurs during the postnatal period and extends up to 5 years of age, followed by a decrease in OPC proliferation efficiency; however, OPC proliferation can be detected in the adult human brain[79].

## OPC differentiation

In the CNS, only OPCs can differentiate into mature OLs through complex and strict regulatory mechanisms. According to different developmental stages, OL lineage cells can be classified as OPCs, immature OLs, and mature OLs. Studies have demonstrated that the maturation of OLs is regulated by factors such as extracellular signaling molecules, epigenetic regulation, and transcription factors. Subsequent chapters will delve into the elucidation of mechanisms influencing OPC differentiation, focusing on miRNA, mitochondrial abnormalities, and immune-related factors.

### *Transcription factors*

Transcriptional regulators play an essential role in maintaining the proliferation and differentiation of OPCs. Common transcriptional regulators include OL transcription factor 2 (Olig2), SRY-box 10 (Sox10), NK2 homeobox 2 (Nkx2.2), and myelin regulatory factor (MYRF)[19]. During the differentiation of NSCs into OPCs, Olig2 is first expressed and can be used as a marker of OPCs[80]. Some researchers have referred to Olig2-positive cells as Pri-OPCs. Olig2 can promote the early differentiation of OPCs, and its expression gradually decreases as differentiation progresses[81]. Wu *et al.* reported that the combination of proline-rich coiled-coil 2A (Prrc2a) and N6-methyladenosine (m6A) maintained the transcription level of Olig2[82]. Moreover, insufficient myelination was observed in mouse models with a specific knockout of Prrc2a in OPCs, suggesting that Olig2 can promote the differentiation of OPCs[82]. Olig2 can induce the expression of Sox10, which acts as a DNA-binding protein to directly regulate the expression of myelin basic protein (MBP) and promote the differentiation of OPCs[83]. Sox10 can directly regulate the transcription factor MYRF[84]. Together, Sox10 and MYRF can collectively regulate the expression of MBP, myelin oligodendrocyte glycoprotein (MOG), and other genes and promote the differentiation of im-OLs to ma-OLs[84,85]. Nkx2.2 plays an important role in the occurrence and differentiation of OPCs. Related studies have demonstrated that Nkx2.2 can directly bind to the PDGF-α promoter to inhibit its expression, thereby promoting OPC differentiation[86]. However, the underlying mechanisms remain unclear. Studies have demonstrated that the transcription factors inhibitor of DNA binding 2/4 (Id2/4), transcription factor 4 (TCF4), and zinc finger protein 24 (ZFP24) play an indispensable role in OPC differentiation and OL maturation[19]. Altogether, recent novel findings may help to elucidate the development of OL lineage cells.

### *Epigenetic regulation*

Studies on OL lineage cells have reported that epigenetic regulation, such as chromatin remodeling, histone modification, and RNA regulation, can promote OPC differentiation and myelin formation. Chromosomal condensation and decondensation during OPC differentiation are mainly mediated by the ATPase subunit Brahma-related 1 (BRG1, also known as Smarca4)[87]. Olig2 can recruit BRG1 to the enhancers and promoters of Sox10, MBP, and other OPC differentiation-related genes to promote their transcription[88].

Chromodomain helicase DNA binding protein 7 (CHD7), another chromatin remodeling-related factor, can promote transcription by forming a complex with BRG1 or with the promoters of genes involved in OPC differentiation, such as Sox10 or Nkx2.2[89]. Furthermore, the acetylation and methylation of histones can regulate the differentiation of OPCs. Loss of the core enzyme EZH2 in polycomb repressive complex 2 (PRC2), a histone methyltransferase, can prevent the differentiation of OPCs and reduce the number of OLs[90]. miRNAs can regulate OPC differentiation and myelin formation through post-transcriptional regulation. For example, miR-219 can promote OPC differentiation by specifically recognizing and inhibiting platelet-derived growth factor receptor, alpha polypeptide (PDGF-α), SRY-box transcription factor 6 (SOX6), hes family bHLH transcription factor 5 (HES5), forkhead box J3 (Foxj3), and other RNAs that inhibit genes related to OPC differentiation[91]. In addition, it can repress the expression of ELOVL fatty acid elongase 7 (Elovl7), a fatty acid elongation factor, to avoid excessive accumulation of fat in OLs, thereby maintaining the activity of OLs[92]. Other miRNAs involved in the regulation of the differentiation of OL lineage cells include miR-338, miR-138, miR-219, miR-200, and miR-9[93,94].

*Signaling molecules*

Extracellular hormones, growth factors, and other related factors promote the proliferation and differentiation of OPCs by activating specific signaling pathways. Some common regulatory factors include Triiodothyronine (T3), platelet-derived growth factor (PDGF), Insulin-like growth factor-1 (IGF-1), and fibroblast growth factor 2 (FGF2). T3 produced and released by the thyroid gland can enter the CNS through the blood–brain barrier to regulate the proliferation and differentiation of OL lineage cells[95]. T3 activates the PI3K/AKT signaling pathway by binding to the thyroid hormone receptor (TR), thereby terminating the cell cycle of OPCs and consequently promoting their differentiation into OLs[96]. In addition, T3 can promote the differentiation of NSCs into OPCs and the morphological and functional maturation of OLs[97]. IGF-1 is primarily synthesized by neurons and glial cells in the CNS. During the development of OPCs, IGF-1 mainly induces the PI3K/AKT and MAPK/ERK signaling cascades by binding to the IGF-1 receptor (IGF-1R), thus inhibiting OPC apoptosis and promoting proliferation[98]. Similar to IGF-1, PDGF is synthesized by neurons and glial cells. PDGF promotes the migration, proliferation, survival, and maturation of OPCs by binding to the PDGF-α receptor on OPCs[99]. In addition, PDGF can maintain the activity of OPCs by activating the JAK/STAT signaling pathway[100]. FGF2 can promote the differentiation of neural progenitor cells into OPCs, and can also induce the differentiation of OPCs into OLs[101]. Other signaling molecules that regulate the development of OPCs include ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and epidermal growth factor (EGF)[102-104]. However, the mechanism of action of these molecules warrants further investigation.

## POTENTIAL MECHANISM OF ACTION OF MECP2 IN OL LINEAGE CELLS

In previous studies, developmental abnormalities in WM have been observed on MRI and pathological examination in both RTT patients and animal models of RTT[16,58]. These abnormalities are characterized by a common trend of decreased WM volume and CC thickness. To verify whether the OL lineage cells lead to developmental abnormalities in WM, mouse models with specific knockdown of MeCP2 in OPCs have been used. According to the results of electron microscopy, these knockout mouse models have decreased CC thickness, decreased abundance of OPCs and OLs, and abnormal number and thicknesses of myelin sheaths in the CC[105]. These findings support the hypothesis that WM abnormalities result from the impaired development of OL lineage cells. However, the mechanisms through which MeCP2 regulates the development of OL lineage cells remain unclear. This section briefly summarizes the developmental process and regulatory mechanisms of OL lineage cells and describes the mechanisms through which MeCP2 regulates their proliferation, differentiation, and function. The findings reported in this section may improve the understanding of WM developmental abnormalities in RTT and even ASD.

### MeCP2 regulates the differentiation of OPCs

Reduced CC thickness has been observed in both Mecp2-knockout mouse models and in the imaging and autopsy reports of human patients[56,105]. These findings suggest that MeCP2 regulates abnormal myelin formation. However, the underlying mechanisms remain elusive. Studies on primary culture of rat OPCs have demonstrated that Mecp2 expression increases with OPC differentiation and that MeCP2 can bind to the promoter regions of genes encoding myelin proteins such as MBP and PLP to regulate myelin formation in mature OLs[106]. Knockdown of MeCP2 can increase the expression of genes encoding MBP, PLP, myelin-associated oligodendrocyte basic protein (MOBP), MOG, brain-derived neurotrophic factor (BDNF), and transcription factor (YY1) and in the levels of MBP, PLP, and BDNF proteins[106]. Given that these genes are involved in OL differentiation and myelin formation, MeCP2 may play a negative regulatory role in myelin formation. A study using Mecp2-knockout mice revealed 130 differentially expressed genes (DEGs) in the brain. Among those DEGs, 34 genes were also abnormally expressed in the autism mouse model ($Pten^{m3m4}$ and $Tcf^{4+/Mut}$). Enrichment analysis of these 34 genes was significantly enriched in several myelin formation-related gene ontology terms[107]. Approximately 15% of genes were associated with myelin regulation, and their expression was significantly increased, which was consistent with the results of *in vitro* experiments[107]. However, studies investigating the role of MeCP2 in regulating the proliferation and differentiation of OLs are limited. Therefore, understanding the precise mechanisms through which MeCP2 regulates OLs proliferation, differentiation, and myelin formation may facilitate the study of pathological mechanisms underlying WM abnormalities in RTT.

### Function of MeCP2 in oligodendrocyte lineage cells

To date, studies on the pathogenesis of RTT have mainly focused on neurons and elucidated the specific mechanisms through which MeCP2 regulates neurogenesis and neuronal maturation. However, only a few studies have investigated the regulatory mechanisms of MeCP2 in OL progenitor cells. This section summarizes the potential functions of MeCP2 in OL progenitor cells based on the understanding of its functions in neurons and from the perspective of miRNAs, mitochondrial abnormalities, and immunity.

#### *miRNA regulation*

MicroRNAs (miRNAs) are small non-coding RNAs that consist of 20-24 nucleotides and typically inhibit gene expression by binding to the 3'-UTR of mRNAs[108]. miRNAs can be categorized into different types and have various biological functions. Recent studies have reported that most miRNAs are located within the introns of protein-coding genes[109]. Transcription of miRNAs results in the production of pri-miRNA transcripts with multiple hairpins in the nucleus. pri-miRNAs are cleaved by the Dorsha enzyme to produce hairpin precursor miRNAs (pre-miRNAs), which are cleaved by the ribonuclease Dicer1 in the cytoplasm to form mature miRNA[108]. miRNAs can regulate various biological functions such as cell proliferation, differentiation, apoptosis, and metabolism at the transcriptional level[110]. In addition, they are involved in regulating developmental processes such as neural development, neuronal maturation, and synaptic plasticity[111]. Abnormal miRNA expression has been observed in patients with RTT, *Mecp2-null* mouse brains, and *in vitro* cultured neurons[112]. As shown in Figure 2, MeCP2 can regulate miRNA expression either directly or indirectly. Although no relevant studies have demonstrated that MeCP2 affects OPCs development by regulating miRNA expression, considering that miRNAs have been reported to play a crucial role in the proliferation, differentiation, and myelination of OPCs[113,114], MeCP2 may regulate the proliferation and differentiation of OPCs through miRNAs.

#### *Direct regulation of miRNA*

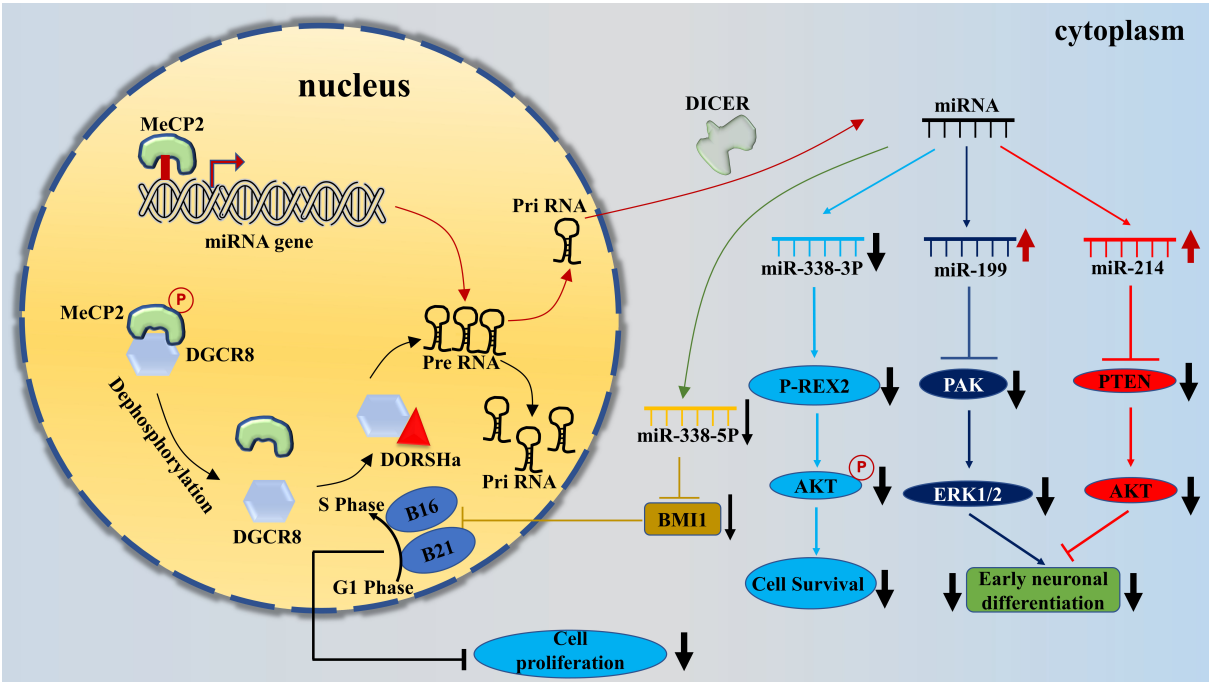


**Figure 2.** Prediction of mechanisms through which MeCP2 regulates miRNAs in oligodendrocyte lineage cells. MeCP2 may regulate the expression of miRNA through two pathways in the nucleus. The first way is that MeCP2 can directly bind to the mCG site of the miRNA gene promoter to inhibit transcription. The second way is that MeCP2 can affect the number of Dorsha complexes by controlling the binding of the Dorsha and DGCR8. Dorsha complexes can cleave pri-miRNAs to generate pre-miRNAs. MeCP2 regulates the expression of pre-miRNAs in the nucleus and then inhibits the translation of downstream target mRNAs by affecting the expression levels of intracellular miRNAs. Black arrows indicate downregulation, and red arrows indicate upregulation.

The way MeCP2 directly regulates transcription is that it can specifically recognize and bind to the mCG site in the miRNA promoter region, inhibit the transcription of pri-miRNA and reduce the expression of miRNA[112] [Figure 2]. MeCP2 exerts direct inhibitory effects on miR-15a transcription, whereas miR-15a, in turn, modulates neuronal growth through the regulation of brain-derived neurotrophic factor (BDNF) expression[45]. The methylation of the 5'-flanking region of miR-7b plays a crucial role in recruiting MeCP2 and subsequently represses miR-7b expression. Simultaneously, miR-7b exhibits a specific binding affinity towards the MECP2-3'UTR region, thereby exerting inhibitory control over its expression. These reciprocal interactions establish a dynamic equilibrium between miR-7b and MeCP2[47]. Studies on gastric cancer cells have demonstrated that MeCP2 specifically recognizes CpG islands in the miR-338 promoter and inhibits the expression of miR-338-3p and miR-338-5p[115,116]. These two miRNAs can suppress the proliferation of gastric cancer cells by regulating the expression of phosphatidylinositol-3,4,5-trisphosphate dependent Rac exchange factor 2 (P-REX2) and BMI1 proto-oncogene, polycomb ring finger (BMI1), respectively[117]. Additionally, miR-338 inhibits the expression of proteins that promote OPC proliferation, thus promoting their differentiation into myelinating Ols. MiR-338-5p and miR-338-3p can promote the differentiation of OPCs by inhibiting the expression of differentiation inhibitors such as Sox6 and HES5[118]. This indicates that MeCP2 may have the ability to regulate the proliferation and differentiation of OPC through miR-338-5p and miR-338-3p.

*Indirect regulation of miRNA*

About indirect regulation in Figure 2, dephosphorylation of MeCP2 at pS80 leads to its dissociation from the chelated DiGeorge syndrome critical region 8 (DGCR8) and allows DGCR8 to recruit Dorsha complexes to cleave pri-miRNAs[48,108]. It is noteworthy that abnormal MeCP2 phosphorylation in different

cell types may be the primary reason for abnormal miRNA expression. Mellios *et al.* found that MeCP2 delayed the early differentiation of neurons by upregulating miR-199 and miR-214 expression. MiR-214 can target and inhibit the expression of PTEN, thereby activating the AKT signaling pathway to inhibit neuronal differentiation[49,119]. Nakashine *et al.* demonstrated that MeCP2 upregulates the expression of miR-199a in NSCs by binding to the Dorsha receptor, while miR-199a promotes NSC differentiation into neurons by decreasing the expression of Smad1[120]. In addition, studies on OPCs derived from human ES cells have reported that miR-199a and miR-214 can inhibit OPC differentiation by suppressing the expression of MOBP and MYRF[121,122]. Therefore, MeCP2 may regulate OPC differentiation by regulating miR-199 and miR-214. In non-classic RTT, the FOXG1 protein regulates miRNA biogenesis by recruiting Dorsha, indirectly indicating the importance of miRNAs in the development of RTT[123].

Based on a literature search and analysis of miRNAs that are commonly regulated by MeCP2 in both neural cells and OPCs, it has been hypothesized that MeCP2 regulates OPC differentiation through miR-26[124,125], miR-30[126,127], miR-146[51,128], and miR-203[52,129], and regulates OLs maturation and myelination through miR-9[130,131], miR-21[132,133], miR-23[130], miR-184[46,134]. Figure 2 shows the potential signaling pathways that are affected by MeCP2 through the regulation of miR-199 and miR-214, and miR-338 in OPCs. This information may guide future studies investigating the regulatory effects of MeCP2 on miRNAs during the proliferation, differentiation, and myelination of OL lineage cells.

*Mitochondrial abnormalities*

RTT is considered a mitochondrial disease because of the shared clinical features between RTT syndrome and mitochondrial diseases, such as oxidative damage, abnormalities in electron transport chain (ETC) complexes, and elevated levels of lactate and pyruvate in the peripheral blood and cerebrospinal fluid[135-137]. Loss of MeCP2 can lead to abnormalities in the structure and function of mitochondria in RTT. Investigation of mitochondria in the muscle, skin, and different brain regions of patients with RTT has revealed pathological features such as abnormally enlarged mitochondria and dumbbell-shaped vacuoles[138-140]. A study demonstrated that loss of Mecp2 in 3-week-old mice resulted in an increase in the volume of mitochondria and the abundance of mitochondrial cristae without forming bubble-like structures[135]. Although no differences in mitochondrial morphology were observed in 12-week-old mice, significant abnormalities were observed in their mitochondrial function[135]. The primary function of mitochondria is to provide energy to cells through ATP synthesis. In addition, they play a role in regulating biological processes such as oxidative stress, lipid metabolism, and cell apoptosis.

To date, no studies have reported mitochondrial abnormalities in OLs in RTT. F2-isoprostanes are biomarkers for OS damage and have been detected in WM from patients with RTT[141], indicating that MeCP2 may induce OS and eventually lead to WM abnormalities by affecting mitochondrial function. OLs synthesize lipids required for myelin sheath formation and provide substances for neurons, such as lactate and pyruvate. Therefore, they require more mitochondria to maintain their energy expenditure[142,143]. To investigate the impact of MeCP2 on the structure and function of mitochondria, Aldosary *et al.* performed an integrated analysis of gene expression data from the brains and blood of patients with RTT and identified 77 common differentially expressed genes[137]. And most of them are involved in mitochondrial dysfunction and oxidative stress (OS) responses, which exacerbate the development of RTT[137].

*OS abnormalities*

OS is primarily caused by abnormal accumulation of ROS, which is mainly produced by mitochondria within cells. Therefore, MeCP2 may induce OS by regulating mitochondrial function. Elevated OS levels have been detected in *Mecp2-null* mice[144,145]. In a study, MeCP2 expression was restored in *Mecp2-null* mice

to verify the causal relationship between Mecp2 and OS. The results revealed that reactivating MeCP2 in the MeCP2-deficient mouse brain restored the levels of OS markers such as F4 NeuroPs, F2 IsoPs, and NPBI[144]. Additionally, a decrease in superoxide dismutase (SOD) and glutathione (GSH) levels have been observed in symptomatic mouse models of RTT[146,147]. Downregulation of SOD and GSH may lead to excessive accumulation of ROS and induce OS responses. In addition, abnormal expression of genes associated with mitochondria or OS, such as uncoupling protein 3 (UCP3), cardiolipin synthase (CRLS1), NADH: ubiquinone oxidoreductase subunit A5 (NDUFA5), mitogen-activated protein kinase 9 (MAPK9), ATP synthase peripheral stalk subunit OSCP (ATP5PO), MAF bZIP transcription factor (MAF), Fos proto-oncogene (FOS), and stress-activated protein kinase (SAPK), has been observed in the brain tissues of mice with RTT[137]. In neurodegenerative diseases such as MS, an abnormal increase in mitochondrial activity in OLs can exacerbate oxidative damage, which may be the cause of demyelination[148]. This phenomenon indirectly verifies our hypothesis. In studies on OLs, abnormal accumulation of ROS has been demonstrated to cause damage to DNA and mtDNA, which not only leads to a decrease in the levels of mitochondrial respiratory chain-related proteins but also reduces the ability of OLs to form myelin[149]. In addition to providing cellular energy, mitochondria play a necessary role in lipid biosynthesis and myelin formation in OLs. Elevated ROS levels can lead to lipid peroxidation (LAHP) and inhibit myelin formation[150]. When ROS levels are extremely high, LAHP is oxidized to MDA, and the abnormal accumulation of MDA can lead to cell apoptosis.

*MeCP2 and electron transport chain abnormalities*

Because intracellular ROS are generated by the mitochondrial respiratory chain complex II, the detection of decreased ATP synthesis in Mecp2-null cells suggests that MeCP2 can affect OS levels by regulating mitochondria[151]. Studies on abnormal mitochondrial function in hippocampal neurons have demonstrated that MeCP2 deficiency significantly reduces the enzymatic activity of respiratory chain complex I, II, and IV and also results in an abnormal increase in ROS levels[152]. MeCP2 can directly upregulate the promoter of the uncoupling CQR-1 complex III protein gene (Uqccr1 complex III) with ubiquinone cytochrome c reductase core protein I[153]. However, Mecp2 knockout can increase the respiratory rate related to complex III in mitochondria in the brains of mice and accelerate the generation of ROS by increasing the electron chain non-coupling rate[138,153]. However, the energy demand of OPCs is higher than that of OLs, indicating that OPC differentiation is a high-energy-consuming process[154]. High-energy-demanding cells lead to an increase in ROS levels, which promotes OPC differentiation and myelin formation[148,155]. MeCP2 deficiency can induce mitochondrial abnormalities in neurons and astrocytes. If this phenomenon occurs in OLs, high energy demand and mitochondrial dysfunction can accelerate the abnormal accumulation of ROS, possibly leading to the release of cytochrome C (Cyt C) in the cytoplasm and inducing OPCs or OLs apoptosis. In addition, calcium ion disorders have been found in MeCP2-deficient astrocytes, and calcium ion accumulation owing to mitochondrial abnormalities can lead to Cyt C release in the cytoplasm and induce cell apoptosis[156].

As shown in Figure 3, we associate the mechanisms underlying MeCP2-induced mitochondrial abnormalities with research on mitochondria in neurodegenerative diseases and infer the role and function of MeCP2 in OLs.

*Immunoregulation*

Loss of MeCP2 function could cause immune dysfunction and chronic inflammation, exacerbating the deterioration of clinical characteristics[157]. Therefore, exploring the regulatory effects of MeCP2 on immune cell function and pro-inflammatory signaling could promote our understanding of the pathogenesis of RTT. As immune cells, microglia produce cytokines, such as interleukin (IL) -1β, tumor necrosis factor (TNF),

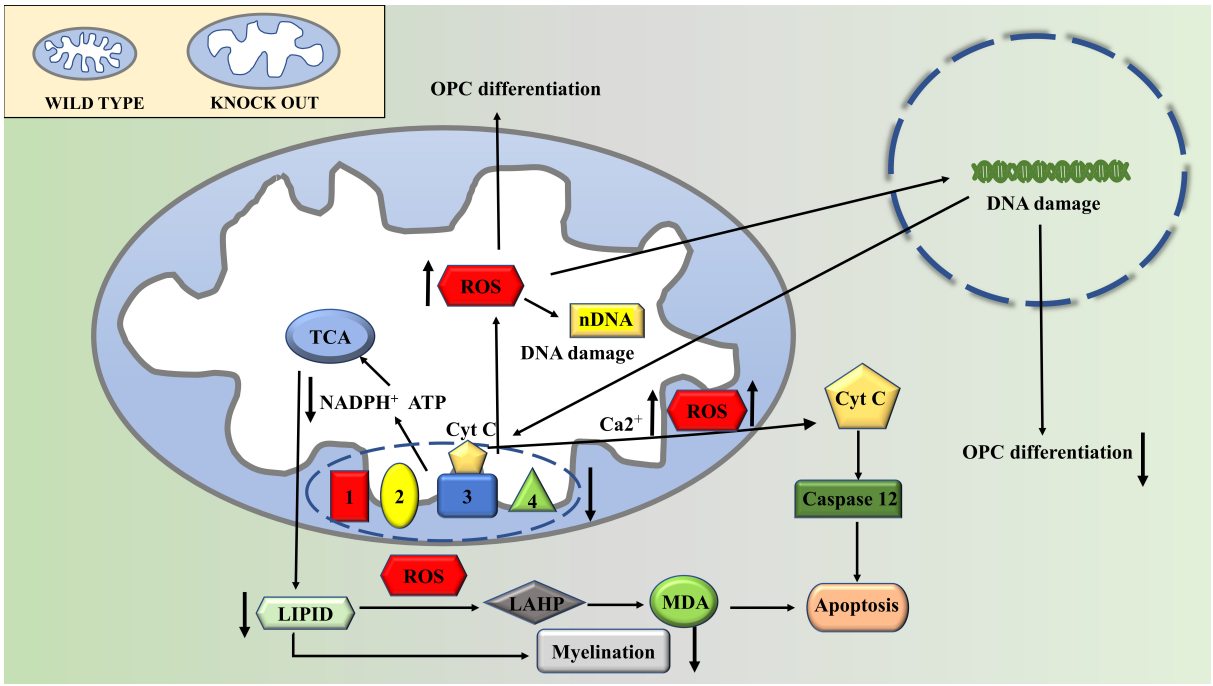


**Figure 3.** Abnormal MeCP2 function may lead to changes in mitochondrial structure and function. MeCP2 may regulate the function of mitochondria by affecting electron transport chain complexes. The loss of MeCP2 function can lead to the release of cytochrome C into the cytoplasm and induce apoptosis. MeCP2 mutations can also lead to abnormal accumulation of reactive oxygen species, resulting in DNA damage and even apoptosis. However, an appropriate increase in ROS can make OPC exit the cell cycle and promote its differentiation. The abnormal function of MeCP2 can also reduce the coenzyme of dehydrogenase (NAD+) and the generation of ATP, thereby reducing the synthesis of lipids by affecting the reaction of tricarboxylic acid. OPC:oligodendrocyte precursor cell; ROS: reactive oxygen species.

and IL-6, in the CNS to regulate the developmental process[158,159]. Although specific knockout *Mecp2* in microglia could not induce RTT pathological phenotypes in mice, specific restoration of Mecp2 in microglia can rescue the pathological phenotype in RTT mice and extend their lifespan, indicating that the microglia play an important role in the pathogenesis of RTT[160]. A recent study showed that the expression of TNF was upregulated in the microglia of an RTT mouse model, which can promote the occurrence of inflammatory reactions[161]. The upregulation of TNF can inhibit the mTOR signaling pathway by activating AMP-activated protein kinase (AMPK), preventing differentiation, and even inducing apoptosis of OPCs[162]. In addition, Feldhaus *et al.* found that TNF can also reduce the expression of MBP during OPC differentiation, which may be the main reason why MeCP2 inhibits OPC differentiation[163]. IL-9, IL-4, IL-1β , and IL-17 were upregulated in the plasma of RTT patients[164,165]. IL-9 can inhibit OPC differentiation, but the mechanism is unclear[166]. IL-4 can stimulate the microglia to secrete IGF-1, inhibiting the apoptosis of OPCs. IL-1β and IL-17 can directly inhibit the apoptosis of OPCs and promote their proliferation[167,168]. The mechanism of MeCP2 in regulating proliferation, differentiation, and apoptosis of OL lineage cells through affecting the expression of immune factors is not yet clear, and further studies are needed.

*OPCs and immunoregulation*

OLs are well-known as myelin-forming cells in the CNS. However, with the in-depth investigation of OL lineage cells, it is reported that OPCs also have immune functions, including secreting inflammatory factors, expressing cytokine receptors, and responding to inflammation[169]. Moyon *et al.* found that OPCs can release immune regulatory factors, such as IL-1β and CCL2, in a demyelination mouse model during the process of proliferation and migration to damaged areas[170]. Zeis *et al.* also confirmed that OPCs can express

various immune regulatory factors, such as chemokines, cytokines, and complement[169]. Zveik *et al.* used cerebrospinal fluid from MS patients to treat OPCs *in vitro* and found that the treated OPCs showed inhibited proliferation and differentiation ability as well as reduced expression of histocompatibility complexes (MHC)-II and reduced secretion of TNF-α and NF-κB, which also provide evidence that OPCs has the immune function[171]. In addition, OPCs can also express immune-related proteins such as interleukin-17A (IL-17A), C-X-C motif chemokine ligand 10 (CXCL10), CD55, CD59, CD200, and CD47, further confirming that OL lineage cells can actively participate in the regulation of CNS inflammation[169,172]. The mechanism of OPCs in secreting immune factors remains unclear. Kishi *et al.* showed that MeCP2 can regulate cytokine expression through the NF-κB signaling pathway. Using RTT mouse cortex, they found that MeCP2 deficiency results in the loss of its transcriptional inhibitory effect on Irak1, which can activate the NF-κB signaling pathway to promote the entry of p65/RelA complex into the nucleus, thereby promoting the transcription of immune factors[173]. This may explain the immune dysfunction in RTT patients. In addition, Falcão *et al.* found that OPCs, like activated microglia, can phagocytose myelin granules[174]. Under inflammatory stimuli, immune-competent OPCs exit the cell cycle, exhibit the immune phenotype, and maintain immune function for a long time[73,175]. It remains unaddressed whether OPCs with an immunophenotype have the potential to differentiate.

*Other regulatory effects*

MeCP2 is involved in regulating the aging phenotype of OPCs and OLs. Studies have shown that MeCP2 is upregulated in primary cultured OPCs from the spinal cords of aged rats; however, the underlying mechanisms require further investigation[106]. Aging is often associated with OS, and MeCP2 may be involved in regulating the aging phenotype by regulating OS[176]. Because OPCs can form synapses with neurons, and this ability gradually disappears as they differentiate, MeCP2 can regulate the formation of OPC-neuron synapses like how it regulates synaptic plasticity in neurons[177-179]. Additionally, OPCs can secrete neuroregulatory factors to participate in cellular interactions, and MeCP2 may be involved in regulating the expression of neurotrophic factors[180,181]. Altogether, aging and OPC-neuron synapses may represent novel perspectives for investigating the regulatory mechanisms of MeCP2 in OL lineage cells.

## CONCLUSION

Although classic RTT occurs owing to the functional loss of MeCP2, the complex types of mutations in the *MECP2* gene and the diversity of MeCP2 protein functions have increased the difficulty of studying the pathogenesis of RTT. The mechanisms through which MeCP2 affects neuronal morphology and function are relatively well-understood, and the corresponding treatment methods or interventions have been shown to restore RTT-like phenotypes and prolong lifespan in mouse models. However, these approaches do not result in successful treatment. Glial cells play an essential role in the development of RTT. However, the underlying mechanisms warrant further investigation. In addition to aberrant neuronal morphology and function, abnormalities in total WM volume and CC thickness are observed in RTT. Abnormal OL function plays an integral role in causing WM abnormalities. Recent advances in epigenomics and transcriptomics, as well as their application in research on CNS, have improved the understanding of the regulation and function of OL lineage cells.

In conclusion, this review summarizes the function of MeCP2 in neurons. MeCP2 regulates various functions in OLs through transcription activation and inhibition, OS, miRNA expression, immunoregulation, and aging-related phenotypes. These findings may provide a rational basis for further investigating the role of MeCP2 in OL lineage cells and expediting research on WM abnormalities.

## DECLARATIONS

### Authors' contributions

Contributed the most to the conception and writing of the manuscript: Zhen Z
Construction of figures: Peng L
Conceived the project and revised the manuscript: Chen YC

### Availability of data and materials

Not applicable.

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### Conflicts of interest

All authors have no conflicts of interest to declare.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.



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