Transcriptional Regulation by MECP2

Christodoulou, J., Krishnaraj, R., Orlic-Milacic, M.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

18/11/2022

https://reactome.org
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 82

This document contains 6 pathways and 17 reactions (see Table of Contents)

https://reactome.org
MECP2 is an X chromosome gene whose loss-of-function mutations are an underlying cause of the majority of Rett syndrome cases. The MECP2 gene locus consists of four exons. Both exon 1 and exon 2 contain translation start sites. Alternative splicing of the second exon results in expression of two MECP2 transcript isoforms, MECP2_e1 (MECP2B or MECP2alpha) and MECP2_e2 (MECP2A or MECP2beta). The N-terminus of the MECP2_e1 isoform, in which exon 2 is spliced out, is encoded by exon 1. The N-terminus of the MECP2_e2 isoforms, which includes both exon 1 and exon 2, is encoded by exon 2, as the exon 2 translation start site is used. Exons 3 and 4 are present in both isoforms. The MECP2_e2 isoform was cloned first and is therefore more extensively studied. The MECP2_e1 isoform is more abundant in the brain (Mnatzakanian et al. 2004, Kriaucionis and Bird 2004, Kaddoum et al. 2013). Mecp2 isoforms show different expression patterns during mouse brain development and in adult brain regions (Dragich et al. 2007, Olson et al. 2014). While Rett syndrome mutations mainly occur in exons 3 and 4 of MECP2, thereby affecting both MECP2 isoforms (Mnatzakanian et al. 2004), some mutations occur in exon 1, affecting MECP2_e1 only. No mutations have been described in exon 2 (Gianakopoulos et al. 2012). Knockout of Mecp2_e1 isoform in mice, through a naturally occurring Rett syndrome point mutation which affects the first translation codon of MECP2_e1, recapitulates Rett-like phenotype. Knockout of Mecp2_e2 isoform in mice does not result in impairment of neurologic functions (Yasui et al. 2014). In Mecp2 null mice, transgenic expression of either Mecp2_e1 or Mecp2_e2 prevents development of Rett-like phenotype, with Mecp2_e1 rescuing more Rett-like symptoms than Mecp2_e2. This indicates that both splice variants can fulfill basic Mecp2 functions in the mouse brain (Kerr et al. 2012). Changes in gene expression upon over-expression of either MECP2_e1 or MECP2_e2 imply overlapping as well as distinct target genes (Orlic-Milacic et al. 2014).

Methyl-CpG-binding protein 2 encoded by the MECP2 gene binds to methylated CpG sequences in the DNA. The binding is not generic, however, but is affected by the underlying DNA sequence (Yoon et al. 2014).
MECP2 binds to DNA containing 5 methylcytosine (5mC DNA), a DNA modification associated with transcriptional repression (Mellen et al. 2012), both in the context of CpG islands and outside of CpG islands (Chen et al. 2015). In addition, MECP2 binds to DNA containing 5 hydroxymethylcytosine (5hmC DNA), a DNA modification associated with transcriptional activation (Mellen et al. 2012). MECP2 binds to DNA as a monomer, occupying about 11 bp of the DNA. Binding of one MECP2 molecule facilitates binding of the second MECP2 molecule, and therefore clustering can occur at target sites. MECP2 binding to chromatin may be facilitated by nucleosome methylation (Ghosh et al. 2010).

MECP2 was initially proposed to act as a generic repressor of gene transcription. However, high throughput studies of MECP2-induced changes in gene expression in mouse hippocampus (Chahrour et al. 2008), and mouse and human cell lines (Orlic-Milacic et al. 2014) indicate that more genes are up-regulated than down-regulated when MECP2 is overexpressed. At least for some genes directly upregulated by MECP2, it was shown that a complex of MECP2 and CREB1 was involved in transcriptional stimulation (Chahrour et al. 2008, Chen et al. 2013).

MECP2 expression is the highest in postmitotic neurons compared to other cell types, with MECP2 being almost as abundant as core histones. Phosphorylation of MECP2 in response to neuronal activity regulates binding of MECP2 to DNA, suggesting that MECP2 may remodel chromatin in a neuronal activity-dependent manner. The resulting changes in gene expression would then modulate synaptic plasticity and behavior (reviewed by Ebert and Greenberg 2013). In human embryonic stem cell derived Rett syndrome neurons, loss of MECP2 is associated with a significant reduction in transcription of neuronally active genes, as well as the reduction in nascent protein synthesis. The reduction in nascent protein synthesis can at least in part be attributed to the decreased activity of the PI3K/AKT/mTOR signaling pathway. Neuronal morphology (reduced soma size) and the level of protein synthesis in Rett neurons can be ameliorated by treating the cells with growth factors which activate the PI3K/AKT/mTOR cascade or by inhibition of PTEN, the negative regulator of AKT activation. Mitochondrial gene expression is also downregulated in Rett neurons, which is associated with a reduced capacity of the mitochondrial electron transport chain (Ricciardi et al. 2011, Li et al. 2013). Treatment of Mecp2 null mice with IGF1 (insulin-like growth factor 1) reverses or ameliorates some Rett-like features such as locomotion, respiratory difficulties and irregular heart rate (Tropea et al. 2009).

MECP2 regulates expression of a number of ligands and receptors involved in neuronal development and function. Ligands regulated by MECP2 include BDNF (reviewed by Li and Pozzo-Miller 2014, and KhorshidAhmad et al. 2016), CRH (McGill et al. 2006, Samaco et al. 2012), SST (Somatostatin) (Chahrour et al. 2008), and DLL1 (Li et al. 2014). MECP2 also regulates transcription of genes involved in the synthesis of the neurotransmitter GABA – GAD1 (Chao et al. 2010) and GAD2 (Chao et al. 2010, He et al. 2014). MECP2 may be involved in direct stimulation of transcription from the GLUD1 gene promoter, encoding mitochondrial glutamate dehydrogenase 1, which may be involved in the turnover of the neurotransmitter glutamate (Livide et al. 2015). Receptors regulated by MECP2 include glutamate receptor GRIA2 (Qiu et al. 2012), NMDA receptor subunits GRIN2A (Durand et al. 2012) and GRIN2B (Lee et al. 2008), opioid receptors OPRK1 (Chahrour et al. 2008) and OPRM1 (Hwang et al. 2009, Hwang et al. 2010, Samaco et al. 2012), GPRIN1 (Chahrour et al. 2008), MET (Plummer et al. 2013), NOTCH1 (Li et al. 2014). Channels/transporters regulated by MECP2 include TRPC3 (Li et al. 2012) and SLC2A3 (Chen et al. 2013). MECP2 regulates transcription of FKBP5, involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urdinguio et al. 2008). MECP2 is implicated in regulation of expression of SEMA3F (semaphorin 3F) in mouse olfactory neurons (Degano et al. 2009). In zebrafish, Mecp2 is implicated in sensory axon guidance by direct stimulation of transcription of Sema5b and Robo2 (Leong et al. 2015). MECP2 may indirectly regulate signaling by neuronal receptor tyrosine kinases by regulating transcription of protein tyrosine phosphatases, PTPN1 (Krishnan et al. 2015) and PTPN4 (Williamson et al. 2015).
MECP2 regulates transcription of several transcription factors involved in functioning of the nervous system, such as CREB1, MEF2C, RBFOX1 (Chahrour et al. 2008) and PPARG (Mann et al. 2010, Joss-Moore et al. 2011).

MECP2 associates with transcription and chromatin remodeling factors, such as CREB1 (Chahrour et al. 2008, Chen et al. 2013), the HDAC1/2-containing SIN3A co-repressor complex (Nan et al. 1998), and the NCoR/SMRT complex (Lyst et al. 2013, Ebert et al. 2013). There are contradictory reports on the interaction of MECP2 with the SWI/SNF chromatin-remodeling complex (Harikrishnan et al. 2005, Hu et al. 2006). Interaction of MECP2 with the DNA methyltransferase DNMT1 has been reported, with a concomitant increase in enzymatic activity of DNMT1 (Kimura and Shiota 2003).

In addition to DNA binding-dependent regulation of gene expression by MECP2, MECP2 may influence gene expression by interaction with components of the DROSHA microprocessor complex and the consequent change in the levels of mature microRNAs (Cheng et al. 2014, Tsujimura et al. 2015).

Increased MECP2 promoter methylation is observed in both male and female autism patients (Nagarajan et al. 2008). Regulatory elements that undergo methylation are found in the promoter and the first intron of MECP2 and their methylation was shown to regulate Mecp2 expression in mice (Liyanage et al. 2013). Mouse Mecp2 promoter methylation was shown to be affected by stress (Franklin et al. 2010).

The Rett-like phenotype of Mecp2 null mice is reversible (Guy et al. 2007), but appropriate levels of Mecp2 expression need to be achieved (Alvarez-Saavedra et al. 2007). When Mecp2 expression is restored in astrocytes of Mecp2 null mice, amelioration of Rett symptoms occurs, involving non-cell-autonomous positive effect on mutant neurons and increasing level of the excitatory glutamate transporter VGLUT1 (Lioy et al. 2011). Microglia derived from Mecp2 null mice releases higher than normal levels of glutamate, which has toxic effect on neurons. Increased glutamate secretion may be due to increased levels of glutaminase (Gls), involved in glutamate synthesis, and increased levels of connexin-32 (Gjb1), involved in glutamate release, in Mecp2 null microglia (Maezawa and Jin 2010). Targeted deletion of Mecp2 from Sim1-expressing neurons of the mouse hypothalamus recapitulates some Rett syndrome-like features and highlights the role of Mecp2 in feeding behavior and response to stress (Fyffe et al. 2008).


**Literature references**


https://reactome.org
## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Regulation of MECP2 expression and activity

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9022692

Transcription of the MECP2 gene is known to be regulated by methylation of the promoter and the first intron, but the responsible methyltransferases are not known (Nagarajan et al. 2008, Franklin et al. 2010, Liyanage et al. 2013).

Translation of MECP2 mRNA is negatively regulated by the microRNA miR-132. Transcription of miR-132 is regulated by BDNF signaling, through an unknown mechanism (Klein et al. 2007, Su et al. 2015).

Binding of MECP2 to other proteins and to DNA is regulated by posttranslational modifications, of which phosphorylation has been best studied. Calcium dependent protein kinases, PKA and CaMK IV, activated by neuronal membrane depolarization, phosphorylate MECP2 at threonine residue T308 (corresponding to T320 in the longer MECP2 splicing isoform, MECP2_e1). Phosphorylation at T308 correlates with neuronal activity and inhibits binding of MECP2 to the nuclear receptor co-repressor complex (NCoR/SMRT) (Ebert et al. 2013). In resting neurons, MECP2 is phosphorylated at serine residue S80, which results in a decreased association of MECP2 with chromatin. Nuclear serine/threonine protein kinase HIPK2 phosphorylates MECP2 on serine residue S80 (Bracaglia et al. 2009). In activity-induced neurons, upon neuronal membrane depolarization, MECP2 S80 becomes dephosphorylated, and MECP2 acquires phosphorylation on serine S423 (corresponding to mouse Mecp2 serine S421). CaMK IV is one of the kinases that can phosphorylate MECP2 on S423. Phosphorylation of MECP2 at S423 increases MECP2 binding to chromatin (Zhou et al. 2006, Tao et al. 2009, Qiu et al. 2012). AURKB phosphorylates MECP2 at serine residue S423 in dividing adult neuronal progenitor cells (Li et al. 2014).

Besides binding to the NCoR/SMRT co-repressor complex (Lyst et al. 2013, Ebert et al. 2013), MECP2 binds the SIN3A co-repressor complex. This interaction involves the transcriptional repressor domain of MECP2 and the amino terminal part of the HDAC interaction domain (HID) of SIN3A. HDAC1 and HDAC2
are part of the SIN3A co-repressor complex that co-immunoprecipitates with MECP2 (Nan et al. 1998). While binding of MECP2 to SIN3A at target genes is associated with transcriptional repression, binding to CREB1 at target genes is associated with transcriptional activation (Chahrour et al. 2008, Chen et al. 2013). Function of MECP2 can be affected by binding to FOXP1, another gene mutated in Rett syndrome besides MECP2 and CDKL5 (Dastidar et al. 2012), and HTT (Huntingtin) (McFarland et al. 2013). The sub-nuclear localization of MECP2 may be affected by binding to the Lamin B receptor (LBR) (Guarda et al. 2009).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds 5mC-DNA

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9022456

Type: binding

Compartments: nucleoplasm

MECP2 binds to DNA containing 5-methylcytosine (5mC-DNA), a DNA modification associated with transcriptional repression (Mellen et al. 2012). MECP2 binds to 5-methyl cytosine both in the context of CpG islands and outside of CpG islands (Chen et al. 2015).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds 5hmC-DNA

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9022453

Type: binding

Compartments: nucleoplasm

MECP2 binds to DNA containing 5-hydroxymethylcytosine (5hmC-DNA), a DNA modification associated with transcriptional activation (Mellen et al. 2012).

Literature references

MECP2 binds DGCR8

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022315

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** MeCP2 binds Dgcr8 (Mus musculus)

![Diagram showing MECP2 and DGCR8 interaction](https://reactome.org)

Based on studies in mice, MECP2, phosphorylated at serine residue S80, binds to DGCR8. The interaction involves the C-terminus of MECP2 and the RNA binding domain-containing C-terminus of DGCR8. Binding to MECP2 may interfere with the interaction between DGCR8 and DROSHA, as well as DGCR8 and primary microRNAs. As DGCR8 and DROSHA form the microprocessor complex which cleaves primary microRNAs (pri-miRNAs) into pre-miRNAs, binding of MECP2 to DGCR8 results in decreased pri-miRNA processing. One of the miRNAs affected by the interaction between MECP2 and DGCR8 is miR-134. miR-134 is highly expressed in brain where it inhibits translation of CREB1, LIMK1 and Pumilio2 mRNAs (Cheng et al. 2014). In addition to DGCR8, MECP2 was reported to bind to other components of the DROSHA microprocessor complex, including DROSHA. Instead of preventing formation of the microprocessor complex, MECP2 was reported to modulate its activity, targeting the complex to specific microRNAs. One of the microRNAs whose processing into a mature product is enhanced in the presence of MECP2 is miR-199a. Expression of several proteins that inhibit mTOR signaling is negatively regulated by miR-199a, creating a mechanistic link between MECP2 loss-of-function and decreased mTOR signaling in Rett syndrome (Tsujimura et al. 2015).

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 regulates neuronal receptors and channels

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9022699

Receptors directly transcriptionally regulated by MECP2 include glutamate receptor GRIA2 (Qiu et al. 2012), NMDA receptor subunits GRIN2A (Durand et al. 2012) and GRIN2B (Lee et al. 2008), opioid receptors OPRK1 (Chahrour et al. 2008) and OPRM1 (Hwang et al. 2009, Hwang et al. 2010, Samaco et al. 2012), GPRIN1 (Chahrour et al. 2008), MET (Plummer et al. 2013), and NOTCH1 (Li et al. 2014). Channels/transporters regulated by MECP2 include TRPC3 (Li et al. 2012) and SLC2A3 (Chen et al. 2013). MECP2 also regulates transcription of FKBP5, involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urdinguio et al. 2008) and is implicated in regulation of expression of SEMA3F (semaphorin 3F) in mouse olfactory neurons (Degano et al. 2009). In zebrafish, Mecp2 is implicated in sensory axon guidance by direct stimulation of transcription of Sema5b and Robo2 (Leong et al. 2015). MECP2 may indirectly regulate signaling by neuronal receptor tyrosine kinases by regulating transcription of protein tyrosine phosphatases, PTPN1 (Krishnan et al. 2015) and PTPN4 (Williamson et al. 2015).

Literature references


https://reactome.org
MECP2 regulates transcription of neuronal ligands

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022702

Ligands regulated by MECP2 include BDNF (reviewed by Li and Pozzo Miller 2014, and KhorshidAhmad et al. 2016), CRH (McGill et al. 2006, Samaco et al. 2012), SST (Somatostatin) (Chahrour et al. 2008), and DLL1 (Li et al. 2014).

**Literature references**


<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 regulates transcription factors

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9022707

MECP2 regulates transcription of several transcription factors involved in functioning of the nervous system, such as CREB1, MEF2C, RBFOX1 (Chahrour et al. 2008) and PPARG (Mann et al. 2010, Joss Moore et al. 2011).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>

https://reactome.org
MECP2 regulates transcription of genes involved in GABA signaling

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022927

MECP2 regulates expression of several genes involved in GABA (gamma-aminobutyric acid) signaling. Transcription of GAD1 (GAD67) and GAD2 (GAD65) genes is directly positively regulated by MECP2. GAD1 and GAD2 are components of the glutamic acid decarboxylase complex involved in production of the neurotransmitter GABA. Mice lacking Mecp2 from GABA-releasing neurons have decreased GABA levels and exhibit multiple Rett syndrome features (Chao et al. 2010).

Mecp2 deletion in mouse GABAergic parvalbumin-expressing (PV) cells, cortical interneurons playing a key role in visual experience-induced ocular dominance plasticity, does not result in Rett-like phenotype, other than defects in motor coordination and motor learning. While functions of the visual cortex are preserved in mice lacking Mecp2 in GABAergic PV cells, the visual input-induced spiking responses are decreased. Mecp2 loss impairs maturation of membrane functions of cortical GABAergic PV cells. Mecp2 may be needed for PV cell-mediated cortical GABA inhibition. Mecp2-deficient cortical PV cells show reduced mRNA levels of several genes involved in GABA signaling, such as Parvalbumin, Gad2, Calretinin, Gabra1 and Gabra2, as well as reduced levels of Glu3, a glutamate receptor subunit, and Kv3.1, a potassium channel (He et al. 2014).

**Literature references**


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds the PVALB gene promoter

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9006503

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Mecp2 binds the Pvalb gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter of the PVALB gene, encoding parvalbumin alpha (Durand et al. 2012).

**Followed by:** PVALB gene expression is repressed by MECP2

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
PVALB gene expression is repressed by MECP2

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9006508

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Pvalb gene expression is repressed by Mecp2 (Mus musculus)

Based on studies in mice, binding of MECP2 to the promoter of the PVALB gene represses PVALB transcription. Pvalb levels are increased in visual cortical neurons of Mecp2 knockout mice, which is thought to contribute to visual regression (Durand et al. 2012).

Preceded by: MECP2 binds the PVALB gene promoter

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds GATM gene promoter

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9021945

Type: binding

Compartments: nucleoplasm

Inferred from: MeCP2 binds GATM gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter region of the GATM gene, encoding guanidinoacetate N-methyltransferase, which plays an important role during nervous system development (Chahrour et al. 2008).

Followed by: GATM gene expression is stimulated by MECP2

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
GAMT gene expression is stimulated by MECP2

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9021953

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Gamt gene expression is stimulated by Mecp2 (Mus musculus)

Based on studies in mice, transcription of the GAMT gene, encoding guanidinoacetate N-methyltransferase, is directly stimulated by MECP2 (Chahrour et al. 2008).

Preceded by: MECP2 binds GAMT gene promoter

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds SGK1 gene promoter

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022770

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** MeCP2 binds Sgk1 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter of the SGK1 gene, encoding serum/glucocorticoid-regulated kinase 1 (Nuber et al. 2005).

**Followed by:** SGK1 gene expression is inhibited by MECP2

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
SGK1 gene expression is inhibited by MECP2

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022764

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Sgk1 gene expression is inhibited by Mecp2 (Mus musculus)

Based on studies in mice, MECP2 directly inhibits transcription of the SGK1 gene encoding serum/glucocorticoid-regulated kinase 1. Sgk1 level is increased in Mecp2 null mice (Nuber et al. 2005).

**Preceded by:** MECP2 binds SGK1 gene promoter

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds MOBP gene promoter

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022872

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** MeCP2 binds Mobp gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds to the promoter of the MOBP gene, encoding myelin-associated oligodendrocyte basic protein (Urdinguio et al. 2008).

**Followed by:** MOBP gene expression is inhibited by MECP2

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MOBP gene expression is inhibited by MECP2

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9022870

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Mobp gene expression is inhibited by Mecp2 (Mus musculus)

Based on studies in mice, MECP2 directly inhibits transcription of the MOBP gene, encoding myelin-associated oligodendrocyte basic protein. Mopb levels are increased in Mecp2 null mice (Urdinguio et al. 2008). MECP2-mediated inhibition of MOBP transcription was also reported in rats (Sharma et al. 2015).

**Preceded by:** MECP2 binds MOBP gene promoter

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-10-02</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 and SOX2 bind MIR137 gene

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9615536

Type: binding

Compartments: nucleoplasm

Inferred from: MeCP2 and Sox2 bind Mir137 gene (Mus musculus)

Based on studies in mouse neurons, MECP2 and SOX2 simultaneously bind to the promoter region of the MIR137 gene, encoding microRNA miR-137 (Szulwach et al. 2010).

Followed by: MIR137 gene expression is inhibited by MECP2 and SOX2

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MIR137 gene expression is inhibited by MECP2 and SOX2

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9615554

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Mir137 gene expression is inhibited by Mecp2 and Sox2 (Mus musculus)

Based on studies in mouse neurons, MECP2 and SOX2 directly repress transcription from the MIR137 gene, encoding microRNA miR-137 (Szulwach et al. 2010, Lyu et al. 2016).

**Preceded by:** MECP2 and SOX2 bind MIR137 gene

**Followed by:** miR-137 binds PTEN mRNA

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
miR-137 binds PTEN mRNA

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9615570

Type: binding

Compartments: cytosol

Based on sequence complementarity and 3'UTR luciferase reporter assays in both human and mouse model systems, microRNA miR-137 binds the 3'UTR of PTEN mRNA (Lyu et al. 2016, Thomas et al. 2017). It is uncertain whether miR-137 functions within the nonendonucleolytic or the endonucleolytic RISC or both.

Preceded by: MIR137 gene expression is inhibited by MECP2 and SOX2

Followed by: PTEN mRNA translation is inhibited by miR-137

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
PTEN mRNA translation is inhibited by miR-137

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9615571

Type: omitted

Compartments: cytosol

Based on studies in both human and mouse model systems, translation of PTEN mRNA is inhibited by microRNA miR-137 (Lyu et al. 2016, Thomas et al. 2017).

Preceded by: miR-137 binds PTEN mRNA

Literature references


Editions

<table>
<thead>
<tr>
<th>Edition</th>
<th>Action</th>
<th>Reviewed/Edited By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MECP2 binds IRAK1 gene

Location: Transcriptional Regulation by MECP2

Stable identifier: R-HSA-9615801

Type: binding

Compartments: nucleoplasm

Inferred from: Mecp2 binds Irak1 gene (Mus musculus)

Based on studies in mice, MECP2 binds to the promoter region of IRAK1 gene, encoding a serine/threonine protein kinase involved in activation of NFKB-mediated transcription. MECP2-mediated regulation of IRAK1 transcription may be specific to cortical neurons (Kishi et al. 2016).

Followed by: IRAK1 gene expression is inhibited by MECP2

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
IRAK1 gene expression is inhibited by MECP2

**Location:** Transcriptional Regulation by MECP2

**Stable identifier:** R-HSA-9615829

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Irak1 gene expression is inhibited by Mecp2 (Mus musculus)

Based on studies in mice, MECP2 represses IRAK1 gene transcription. MECP2-mediated regulation of IRAK1 gene expression may be limited to cortical neurons. IRAK1 is a serine/threonine protein kinase that activates NFKB-mediated transcription. Irak1 is upregulated in the cortex of Mecp2 null mice and some of the Rett syndrome features, such as reduced dendritic complexity and decreased life span, can be ameliorated by attenuation of Nfkb signaling (Kishi et al. 2016). MECP2 may also regulate IRAK1 levels indirectly, by up-regulating microRNA miR-146a, which targets IRAK1 mRNA (Urdinguio et al. 2010).

**Preceded by:** MECP2 binds IRAK1 gene

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-08-07</td>
<td>Reviewed</td>
<td>Christodoulou, J., Krishnaraj, R.</td>
</tr>
<tr>
<td>2018-08-08</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

Transcriptional Regulation by MECP2 2

Regulation of MECP2 expression and activity 6

MECP2 binds 5mC-DNA 8

MECP2 binds 5hmC-DNA 9

MECP2 binds DGCR8 10

MECP2 regulates neuronal receptors and channels 11

MECP2 regulates transcription of neuronal ligands 13

MECP2 regulates transcription factors 15

MECP2 regulates transcription of genes involved in GABA signaling 16

MECP2 binds the PVALB gene promoter 18

PVALB gene expression is repressed by MECP2 19

MECP2 binds GAMT gene promoter 20

GAMT gene expression is stimulated by MECP2 21

MECP2 binds SGK1 gene promoter 22

SGK1 gene expression is inhibited by MECP2 23

MECP2 binds MOBP gene promoter 24

MOBP gene expression is inhibited by MECP2 25

MECP2 and SOX2 bind MIR137 gene 26

MIR137 gene expression is inhibited by MECP2 and SOX2 27

miR-137 binds PTEN mRNA 28

PTEN mRNA translation is inhibited by miR-137 29

MECP2 binds IRAK1 gene 30

IRAK1 gene expression is inhibited by MECP2 31

Table of Contents 32