**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.

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**Literature references**


Reactome database release: 79

This document contains 6 pathways and 17 reactions (see Table of Contents)
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 changes in 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 KhorsheidAhmad 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 αζ“ 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 PPARγ (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**


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

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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 FOXG1, 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**

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MECP2 binds 5mC-DNA

Location: Transcriptional Regulation by MECP2

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