MECP2 regulates neuronal receptors and channels

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

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24/06/2020
Introduction

Reactome is an 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: 73

This document contains 1 pathway and 26 reactions (see Table of Contents)
MECP2 regulates neuronal receptors and channels

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


**Editions**

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MECP2:SIN3A complex binds GRIA2 gene promoter

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9022359

Type: binding

Compartments: nucleoplasm

Inferred from: MeCP2:Sin3a complex binds Gria2 gene promoter (Rattus norvegicus)

Based on studies in rat neurons, neuronal activity induces binding of the MECP2, in complex with SIN3A and HDAC1, to the promoter of the GRIA2 (GLUR2) gene, encoding glutamate receptor 2. Prior phosphorylation of MECP2 on serine residue S423 (corresponding to mouse and rat S421), triggered by neuronal activity, may be required (Qiu et al. 2012).

Followed by: GRIA2 gene expression is inhibited by MECP2:SIN3A complex

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GRIA2 gene expression is inhibited by MECP2:SIN3A complex

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9022365

Type: omitted

Compartments: nucleoplasm, plasma membrane

Inferred from: Gria2 gene expression is inhibited by Mecp2:Sin3a complex (Rattus norvegicus)

Based on studies in rat, transcription of the GRIA2 (GLUR2) gene, encoding glutamate receptor 2, is inhibited by binding of the MECP2:SIN3A:HDAC1 complex to the GRIA2 gene promoter. MECP2-mediated regulation of GRIA2 expression is involved in synaptic scaling (Qiu et al. 2012).

Preceded by: MECP2:SIN3A complex binds GRIA2 gene promoter

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Based on studies in mice, MECP2 binds to the promoter of the GRIN2A gene, encoding NMDA receptor 2A (Durand et al. 2012).

Followed by: GRIN2A gene expression is stimulated by MECP2
GRIN2A gene expression is stimulated by MECP2

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9006507

Type: omitted

Compartments: nucleoplasm, plasma membrane

Inferred from: Grin2a gene expression is stimulated by Mecp2 (Mus musculus)

Based on studies in mice, MECP2 stimulates transcription of the GRIN2A gene, encoding NMDA receptor 2A (Durand et al. 2012).

Preceded by: MECP2 binds the GRIN2A gene promoter

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MECP2 binds GRIN2B gene promoter

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9020504

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** MeCP2 binds to Grin2b gene promoter (Rattus norvegicus)

Based on study in rats, MECP2 binds to methylated GRIN2B (NR2B) gene promoter, encoding glutamate (NMDA) receptor subunit epsilon-2. Methylation of the GRIN2B promoter and the subsequent MECP2 binding is promoted by increased neuronal activity and suppressed by low neuronal activity (Lee et al. 2008).

**Followed by:** GRIN2B gene expression is inhibited by MECP2

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GRIN2B gene expression is inhibited by MECP2

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9020513

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

**Inferred from:** Grin2b gene expression is inhibited by Mecp2 (Rattus norvegicus)

Based on the study in rats, transcription of the GRIN2B (NR2B) gene, encoding glutamate (NMDA) receptor subunit epsilon-2, is inhibited by promoter methylation and subsequent MECP2 binding. GRIN2B promoter methylation and MECP2 binding are stimulated by neuronal activity. Suppression of neuronal activity leads to demethylation of the GRIN2B promoter and increased GRIN2B transcription (Lee et al. 2008).

**Preceded by:** MECP2 binds GRIN2B gene promoter

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MECP2 binds OPRK1 gene promoter

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9021954

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** MeCP2 binds Oprk1 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter region of the OPRK1 gene, encoding G-protein coupled kappa-type opioid receptor (Chahrour et al. 2008).

**Followed by:** OPRK1 gene expression is stimulated by MECP2

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OPRK1 gene expression is stimulated by MECP2

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9021951

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

**Inferred from:** Oprk1 gene expression is stimulated by Mecp2 (Mus musculus)

Based on studies in mice, MECP2 stimulates transcription of the OPRK1 gene, encoding G-coupled kappa-type opioid receptor (Chahrour et al. 2008).

**Preceded by:** MECP2 binds OPRK1 gene promoter

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MECP2:SIN3A complex binds OPRM1 gene promoter

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9017954

Type: binding

Compartments: nucleoplasm

Inferred from: MeCP2:Sin3a complex binds Oprm1 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds to the promoter of the OPRM1 gene, encoding Mu-type opioid receptor (Hwang et al. 2008, Hwang et al. 2010, Vucetic et al. 2011, Samaco et al. 2012). MECP2 binds to the OPRM1 promoter together with the SIN3A co-repressor complex, and MECP2 binding correlates with hypermethylation of the promoter region of OPRM1 (Hwang et al. 2009, Hwang et al. 2010).

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OPRM1 gene expression is repressed by MECP2

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9017921

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

**Inferred from:** Oprm1 gene expression is repressed by Mecp2 (Mus musculus)

Based on studies in mice, association of MECP2 with the hypermethylated OPRM1 gene promoter, encoding Mu-type opioid receptor (MOR), correlates with transcriptional repression of OPRM1 in the cerebellum. MECP2-mediated transcriptional repression of OPRM1 may be relieved by interaction of MECP2 with SMARCA4 (BRG1), a component of the chromatin remodeling SWI/SNF complex (Hwang et al. 2009). MECP2-mediated repression of OPRM1 involves the SIN3A co-repressor complex (Hwang et al. 2010). In the mouse model of MECP2 duplication syndrome, OPRM1 transcription in the amygdala and hippocampus is increased compared to wild-type mice (Samaco et al. 2012).

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MECP2 binds GPRIN1 gene promoter

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9021946

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** MeCP2 binds Gprin1 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter region of the GPRIN1 gene, encoding G protein-regulated inducer of neurite outgrowth 1 (Chahrour et al. 2008).

**Followed by:** GPRIN1 gene expression is stimulated by MECP2

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GPRIN1 gene expression is stimulated by MECP2

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9021948

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

**Inferred from:** Gprin1 gene expression is stimulated by Meco2 (Mus musculus)

Based on studies in mice, MECP2 directly stimulates transcription of the GPRIN1 gene, encoding G protein-regulated inducer of neurite outgrowth 1 (Chahrour et al. 2008).

**Preceded by:** MECP2 binds GPRIN1 gene promoter

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MECP2 binds the promoter of the MET gene, encoding receptor tyrosine kinase MET. The MECP2 binding site in the MET promoter contains the SNV sequence whose rs1858830 C 'low activity' allele is associated with an increased risk for autism spectrum disorders (ASD) (Plummer et al. 2013).

**Followed by:** MET gene transcription is stimulated by MECP2

**Literature references**

MECP2 directly stimulates transcription of the MET gene, encoding MET receptor tyrosine kinase. MET promoter SNV rs1858830 C 'low activity' allele is associated with low expression of MET in autism spectrum disorders (ASD). Although this MET promoter SNV overlaps with the MECP2 binding site, presence of the low activity allele does not inhibit MECP2-mediated stimulation of MET transcription. Mutant MECP2 proteins associated with Rett syndrome show reduced transactivation of the MET gene. MET expression is significantly decreased in the temporal cortex of female Rett patients (Plummer et al. 2013).

Preceded by: MECP2 binds MET gene promoter

Literature references

MECP2 binds NOTCH1 gene promoter

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9023346

Type: binding

Compartments: nucleoplasm

Inferred from: MeCP2 binds Notch1 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter of the NOTCH1 gene. Binding of MECP2 to the NOTCH1 gene promoter is inhibited by AURKB-mediated phosphorylation of MECP2 at serine residue S423 (Li et al. 2014).

Followed by: NOTCH1 gene expression is inhibited by MECP2

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**NOTCH1 gene expression is inhibited by MECP2**

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9023345

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Notch1 gene expression is inhibited by Mecp2 (Mus musculus)

Based on studies in mice, increased MECP2 occupancy of the NOTCH1 gene promoter, correlates with decreased transcription of NOTCH1. MECP2 therefore inhibits NOTCH1 transcription. Increased occupancy of the NOTCH1 promoter by MECP2 also results in decreased expression of NOTCH targets HES3 and HES5 (Li et al. 2014).

**Preceded by:** MECP2 binds NOTCH1 gene promoter

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MECP2 binds the TRPC3 gene

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9005988

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Mecp2 binds Trpc3 gene (Mus musculus)

MECP2 binds to the TRPC3 gene, a couple of kilobases upstream of the transcription start site (Li et al. 2012).

**Followed by:** TRPC3 gene transcription is stimulated by MECP2

**Literature references**


**Editions**

- 2017-10-02: Authored by Orlic-Milacic, M.
- 2018-08-07: Reviewed by Christodoulou, J., Krishnaraj, R.
- 2018-08-08: Edited by Orlic-Milacic, M.
TRPC3 gene transcription is stimulated by MECP2

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9005994

Type: omitted

Compartments: nucleoplasm, plasma membrane

Inferred from: Trpc3 gene expression is stimulated by Mecp2 (Mus musculus)

Binding of MECP2 to the TRPC3 gene stimulates transcription of TRPC3, which encodes a BDNF-responsive transient receptor potential canonical channel (Li et al. 2012).

Preceded by: MECP2 binds the TRPC3 gene

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MECP2:CREB1 complex binds SLC2A3 gene

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9022175

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Mecp2:Creb1 binds Slc2a3 gene (Mus musculus)

Based on studies in mice, the complex of MECP2 and CREB1 binds to a hypermethylated CpG island in the 5' flanking region of the SLC2A3 (GLUT3) gene, encoding solute carrier family 2, facilitated glucose transporter member 3 (Chen et al. 2013).

**Followed by:** SLC2A3 gene expression is stimulated by MECP2:CREB1 complex

**Literature references**


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SLC2A3 gene expression is stimulated by MECP2:CREB1 complex

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9022186

**Type:** omitted

**Compartments:** nucleoplasm, plasma membrane

**Inferred from:** Slc2a3 gene expression is stimulated by Mecp2:Creb1 complex (Mus musculus)

Based on studies in mice, transcription of the SLC2A3 (GLUT3) gene, encoding solute carrier family 2, facilitated glucose transporter member 3, is directly stimulated by the complex of MECP2 and CREB1. In the mouse brain, expression of the Slc2a3 gene is developmentally regulated, peaking at postnatal day 14, which correlates with hypermethylation of the 5' flanking region CpG island (Chen et al. 2013).

**Preceded by:** MECP2:CREB1 complex binds SLC2A3 gene

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[https://reactome.org](https://reactome.org)
MECP2 binds FKBP5 gene promoter

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9022734

Type: binding

Compartments: nucleoplasm

Inferred from: MeCP2 binds Fkbp5 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the methylated promoter region of the FKBP5 gene, encoding peptidyl-prolyl cis-trans isomerase involved in trafficking of glucocorticoid receptors (Nuber et al. 2005, Urduinguio et al. 2008).

Followed by: FKBP5 gene expression is inhibited by MECP2

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**FKBP5 gene expression is inhibited by MECP2**

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9022728

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Fkbp5 gene expression is inhibited by Mecp2 (Mus musculus)

Based on studies in mice, MECP2 directly inhibits transcription of the FKBP5 gene, encoding peptidyl-prolyl cis-trans isomerase involved in trafficking of glucocorticoid receptors. Fkbp5 level is increased in Mecp2 null mice (Nuber et al. 2005, Urdinguio et al. 2008).

**Preceded by:** MECP2 binds FKBP5 gene promoter

**Editions**

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**MECP2 binds PTPN1 gene promoter**

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9023538

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Mecp2 binds Ptpn1 gene promoter (Mus musculus)

Based on studies in mice, MECP2 binds the promoter region of the PTPN1 (PTP1B) gene, encoding Tyrrosine-protein phosphatase non-receptor type 1 (Krishnan et al. 2015).

**Followed by:** PTPN1 gene expression is inhibited by MECP2

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PTPN1 gene expression is inhibited by MECP2

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9023549

Type: omitted

Compartments: nucleoplasm, cytosol

MECP2 directly represses PTPN1 (PTP1B) gene transcription in both human and mouse cells (Krishnan et al. 2015). PTPN1 can dephosphorylated BDNF receptor TRKB, which negatively regulates BDNF signaling. Increased PTPN1 level, which is a consequence of the loss of function of MECP2, interferes with BDNF signaling (Krishnan et al. 2015).

Preceded by: MECP2 binds PTPN1 gene promoter

Literature references


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MECP2 binds the PTPN4 gene promoter

**Location:** MECP2 regulates neuronal receptors and channels

**Stable identifier:** R-HSA-9006588

**Type:** binding

**Compartments:** nucleoplasm

MECP2 binds to the promoter of the PTPN4 gene, encoding protein tyrosine phosphatase, non-receptor type 4, also known as MEG, PTPase-MEG1 or PTPMEG (Williamson et al. 2015).

**Followed by:** PTPN4 gene expression is stimulated by MECP2

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PTPN4 gene expression is stimulated by MECP2

Location: MECP2 regulates neuronal receptors and channels

Stable identifier: R-HSA-9006585

Type: omitted

Compartments: nucleoplasm, cytosol

Binding of MECP2 to the PTPN4 gene promoter stimulates PTPN4 transcription. PTPN4 gene encodes a protein tyrosine phosphatase, non-receptor type, also known as MEG, PTPase-MEG1 or PTPMEG. Expression of Ptpn4 is reduced in Mecp2 null mice used as a Rett syndrome model. A hemizygous PTPN4 gene deletion was found in twins with a Rett-like phenotype (Williamson et al. 2015).

Preceded by: MECP2 binds the PTPN4 gene promoter

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