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REVIEW

MeCP2 at the crossroads of hypoxia, oxidative stress, and gene regulation in Rett syndrome

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ABSTRACT

Rett syndrome (RTT) is a severe neurodevelopmental disorder primarily affecting females, caused by mutations in the X-linked gene *MECP2*. This gene encodes methyl CpG binding protein 2 (MeCP2), a multifunctional epigenetic regulator critical for neuronal gene regulation. In addition to well-characterized neurological symptoms, such as seizures and motor abnormalities, RTT patients frequently present with irregular breathing patterns that induce intermittent hypoxia, suggesting that MeCP2 contributes to respiratory regulation as well as the brain's cellular and molecular response to hypoxia. Mechanistically, MeCP2 appears to influence hypoxia-induced expression of the neuroprotective peptide brain-derived neurotrophic factor (BDNF), as impaired BDNF regulation in MeCP2-deficient neurons contributes to hypoxia vulnerability. RTT patients also display increased oxidative stress, marked by elevated lipid peroxidation, DNA damage, and reduced antioxidant production. Dysfunctional mitochondria in MeCP2-deficient astrocytes and neurons further propagate oxidative damage and non-cell-autonomous effects of MeCP2 loss. Moreover, recent transcriptomic studies revealed widespread transcriptional dysregulation in RTT, including pathways associated with mitochondrial function and oxidative stress. We review and discuss an expanded role for MeCP2 as a critical integrator of hypoxia sensing, oxidative stress regulation, and transcriptional adaptation in the developing brain, offering new insights into treatments targeting the complex pathophysiology of RTT.

PLAIN LANGUAGE SUMMARY

The protein methyl CpG binding protein 2 (MeCP2) is involved in multiple processes that affect how our genes are turned on and off. Although MeCP2 is present in most cells throughout the body, it is particularly important for proper development of neurons in the brain. Defects in MeCP2 are responsible for most cases of Rett Syndrome, while excess amounts lead to MeCP2 Duplication Syndrome; both are disorders of abnormal brain development. One common symptom of these disorders is disturbances in breathing patterns, such as breath holding or temporary pauses in breathing. These symptoms are associated with lower oxygen levels in the blood, leading to an increase in free radicals produced by the mitochondria. Excess amounts of free radicals can change or damage molecules within the body, and many of these damage indicators are found at higher levels within patients in which MeCP2 is not functioning normally. This ultimately results in damage to cells and DNA. MeCP2 also plays a role in helping the brain respond to low oxygen levels. One of the potential ways it achieves this is by promoting the production of factors that help protect neurons from cell death. Furthermore, studies on genes that display altered expression patterns in Rett syndrome reveal that many of these genes are involved in processes related to mitochondria, which generate energy but also free radicals, and oxygen response. Overall, this review discusses the role of MeCP2 in responding to low oxygen levels through its control over switching genes on or off.

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KEYWORDS
MeCP2; hypoxia; oxidative stress; mitochondria; Rett syndrome; BDNF

1. Introduction

Mutations in the X-linked gene *MECP2*, encoding the protein methyl CpG binding protein 2 (MeCP2), are found in up to 95% of patients with classical Rett syndrome (RTT) [1]. RTT is an X-linked dominant disorder that predominantly affects females who are heterozygous and mosaic for mutant *MECP2* expression due to X chromosome inactivation [2]. *MECP2* transcript is expressed in nearly all tissues of the body, although MeCP2 protein levels are highest in mature neurons in the central nervous system. As an important epigenetic "reader," MeCP2 primarily binds to methylated cytosines throughout the genome [3]. While MeCP2 has many functions, one key function is to regulate transcription in cells of the central nervous system [4]. Central nervous system related symptoms such as ataxia, seizures, and respiratory abnormalities caused by loss of MeCP2 activity are hallmarks of RTT pathologies [5]. However, other peripheral systems are involved in RTT symptomology, including the gastrointestinal, immune, and cardiac systems [5]. Furthermore, when transcriptomic changes are

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Article highlights

- Rett syndrome, an X-linked dominant neurodevelopmental disorder in females caused by *MECP2* mutation, is characterized by hypoxia and oxidative stress.
- Mechanistically, MeCP2 regulates BDNF expression in response to hypoxia, with its stability and adaptive responses regulated by PARP1. MeCP2 may also be responsive to genome-wide DNA methylation and chromatin changes following hypoxia responses.
- Mitochondria and oxidative phosphorylation leading to excessive ROS levels may spread the MeCP2 deficiency across neighboring cell types, resulting in non-cell autonomous effects also affecting wild type expressing cells in female RTT mosaic brain.
- Hypoxia in Rett syndrome is likely to be both a consequence and cause of abnormal breathing patterns.
- Novel therapeutic approaches to counteract the systemic oxidative stress responses in Rett syndrome are warranted that could be used in combination with gene therapy approaches.

examined at a single cell resolution level in RTT brain, gene pathways involved in cellular metabolic homeostasis and brain energetics emerge that are likely to impact multiple systems [6]. Brain energy and oxidative phosphorylation within mitochondria rely upon homeostatic mechanisms to avoid oxidative stress, which is defined as an imbalance in the production of reactive oxygen species (ROS) with the body's ability to neutralize ROS with antioxidants. Cardiorespiratory coupling, which involves complex homeostatic interactions that couple breathing to heart rate, is responsive to ROS and hypoxia, or insufficient oxygen levels. Interestingly, RTT pathogenesis involves both hypoxia (due to breath holding and other breathing abnormalities) and oxidative stress observed in multiple organs [5].

This narrative review will explore the somewhat novel perspective on the emerging role of MeCP2 in the response to hypoxia and oxidative stress in the brain and periphery. A literature search was conducted on Google Scholar for peer-reviewed studies published up until June 2025. The search terms used were "mecp2," "rett syndrome," or "mecp2 duplication syndrome" along with "hypoxia," "oxidative stress," "reactive oxygen species," or a combination of the previous three terms. Conference abstracts and articles not written in English were excluded.

2. Breathing abnormalities and hypoxia in Rett syndrome

The majority of RTT patients display abnormal breathing patterns during their lifespan [7–10]. Typically, RTT patients are female with heterozygous *MECP2* (*MECP2*$^{-/+}$) mutations [2]. The RTT patients with *MECP2* mutations are more likely to experience breathing dysfunction than those with mutations in other genes [11]. Breathing irregularities include breath holding, apneas, hyperventilation, and Valsalva maneuvers, and the resulting pathophysiology has been thoroughly characterized previously [12]. Breathing defects in female RTT patients result from brain stem neuronal circuit defects and are generally present during awake periods but not during sleep [13,14]. Similarly, males with *MECP2* mutation on their only X chromosome can also display irregular respiratory patterns, with some unfortunately dying prematurely due to severe apnea, respiratory failure and/or seizures [15,16]. On the opposite side of the spectrum, individuals with MeCP2 Duplication syndrome can also present with breathing disturbances, although at a lower overall frequency [17]. These results suggest that *MECP2*/MeCP2 plays an important role in central regulation of respiration, and that both abnormally low or abnormally high levels can lead to dysfunctions.

Multiple regions of the brain stem that regulate key aspects of breathing are defective in RTT. Defective MeCP2 expression in nucleus tract solitarius (NTS) glutamatergic neurons results in blunted CO_2 sensitivity [18]. Loss of wild-type MeCP2 function in RTT affects respiratory rhythm in the pre-Bötzinger complex (pre-BötC) [19]. Reduced wild-type MeCP2 levels in noradrenergic neurons on the locus coeruleus impairs excitation of the NTS and pre-BötC, weakening breathing rhythm [19]. Serotonergic neurons in Raphe nuclei normally express high levels of MeCP2 [20]. However, defective MeCP2 in RTT results in apneas [20]. The role of brain regions involved in RTT breathing defects is well summarized in [12].

When the demand for oxygen in the developing human brain exceeds its supply, hypoxia is induced. Hypoxia in the brain is defined as less than normal oxygen levels, which range from 0.5 to 8% [21]. Hypoxia alters mitochondrial respiration, protein translation, and produces oxidative stress that results in encephalopathy [22]. Many of the abnormal breathing patterns displayed by RTT patients, including breath holding and apnea, lead to decreased oxygen intake and therefore hypoxia. Many RTT patients with irregular breathing patterns experience decreased oxygen levels [23,24], with some measurements showing a partial pressure of oxygen as low as 50 mm Hg in about half of RTT patients [14]. Breathing abnormalities in RTT patients are more severe during wakefulness, and some studies report that RTT patients can also display hyperventilation, apneas, and varying degrees of oxygen desaturation [25–27]. Defects in MeCP2 resulting from *MECP2* mutations are therefore associated with periods of chronic or intermittent hypoxia within the lifespan of the patient.

Irregular breathing patterns have been recapitulated in several mouse models of *Mecp2*/MeCP2 deficiency. Specifically, studies in RTT mouse models found that hypoxia exposure led to increased minute ventilation, which is determined by both rate of respiration and volume of air moving in and out of the lungs [28]. This breathing phenotype was observed in both *Mecp2*$^{-/+}$ female and *Mecp2*$^{-/y}$ male mice with either ubiquitous *Mecp2* deficiency or neuron-specific *Mecp2* deficiency using the Nestin-Cre driver [28]. However, only *Mecp2*$^{-/+}$ female and *Mecp2*$^{-/y}$ male mice with whole body *Mecp2* deficiency exhibited decreased breathing frequency and increased apnea incidence following hypoxia exposure [28], implicating peripheral system involvement. Other groups have seen similar breathing phenotypes, although most of these studies were conducted only in male *Mecp2*$^{-/y}$ mice [18,29,30]. Specific deletion of *Mecp2* in the mouse hindbrain using the *HoxB1*-Cre line and in the caudal portion of the medulla using the *HoxA4*-Cre line were also sufficient for an increased breathing rate in response to hypoxia [30,31]. The use of *VGLUT2*-Cre, *VIAAT*-Cre, and *TH1*-Cre to delete *Mecp2* in excitatory, inhibitory, or modulatory neurons, respectively, demonstrated that *Mecp2* deficiency in any of these three neuronal populations is sufficient for increased breathing rates in response

to hypoxia [32]. Female *Mecp2*$^{+/T158A}$ and *Mecp2*$^{+/R168X}$ mice bearing RTT patient relevant *MECP2* mutations also exhibited similar responses to hypoxia as mice with *Mecp2* deletion [33]. Although *Mecp2* mutant mouse models exhibit increased breathing frequency in response to hypoxia, hyperventilation appears to occur independently of hypoxemia in RTT patients [34]. Furthermore, the characteristic hyperventilation and breath holding episodes in RTT patients are more frequent during wake than sleep and only correlate with plasma markers of oxidative stress during wakefulness [35]. Together, these studies demonstrate that breathing abnormalities following hypoxia in RTT result directly from *Mecp2* deficiency within multiple neuronal sub-types but also involve homeostatic control mechanisms across the conscious brain-body axis.

Although defects in *MECP2*/MeCP2 interact with hypoxia in RTT pathology, relatively little research has addressed the direct mechanistic link. It is possible that MeCP2 may normally play a role in the response to hypoxia. For example, astrocytes differentiated from human stem cells with the *MECP2 R270X* mutation were found to have differential expression in genes involved in response to oxygen levels and response to hypoxia [36]. These *MECP2* mutant astrocytes also had decreased oxygen respiration and higher lactate levels that suggest a hypoxic state and increased reactive oxygen species levels [36]. Altogether, these suggest that MeCP2 is important not only for normal respiratory function but also for response to hypoxia.

2.1. The role of MeCP2 and BDNF in hypoxia

A potential molecular mechanism for the role of MeCP2 in hypoxia response is its transcriptional regulation of the *BDNF* gene, which produces the brain-derived neurotrophic factor (BDNF), a neuroprotective peptide (Figure 1). In the absence of MeCP2, *BDNF* expression is decreased [37]. A meta-analysis of transcriptomics data from human, mouse, and stem-cell derived neural samples identified *MECP2* and *BDNF* as two hub genes that interact with many other differentially expressed genes, and confirmed that decreased *MECP2* expression is associated with decreased *BDNF* expression [38].

In the developing human brain, the response to hypoxia is mediated primarily through the activity of the hypoxia-inducible factor 1 (HIF-1) pathway. Poly(ADP-ribose) polymerase 1 (PARP1) plays a crucial role in the regulation of HIF-1α, a key transcription factor that modulates cellular responses to low oxygen conditions. Specifically, under hypoxic conditions PARP1 poly-ADP-ribosylates HIF-1α, which stabilizes the protein and enhances HIF-1 interaction with HIF-1β; this induces the expression of the hypoxia-responsive gene *BDNF*, which is essential for neuronal metabolism and survival [39]. *BDNF* expression in response to hypoxia allows neurons to survive and adapt to intermittent low oxygen levels by regulation of transcription of survival factors [40]. Interestingly, poly ADP ribosylation of MeCP2 by PARP1 regulates chromatin condensation activity and repression of *BDNF* transcription through MeCP2 promoter binding [41]. Therefore, although

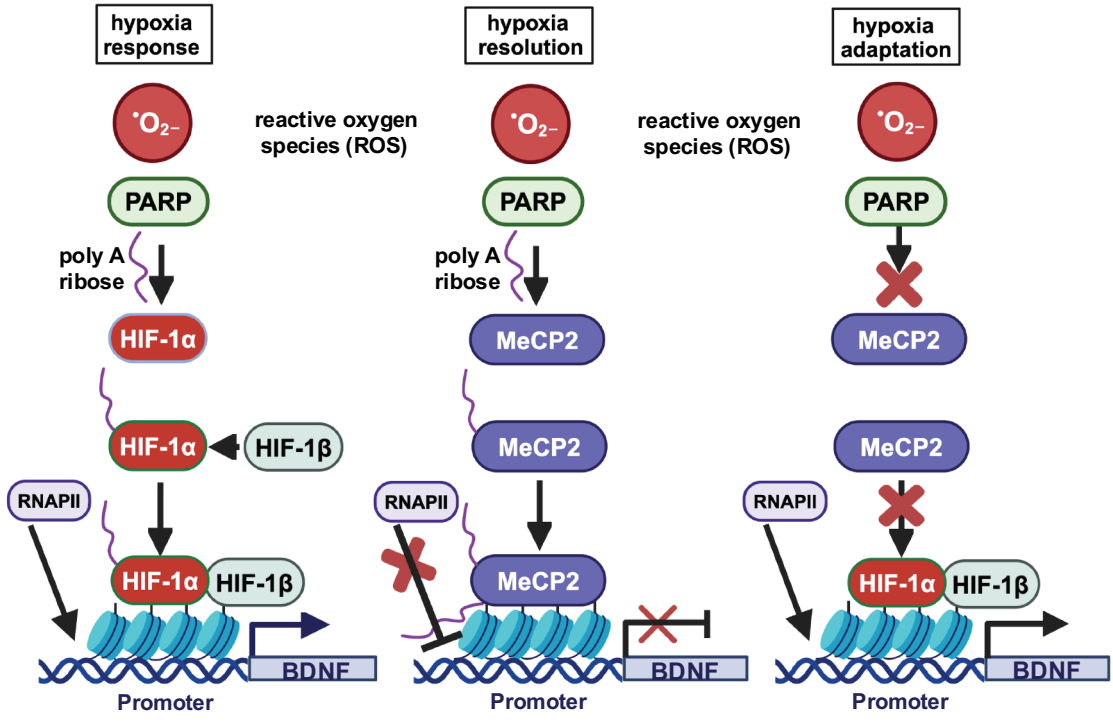

Figure 1. Regulation of brain-derived neurotrophic factor (BDNF) signaling by methyl CpG-binding protein 2 (MeCP2) in hypoxia response and adaptation. Left panel; the initial hypoxia response triggers reactive oxygen species (ROS) production that activates poly ADP-ribosylation of hypoxia-inducible factor 1-alpha (HIF-1α) by poly ADP-ribose polymerase 1 (PARP1) thereby protecting HIF1α from degradation and allowing dimerization with hypoxia-inducible factor 1-beta (HIF-1β) and recruitment of RNA polymerase II (RNAP) activity and transcriptional activation of the *BDNF* promoter. Middle panel; at the same time that HIF1 (stabilization is triggered by hypoxia and ROS, PARP1 poly ADP ribosylates MeCP2 triggering engagement with the *BDNF* promoter and transcriptional repression during hypoxia resolution. Right panel; adaptation to hypoxia no longer triggers poly ADP-ribosylation of MeCP2, allowing transcription of BDNF via HIF1α/HIF1β recruitment of RNAP. Created in BioRender. Yasui, D. (2025) https://biorender.com/y5bygnl.

speculative, these results suggest that MeCP2-PARP1 interactions are involved in the resolution stage that result from adaptation to hypoxia. Consistent with these findings, a recent study found increased stabilization of MeCP2 under conditions of hypoxia followed by reoxygenation [42]. Ultimately, long-term adaptation to hypoxia in brain is expected to reduce PARP1 modification of MeCP2, thereby reducing MeCP2 binding to the *BDNF* promoter and enabling BDNF transcription to future hypoxic challenges (Figure 1).

The link between MeCP2 and BDNF was established in a mouse model of postnatal deletion of *Mecp2* in neurons. *Mecp2* deficiency in postnatal neurons accelerated disease progression while genetic overexpression of BDNF delayed symptoms in this RTT model [37]. Also, acute intermittent hypoxia led to increased BDNF protein levels in wild-type *Mecp2*$^{+/y}$, but not *MeCP2*$^{-/y}$ mice, suggesting that MeCP2 is necessary for the protective upregulation of BDNF in response to hypoxia [43]. Studies of brain slices obtained from the *MeCP2*$^{-/y}$ mouse brainstem displayed a more prolonged increase in calcium levels in response to cyanide-induced hypoxia, but pre-culture with BDNF led to a comparable recovery time as wild-type *Mecp2*$^{+/y}$ brainstem slices [44]. It is possible that the increased calcium activity leads to excitotoxicity and contributes to the observed decrease in viability of cerebellar granule neurons derived from female *MeCP2*$^{-/+}$ mice, but the reintroduction of MeCP2 improved cellular viability [45]. Interestingly, a meta-analysis of key proteins involved in perinatal hypoxia identified MeCP2 and BDNF as a key protein-protein interaction, suggesting that the interaction between the MeCP2 protein and BDNF peptide also contributes to hypoxia response [46]. One unproven hypothesis is that breath holds, which induce intermittent hypoxia, may be a way that the body attempts but fails to increase BDNF levels in RTT patients. The inability to increase BDNF levels in the absence of functional MeCP2 would prevent its protective effect against hypoxia. Without BDNF-mediated neuroprotection in response to hypoxia, RTT patients may be unable to adapt to repeated hypoxic insults. In mice, repeated exposure of brain stem slices to hypoxia led to a shortened post-hypoxic recovery time in wild-type slices, but an increased recovery time in a subset of *MeCP2*$^{-/y}$ slices, suggesting reduced adaptive ability [47]. This was attributed to the decreased incidence of hypoxia-induced spreading depression into the pre-BötC, which in the short term may be beneficial as it allows the mice to respond with gasping activity to compensate for low oxygen levels, but in the long term can lead to failure to adapt to future incidents of hypoxia. The reduced dendritic density associated with absence of MeCP2 likely contributes to the decreased spreading. Since BDNF plays an important role in dendritic growth, and *BDNF* overexpression has been shown to rescue dendritic growth in a *MeCP2*-knockdown model [48], this is one potential way that the absence of BDNF contributes to failure of long-term adaptation to hypoxia. However, the role of BDNF in hypoxia adaptation in the context of RTT and RTT mouse models, particularly females, remains an open question to be explored. An extensive review of the role of BDNF in RTT is provided in Gold et al. [49].

As a reader of DNA methylation changes, MeCP2 may also alter its binding in response to DNA methylation changes following hypoxia. Interestingly, the HIF-1α binding site sequence '5-RCGTG-3' contains a CpG dinucleotide [50]. Multiple studies have identified both DNA methylation and chromatin changes in response to acute or intermittent hypoxia, but the changes are context and tissue-specific (reviewed in Naduri et al. [51]). The DNA methylation changes following hypoxia are likely to be mediated by the demethylation enzymes TET (Ten-Eleven-Translocation) that catalyze the conversion of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), which then get repaired to unmethylated cytosines [52]. Treatment of a variety of neuroblastoma cells with 1% oxygen increased global levels of 5hmC and TET1 activity was necessary for activation of some genes induced by HIF-1 [53]. Together, these studies suggest that MeCP2 binding may be sensitive to the DNA methylation changes in response to hypoxia, but these specific experiments have not been previously performed.

2.2. MeCP2 and oxidative stress

Dysfunction of MeCP2 is associated with oxidative stress, which is an underlying contributor to RTT and many other neurological diseases [54]. Oxidative stress is defined as the imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract ROS with antioxidants. Rodent studies have established that intermittent hypoxia leads to increased oxidative stress [55,56]. The increase in ROS and subsequent oxidative stress is generally attributed to the reoxygenation phase of intermittent hypoxia [55]. However, hypoxia alone has also been shown to induce higher ROS and oxidative stress [57]. In RTT patients, lower blood oxygen levels and lower oxygen saturation were significantly correlated with higher oxidative stress, as well as a higher degree of phenotype severity [58]. Elevated oxidative stress has also been observed in patients with *MECP2* Duplication Syndrome [59]. Whether the increase in oxidative stress markers is a direct consequence of the hypoxic state of the RTT patients, or a consequence of intermittent hypoxia or other abnormalities such as mitochondrial dysfunction (discussed in the next section), remains an unanswered question.

Generally, ROS are produced by mitochondria during the process of oxidative phosphorylation and include hydrogen peroxide, superoxide anion radicals, and hydroxyl radicals; although they are important signaling molecules and play important roles in cellular processes such as differentiation, their highly reactive nature makes them dangerous as they can oxidize lipids, proteins, and nucleic acids, leading to damage and cellular injury as well as genetic mutation [60]. Oxidative damage also affects MeCP2 binding, as both oxidation of the methyl group on cytosine and the presence of oxidized guanine (8-OHdG) impede the binding of MeCP2 to DNA [61]. In typical brain function, ROS serve as signaling messengers, and antioxidant enzymes help reduce ROS levels to avoid oxidative damage. Many of these enzymes and other anti-ROS mechanisms are triggered by the activity of the transcriptional regulator, nuclear factor erythroid 2-related factor 2 (Nrf2) [62]. This includes superoxide dismutase, which breaks superoxide radicals down into water and

hydrogen peroxide, and catalase and glutathione peroxidase, which break hydrogen peroxide down into water. Glutathione is one of the primary antioxidant molecules that sequester ROS, which converts it from its reduced form (GSH) to its oxidized form (GSSG) [63]. Glutathione reductase converts GSSG back to GSH. The ratio of GSH to GSSG is one of the main indicators of redox state; a decreased GSH:GSSG ratio reflects a shift toward a more oxidized state that is widely used as a marker of increased oxidative stress [64]. A summary of the various antioxidant molecules and oxidative stress markers measured in RTT patients from different studies is reported in Table 1 [58,65–77].

One of the initial reports of oxidative stress in RTT syndrome reported decreased levels of the antioxidants ascorbic acid and GSH from a single postmortem brain [65]. A subset of RTT patients have also been found to have lower levels of the antioxidant vitamin E in their serum [66]. Other researchers found decreased levels of superoxide dismutase activity in erythrocytes, suggesting lower antioxidant activity, although they did not observe any significant differences in glutathione peroxidase, glutathione reductase, or catalase activities [67]. They also found increased plasma levels of malondialdehyde, a marker of lipid peroxidation that is commonly used as a marker for oxidative stress [78].

Researchers at the University of Siena have extensively studied oxidative stress markers in RTT patients, and consistently found increases in markers such as non-protein-bound iron (NPBI), free and esterified F_2-isoprostanes (F_2-IsoPs), F_4-neuroprostanes (F_4-NeuroPs), and 4-hydroxynonenal (4-HNE) protein adducts in plasma, erythrocytes, and skin fibroblasts obtained from RTT patients [58,69–71,73,74,79,80]. NPBI, or free iron, is capable of generating oxidative stress by reacting with hydrogen peroxide through the Fenton reaction to form hydroxyl radicals [81]. F_2-IsoPs and F_4-NeuroPs are two markers of lipid peroxidation formed by peroxidation of the polyunsaturated fatty acids arachidonic acid and docosahexaenoic acid, respectively [82]. 4-HNE protein adducts, as well as malondialdehyde, are aldehydes also formed by peroxidation of polyunsaturated fatty acids [78]. The same group of scientists have also shown that treatment with antioxidants such as omega-3 polyunsaturated fatty acids decreased the levels of most of these oxidative stress markers in RTT patients and improved some symptoms [70]. These results suggested that oxidative stress may contribute to the pathology of RTT. They have also reported increased levels of GSH in erythrocytes and plasma, although the overall ratio of reduced and oxidized glutathione appears to be decreased [79]. However, GSH levels were decreased in skin fibroblasts [74], so it is possible that changes in GSH levels differ between tissue types. Another research group has demonstrated an increase in oxidative damage of DNA in RTT samples, marked by increased levels of 8-OHdG, an oxidized form of guanosine [77]. Overall, markers of oxidative stress such as malondialdehyde and a decreased GSH:GSSG ratio appear to be consistently associated with MeCP2 deficiency, but activity of antioxidant enzymes varies across different samples.

2.3. MeCP2 and mitochondria

Mitochondria are responsible for supplying energy for the cell, largely through oxidative phosphorylation. The byproducts of this process include ROS such as the superoxide anion radical and hydrogen peroxide. These ROS molecules can play important roles in signaling and cellular differentiation, but excess amounts are damaging to the cell. Mitochondrial abnormalities in the brain and samples from RTT patients have been reported as far back as 1986 [83].

Many studies have reported that dysfunctions in MeCP2 lead to aberrant mitochondrial electron transport chain activity. For example, *MeCP2*$^{-/y}$ mice have been reported to have increased transcript levels of *Uqcrc1*, which encodes a core subunit of ubiquinol cytochrome c reductase (UQCR), also known as complex III [84]. Increased activity of complex III would contribute to increased ROS and oxidative stress. It is thought that complex III

Table 1. Antioxidant molecules and oxidative stress markers in human RTT patients.

Publication	Reference	Sample type	Markers
Sofić et al.	[65]	Postmortem brain	Ascorbic acid ↓, GSH ↓
Formichi et al.	[66]	Serum	Vitamin E ↓
Sierra et al	[67]	Erythrocytes	SOD ↓, GPx —, GR —, catalase —
		Plasma	Malondialdehyde ↑
De Felice et al.	[58]	Erythrocytes	NPBI ↑
		Plasma	NPBI ↑, free F_2-IsoPs ↑, esterified F_2-IsoPs ↑, total F_2-IsoPs ↑, protein carbonyls ↑
Carmeli et al.	[68]	Serum	H_2O_2 ↑
Signorini et al.	[69]	Plasma	F_4-NeuroPs ↑
De Felice et al.	[70]	Erythrocytes	NPBI ↑
		Plasma	NPBI ↑, F_2-IsoPs ↑, F_3-IsoPs ↑, F_4-NeuroPs ↑, F_2-dihomo-IsoPs ↑
Ciccoli et al.	[71]	Erythrocytes	NPBI ↑, membrane esterified F_2-IsoPs ↑, membrane 4-HNE protein adducts ↑, GSH ↑
		Plasma	NPBI ↑
De Felice et al.	[72]	Erythrocytes	NPBI ↑
		Plasma	NPBI ↑, F_2-IsoPs ↑, GSH ↑, GSSG ↑, GSH:GSSG ratio ↓
Signorini et al.	[73]	Skin fibroblasts	Total F_2-IsoPs ↑, total F_4-NeuroPs ↑, 4-HNE protein adducts ↑, NPBI ↑, GSH ↓, GSSG ↑, GSH:GSSG ratio ↓
Cervellati et al.	[74]	Skin fibroblasts	H_2O_2 ↑, 4-HNE protein adducts ↑, NOX2 activity ↑, GPx ↓, GR ↓, SOD ↓, TrxR ↓
Pintaudi et al.	[75]	Erythrocytes	Malondialdehyde ↑, SOD —, catalase —
Ciaccio et al.	[76]	Erythrocytes	Malondialdehyde ↑
Varone et al.	[77]	Skin fibroblasts	8-OHdG ↑, 4-HNE protein adducts ↑, SOD1 —, SOD2 ↓, catalase ↓, TrxR1 ↓, Gpx1 ↓, GSH ↓, NOX4 ↑, NRF2 ↑

Abbreviations: 4-HNE protein adducts: 4-hydroxynonenal protein adducts; 8-OHdG: oxidized guanine; F2-IsoPs: F2-isoprostanes; F2-dihomo-IsoPs: F2-dihomo-isoprostanes; F3-IsoPs: F3-isoprostanes; F4-NeuroPs: F4-neuroprostanes; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: reduced glutathione; GSSG: oxidized glutathione; H2O 2: hydrogen peroxide; NOX: NADPH oxidase; NPBI: non-protein bound iron; NRF2: nuclear factor erythroid 2-related factor 2; SOD: superoxide dismutase; TrxR: thioredoxin reductase

in the mitochondria is primarily responsible for hypoxia-induced ROS generation [85], so there is also a possibility that elevated *Uqcrc1* levels may contribute to the increased production of ROS in brain in the context of hypoxia. Reduced expression of the mitochondrial COX1 gene, which encodes a subunit of Complex IV, was found in a microarray study using frontal cortex brain samples from RTT patients, and decreased Complex IV activity was confirmed by MeCP2 knockdown in the SH-SY5Y neuroblastoma cell line [86]. Changes in genes related to mitochondrial function and oxidative stress have also been identified in peripheral blood lymphomonocytes isolated from RTT patients [87],

Mitochondria from astrocytes also appear to play an important role. In a recent study, embryonic stem cells engineered to have MeCP2 deficiency were differentiated into organoids containing both neurons and astrocytes. The MeCP2-deficient cells had smaller mitochondria [88]. When wild-type neurons were cultured with mitochondria from MeCP2-deficient astrocytes, they began to show the same deficiencies as the MeCP2-deficient neurons [88,89]. When *Mecp2*-deficient neurons were cultured with mitochondria from *Mecp2* WT astrocytes, their phenotypes were rescued [88]. Mitochondria have been documented to move from neurons to glial cells [90], and vice versa [91]. This may account for the observed non-cell autonomous effect, where mitochondria from MeCP2-mutant cells affect neighboring neurons that have wild-type MeCP2 [88]. This suggests that wild-type neurons may be taking up the dysfunctional mitochondria from neighboring astrocytes, demonstrating the importance of neighboring cells and mitochondria to the progression of RTT. These mechanisms have been more recently explored at the single cell level for the impact of cellular mosaicism in RTT, discussed in the next section.

3. Transcriptomic studies in Rett syndrome and oxidative stress

As a global transcriptional regulator and a recruiter of chromatin remodeling complexes such as cAMP responsive element binding protein 1 (CREB1), MeCP2 is essential for modulating gene expression networks through both direct and indirect mechanisms [92]. Recent advances in RNA sequencing and transcriptomic technologies have enhanced our understanding of MeCP2-mediated gene dysregulation in RTT, particularly revealing effects of MeCP2 loss on transcriptional networks governing oxidative stress response, mitochondrial function, and cellular adaptation to hypoxia. An integrative analysis of 115 transcriptomic studies across neurodevelopmental disorders has provided insights into the molecular landscape of MeCP2-regulated pathways, highlighting the central role of these three biological processes in RTT pathogenesis [93]. One of the interesting functions of MeCP2 include modulating gene expression through RNA splicing through recruiting splicing factors such as Y box protein 1 (YB-1) [94]. Recent reviews have highlighted that while MeCP2 protein binds to DNA and affects transcription, the true range of MeCP2 function extends beyond traditional transcriptional regulation, encompassing complex molecular interactions that are still being elucidated in the context of RTT pathology [4,5].

Integrated gene expression and alternative splicing analysis in human and mouse models of RTT has provided insights into downstream effects of the loss or defective function of MeCP2. A bulk RNA sequencing dataset of postmortem brain tissue from RTT females and age-matched controls examined transcriptomes across frontal and temporal cortex regions and identified changes in the complement complex genes [95]. A Cre-inducible MeCP2 approach in *Mecp2*-deficient cortical excitatory and inhibitory neurons have revealed that transcriptomic changes are cell type and mutation specific [96]. RNA sequencing and proteomics approaches have revealed novel deficits in the cortex of Mecp2-deficient mice, identifying 391 significant, differentially expressed genes with 132 genes showing increased expression and 259 showing decreased expression [97]. The most consistently disrupted pathways across both data sets involved cellular metabolism and calcium signaling. In contrast, expression profiling studies using microarrays on clonal lymphoblastoid cell cultures from RTT patients only identified 49 upregulated and 21 downregulated genes, with comparative analyses across independent microarray experiments helping to establish candidate MeCP2 target gene networks [87].

The field has increasingly adopted integrated multi-omics approaches to uncover the complex molecular signatures underlying RTT pathology. Integration of transcriptomics and proteomics data represents a promising approach for identifying new potential therapeutic targets and biomarkers in RTT research [97]. Multi-omics studies demonstrate that cross-layer integration of modalities improves prioritization of therapeutic targets and biomarkers by converging on recurrently perturbed networks across cohorts, species and modalities [98]. Multiple lines of evidence also revealed significant dysregulation of long non-coding RNA transcriptomes in *Mecp2*-deficient models, indicating that transcriptional dysregulation of long non-coding RNAs (lncRNAs) contributes to RTT neurological phenotypes and highlighting complex interactions between non-coding and coding RNAs [99]. Broad dysregulation of lncRNAs includes functional links to neuronal gene expression, while newer studies implicate specific lncRNAs such as NEAT1 in proteostasis and RNA-processing defects under MeCP2 deficiency [100]. In parallel, cell cloning-based transcriptome analyses in RTT patients have been particularly valuable for identifying new human MeCP2 target genes relevant to disease pathogenesis, accounting for the complexities of X-chromosome inactivation patterns in affected females [101]. Recent advances in single-cell transcriptomics have provided unprecedented insights into sex-specific transcriptomic signatures during RTT disease progression, revealing cell type-specific alterations that were previously masked in bulk tissue analyses [6]. Among the insights gained from single cell transcriptomes include the discovery of dynamic changes to homeostatic gene networks during the progression of RTT symptoms that is largely due to non-cell autonomous effects of the wild-type expressing neurons and astrocytes within the mosaic female RTT brain [6]. Complementing these findings, classic non-cell-autonomous mechanisms where MeCP2-deficient astrocytes perturb wild-type neurons have demonstrated restoration of MeCP2 activity in astrocytes partially

rescues neuronal morphology, breathing abnormalities, and lifespan in mice [102].

A critical aspect of RTT pathophysiology involves respiratory irregularities and hypoxia susceptibility, which significantly impact patient quality of life and may influence gene expression patterns [103]. RTT patients characteristically suffer from episodic respiratory irregularities and reduced arterial oxygen levels, with irregular breathing patterns representing a consequence of brainstem functional immaturity [14]. Studies using mouse models of RTT have demonstrated enhanced hypoxia susceptibility in hippocampal brain slices, suggesting that MeCP2 deficiency increases neuronal vulnerability to oxygen deprivation and implicating ionic homeostasis such as potassium channel dysfunction [104,105]. Furthermore, cerebellar granule neurons from MeCP2-null mice show enhanced cell death when exposed to hypoxic conditions and exhibit enhanced, caspase- and AIF-dependent apoptosis, indicating that loss of MeCP2 function compromises cellular responses to hypoxic stress and may contribute to the neurodegeneration observed in RTT patients [45]. These findings highlight the importance of considering hypoxia-related mechanisms when studying gene expression alterations in RTT, as hypoxia may create a secondary layer of transcriptional dysregulation beyond the direct effects of MeCP2 loss.

4. Conclusion and clinical relevance

A major clinical feature of RTT is the distinct stages of disease progression that suggest the pathogenesis of mosaic *MECP2* mutation results in a series of steps of dysregulation of brain homeostasis. RTT girls are born asymptomatic and are not typically diagnosed until 6–18 months of age, when they begin to show signs of regression in developmental milestones. RTT symptoms then progress through a series of plateaus followed by regressions. Since MeCP2 expression increases with brain maturation, it is likely that MeCP2 dysfunction causes epigenetic changes long before symptoms manifest, and the increase in adverse epigenetic and transcriptional events over time likely contribute to the neurological regression displayed by RTT patients [106]. Defects in signaling pathways and single cell transcriptomics suggest that RTT disease progression is not caused exclusively by autonomous transcriptional changes in individual cells, but rather due to a failure of wild-type *MECP2* expressing cells to compensate for mutant *MECP2* expressing cells [6]. In this context, it is important to reconsider the role that hypoxia and oxidative stress reactions may play in the complex progression of disease symptoms in RTT.

Breathing abnormalities in RTT are intrinsic to MeCP2 deficiency, as have been shown by multiple neuron-specific *Mecp2* deletion models. However, the brain-body axis and homeostatic cardiorespiratory mechanisms are also critical to the response of breathing to hypoxic challenges. Specifically, the central autonomic network (CAN), which comprises homeostatic networks of multiple brain regions including the hypothalamus, nucleus tractus solitarius, parabrachial complex, amygdala, and insular cortex, promotes long-term adaptations to hypoxia in neurons. In RTT, heterozygous mosaic mutations in *MECP2* in half of the neurons appear to impair the adaptability of the CAN, resulting in irregular breathing, autonomic instability and diminished heart rate variability, in addition to the excitatory/inhibitory imbalance resulting in impaired plasticity [107]. Furthermore, MeCP2 is required for modulating BDNF responses to hypoxia, and oxidative stress can result in impaired binding of MeCP2 to its target genes. Together, these findings suggest circular feedback loops within the CAN in which MeCP2 is both required for responding to oxygen and ROS levels as well as regulated by these responses. Thinking about MeCP2 deficiency in RTT as a network problem rather than a single functional molecular change may be important in the future for the design of more effective therapies.

5. Future perspective on therapeutic implications

RTT has attracted attention of pharmaceutical companies because the rapid regression of motor and language skills in late infancy allows a window for early intervention after the initial genetic diagnosis. However, the complexities of X-linked cellular mosaicism in RTT presents both challenges and opportunities and for drug design. Current gene therapy trials get around the inherent problem of potentially toxic over-expression of *MECP2* in wild-type -expressing neurons by engineering self-correcting microRNA feedback loops in the construct designs, but getting the dosage and delivery to be nontoxic is still a major challenge.

As a major opportunity, *MECP2* mutation results in both cell-autonomous and non-cell-autonomous "bad neighborhood" effects affecting neuronal health and maturation even in wild-type expressing neurons [6,89,108]. Improving the cellular neighborhood is the likely mechanism behind the only existing FDA-approved therapy for RTT, called Trofinetide (NNZ-2566, Daybue). Trofinetide is a synthetic glycine-proline-glutamate analog, derived from IGF-1 (Insulin-like Growth Factor-1) [109]. While full length IGF-1 is a known growth factor, the mechanism of action for Trofinetide is currently unknown. Trofinetide likely acts by upregulating BDNF signaling and activating the BDNF receptor tropomyosin receptor kinase B (TrkB) and its downstream pathways [110]. A Phase 3 clinical trial showed significant changes from baseline to week 12 in the Rett Syndrome Behavior Questionnaire and Clinical Global Impression for Trofinetide versus placebo [111]. However, a major side effect of Trofinetide was that >80% of patients had diarrhea, compared to <20% for placebo [111]. Some recommendations for reducing diarrhea on Trofinetide have since been published [112]. A second challenge is getting patients to take the very large volume oral dose twice daily (60 mL per dose, 12,000 mg/day for ≥50 kg patients).

Future therapies for RTT that could be used in combination with either gene therapy or Trofinetide could potentially involve repurposing antioxidants or small molecules regulating BDNF responses [113]. BDNF and BDNF mimetics have been considered for RTT, but they do not cross the blood-brain barrier, and it is difficult to control the timing [114]. In addition, several existing drugs, including serotonergic and norepinephine modulators, as well as ketamine have improve breathing regularity likely by countering CAN dysregulation in mouse models of RTT [115,116].

There are still several critical gaps in understanding the molecular pathogenesis of RTT that are important for the design of better therapeutics. First, it is important to use female construct-relevant models of *Mecp2* mutations in mouse models, since disease progression is inherently quite different than in male *Mecp2* null mice. Second, it is currently unclear whether recurrent hypoxia due to irregular breathing in RTT is a cause or consequence of CAN dysregulation, so studies examining RTT neurons long-term adaptation in response to chronic hypoxia are warranted. Third, of current therapies that improve breathing regularity, the mechanistic understanding of BDNF regulation by MeCP2 is speculative, and could be improved. Fourth, more attention to testing repurposed therapeutics that may counteract problems with mitochondrial, energy balance, and oxidative stress in RTT is needed [117,118]. A recent meta-analysis of 151 RNA transcriptomic data sets revealed that inflammation, RNA translation, ATP synthesis and immune pathways are common to RTT, Fragile X syndrome, Down syndrome and Duchenne muscular dystrophy suggesting potential therapeutic strategies [93]. In the future, an improved understanding of natural modulators of the MeCP2-BDNF-PARP1 interaction in regulation of CAN may open up new therapeutics for RTT that consider the dysregulated network problem.

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