EGR2 and SOX10-mediated initiation of Schwann cell myelination

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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.

12/11/2022
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 1 pathway and 26 reactions (see Table of Contents)
Schwann cells are glial cells of the peripheral nervous system that ensheathe the peripheral nerves within a compacted lipid-rich myelin structure that is required for optimal transduction of nerve signals in motor and sensory nerves. Schwann cells develop from the neural crest in a differentiation process driven by factors derived from the Schwann cell itself, from the adjacent neuron or from the extracellular matrix (reviewed in Jessen and Mirsky, 2005). Upon peripheral nerve injury, mature Schwann cells can form repair cells that allow peripheral nerve regeneration through myelin phagocytosis and remyelination of the peripheral nerve. This process in some ways recapitulates the maturation of immature Schwann cells during development (reviewed in Jessen and Mirsky, 2016). Mature, fully myelinated Schwann cells exhibit longitudinal and radial polarization. The axon-distal abaxonal membrane interacts with elements of the basal lamina through integrins and lamins and in this way resembles the basolateral domain of polarized epithelial cells. In contrast, the axon-proximal adaxonal membrane resembles the apical domain of an epithelial cell, and is enriched with adhesion molecules and receptors that mediate interaction with ligands from the axon (reviewed in Salzer, 2015).

Schwann cells express a number of Schwann-cell specific proteins, including components of the myelin sheath such as myelin basic protein (MBP) and myelin protein zero (MPZ). In addition, Schwann cells have high lipid content relative to other membranes, and are enriched in galactosphingolipids, cholesterol and saturated long chain fatty acids (reviewed in Garbay et al, 2000). This protein and lipid profile is driven by a Schwann cell myelination transcriptional program controlled by master regulators SOX10, POU3F1 and EGR2, among others (reviewed in Svaren and Meijer, 2008; Stolt and Wegner, 2016).

**Literature references**


**Editions**

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SOX10 dimer binds the POU3F1 promoter

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9613648

Type: binding

Compartments: nucleoplasm

Inferred from: Sox10 and Hdac2 interact to regulate expression of genes involved in peripheral myelination (Rattus norvegicus)

SOX10 binds as a dimer to the Schwann cell enhancer (SCE) element in the promoter of the POU3F1 gene (Jagalur et al, 2011; Schreiner et al, 2007; Ghazvini et al, 2002; Mandemakers et al, 2000). SOX10 mediates recruitment of chromatin remodeling complexes and histone deacetlyases, including HDAC2 and SMARCA4, promoting transcriptional activation of POU3F1 (Jacob et al, 2011; Weider et al, 2012).

POU3F1 protein (also known as OCT6) is required in conjunction with EGR2 to ensheathe axonal neurons of the peripheral nervous system with myelin (reviewed in Svaren and Meijer, 2008). The myelination program is initiated by extracellular axonal signals such as NRG, Neuregulin1, Notch ligands and neurotrophins and is transmitted to the nucleus, ultimately controlling expression of myelin-related genes, including myelin protein zero (MPZ) and myelin basic protein (MBP), among others. After synthesis, OCT6 acts in conjunction with SOX10 and EGR2, a master regulator of myelination, to drive expression of these genes (reviewed in Svaren and Meijer, 2008; Stolt and Wegner, 2016).

Literature references


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## Editions

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POU3F1, also known as OCT6, is a transcription factor involved in early embryogenesis and neuronal development, particularly the myelination of Schwann cells in the peripheral nervous system (Monuki et al, 1990; Jaegle et al, 1996; Ryu et al, 2007; reviewed in Zhao, 2013; Svaren and Meijer, 2008). Expression of POU3F1 in Schwann cells is transient, and peaks at the promyelination stage, and loss of POU3F1 causes a delay in myelination (Jaegle et al, 2003; Jaegle et al, 1996).

Expression of POU3F1 is driven in part by the Schwann Cell Enhancer (SCE), which is bound by a dimer of SOX10, a key regulator of Schwann cell development (Jagalur et al, 2011). POU3F1 expression is also regulated by the adhesion GPCR ADGRG6 (also known as GPR126). Expression of POU3F1 and EGR2 is lost in grp126 mutant, which arrest at a promyelinating stage (Monk et al, 2009; Monk et al, 2011). ADGRG6 elevates cAMP levels through G alpha s G proteins, and may control POU3F1 expression through the cAMP-PKA-CREB pathway (Morgan et al, 1991; Lee et al, 1999; Mandemakers et al, 2000; Monk et al, 2009; Monk et al, 2011; Mogha et al, 2013; reviewed in Svaren and Meijer). CREB phosphorylation may also be regulated by the NRG1-ERBB2:ERBB3 pathway (reviewed in Newbern and Birchmeier, 2010).

After induction, POU3F1, POU3F2 (also known as OCT7) and SOX10 work together in a feedforward mechanism to activate expression of EGR2, which ultimately promotes expression of genes encoding myelin components, such as myelin protein zero (MPZ) and myelin basic protein (MBP) (Ghislain and Charnay, 2006; Le Blanc et al, 2006; Le Blanc et al, 2007; Marathe et al, 2013; reviewed in Stolt and Wegner, 2016; Svaren and Meijer, 2008)

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SOX10, POU3F1 and POU3F2 bind EGR2 gene

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9613768

**Type:** binding

**Compartments:** nucleoplasm

During the process of peripheral nerve myelination, EGR2 expression is controlled by a feedforward transcriptional program initiated by SOX10 and maintained by POU3F2, POU3F1 and EGR2 itself (reviewed in Svaren and Meijer, 2008). Expression of EGR2 during the myelination process is controlled by a myelinating Schwann cell enhancer (MSE) 35 kb downstream of the gene (Ghislain et al, 2002). The MSE is bound by SOX10, POU3F1 and POU3F2 (Ghislain and Charnay, 2006; Reiprich et al, 2010). SOX10 in turn recruits SMARCA4, HDAC1 and HDAC2 to play overlapping but non-redundant roles in activating EGR2 expression (Jacob et al, 2011; Chen et al, 2011; Weider et al, 2012).

Followed by: EGR2 gene expression

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EGR2 gene expression

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9613760

Type: omitted

Compartments: nucleoplasm

EGR2 (also known as KROX20) is a member of the Early Growth Response (EGR) gene family encoding sequence-specific Cys2-His2 DNA binding transcription factors. The EGR family are immediate early genes (IEGs) whose expression is rapidly upregulated in response to a number of external stimuli to control activation of genes involved in stress response and differentiation (reviewed in Pagel and Deindl, 2001; Bahrami and Drabløs, 2016). Roles for EGR proteins are well established in the nervous system, with EGR target genes contributing to synaptic plasticity, long-term potentiation, peripheral nerve myelination and NGF-induced neurite outgrowth (reviewed in Perez-Cadahia et al, 2011; Herdegen and Leah, 1998; O'Donovan et al, 1999)

In addition to its other roles, EGR2 is a critical regulator of myelination by Schwann cells in the peripheral nervous system (reviewed in Svaren and Meijer, 2008). Consistent with this, Schwann cells are blocked at the promyelinating stage in EGR2 knockouts in mice (Topilko et al, 1994). Expression of EGR2 during the myelination process is controlled by a myelinating Schwann cell enhancer (MSE) 35 kb downstream of the gene (Ghislain et al, 2002). The MSE is bound by SOX10, POU3F1 and POU3F2 (Ghislain and Charnay, 2006; Reiprich et al, 2010). SOX10 in turn recruits SMARCA4, HDAC1 and HDAC2 to play overlapping but non-redundant roles in activating EGR2 expression (Jacob et al, 2011; Chen et al, 2011; Weider et al, 2012).

Preceded by: SOX10, POU3F1 and POU3F2 bind EGR2 gene

Literature references


Deindl, E., Pagel, JI. (2011). Early growth response 1--a transcription factor in the crossfire of signal transduction cas-

Baraban, JM., Millbrandt, J., Tourtellotte, WG., O'Donovan, KJ. (1999). The EGR family of transcription-regulatory 

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Autocleavage of ADGRG6

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9614271

Type: transition

Compartments: endoplasmic reticulum membrane

ADGRG6, also known as GPR126, is a member of the adhesion class of G-protein coupled receptors (aGPCRs). aGPCRs are characterized by a 7 transmembrane-spanning domain that couples to G-protein signaling and an extracellular N-terminal extension that mediates cell-cell or cell-matrix adhesion (reviewed in Langenhan et al, 2013). Like most aGPCRs, ADGRG6 is subject to autocatalytic processing during maturation, yielding a C-terminal fragment containing the 7-TM region, and an N-terminal fragment containing the extracellular region. Cleavage occurs at the conserved GPCR proteolytic site (GPS), part of the larger GPCR autoproteolysis-inducing (GAIN) domain (Moriguchi et al, 2004; Arac et al, 2012). As with other aGPCRs, these two domains remain associated in a heterodimer at the plasma membrane where they mediate signaling and cell adhesion (Moriguchi et al 2004; Arac et al, 2012; Lin et al, 2004; reviewed in Langenhan et al, 2013; Mehta et al, 2017).

Followed by: ADGRG heterodimer translocates to plasma membrane

Literature references


ADGRG heterodimer translocates to plasma membrane

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9614273

Type: omitted

Compartments: plasma membrane

Mature ADGRG6 is expressed at the plasma membrane as a non-covalently associated heterodimer of the N- and C terminal fragments (Moriguchi et al, 2004; Arac et al, 2012; reviewed in Langenhan et al, 2013; Mehta et al, 2017). In addition to cleavage at the GPS site, ADGRG6 may additionally be cleaved in the trans-Golgi network by a furin-like protease at an S2 site upstream of the GPS site. This cleavage yields a soluble N-terminal-most subfragment that may have roles in non cell autonomous signaling or contribute to regulation of ADGRG6 activation/inactivation (Moriguchi et al, 2004; reviewed in Langenhan et al, 2013).

Preceded by: Autocleavage of ADGRG6

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EGR2 and SOX10 bind the MAG gene

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9616116

Type: binding

Compartments: nucleoplasm

EGR2 and SOX10 bind to elements in the MAG gene to promote expression during myelination in the peripheral and central nervous system (Jones et al, 2007; Jang et al, 2006; LeBlanc et al, 2007).

Followed by: MAG gene expression

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MAG gene expression

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9614778

**Type:** omitted

**Compartments:** plasma membrane, nucleoplasm

**Inferred from:** Egr2 and Sox10 bind the Mag gene (Rattus norvegicus)

Myelin associated glycoprotein (MAG) is a low abundant component of the myelin sheath and is synthesized by oligodendrocytes and Schwann cells in the central and peripheral nervous system, respectively. MAG is also an adhesion molecule that binds to gangliosides and glycoproteins such as RTN4R and RTN4RL2 to mediate interaction between myelinating cells and neurons, and additionally functions after injury in the CNS to inhibit axon regeneration through the RHO A signaling pathway (reviewed in Schnarr and Lopez, 2009; Mehta et al, 2017; McKerracher and Rosen, 2015).

MAG expression is regulated in part by the binding of EGR2 and SOX10 to elements in the second intron of the gene (LeBlanc et al, 2007; Jang et al, 2006; Jones et al, 2007). Consistent with this, MAG expression is abrogated in EGR2-depleted mice and stimulated by ectopic EGR2 expression (Le et al, 2005; Nagarajan et al, 2001). At the protein level, MAG stability is positively regulated by the adhesion GPCR protein GPR98 (also known as VLGR1). GPR98 signals through G proteins, PKA and PKA to limit MAG ubiquitination and subsequent degradation, although the mechanism remains to be elucidated (Shin et al, 2013; reviewed in Mehta and Piao, 2017).

**Preceded by:** EGR2 and SOX10 bind the MAG gene

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Myelin basic protein (MBP) is a key component in the myelin sheath that coats axons of the peripheral nervous system. MBP expression is regulated by EGR2 binding to sites in an enhancer that lies ~9kb upstream of the transcriptional start site, as well as to a binding site in the first intron (Forghani et al, 2001; Denarier et al, 2005; Jang et al, 2006; Jones et al, 2007). Based on conservation of binding sites, SOX10 is predicted to also contribute to MBP expression during myelination (Jones et al, 2007), and this is substantiated by ChIP seq analysis and Sox10 knockdown studies in mouse (Arido-Lopez et al, 2015).

Followed by: MBP gene expression

Literature references


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**MBP gene expression**

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9614773

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

Myelin basic protein (MBP) is a key component of the myelin sheath synthesized by Schwann cells in the peripheral nervous system (Garbay et al, 2000). MBP expression is regulated by EGR2, which binds to both to an upstream enhancer and to sites within the first intron of the MBP gene (Forgahni et al, 2001; Denarier et al, 2005; Jang et al, 2006). Consistent with this, MBP expression is decreased in EGR2 knockout mice (Topilko et al, 1994, Le et al, 2005). Sequence analysis suggests that, as is the case for MPZ, SOX10 may act in conjunction with EGR2 to regulate MBP expression (Jones et al, 2006).

**Preceded by:** EGR2 and SOX10 bind the MBP gene

**Literature references**


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MPZ is a key component of the myelin sheath that surrounds axons of the peripheral nervous system. Expression of MPZ is dependent on binding of transcriptional regulators EGR2 and SOX10 to response elements in intron 1, where they recruit SMARCA4 to the gene (Le Blanc et al, 2006; Le Blanc et al, 2007; Marathe et al, 2013). SOX10 additionally binds to elements in the promoter of MPZ (Peirano et al, 2000).

Followed by: MPZ gene expression

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MPZ gene expression

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9614787

Type: omitted

Compartments: plasma membrane, nucleoplasm

MPZ is the most abundant component of the myelin sheath that surrounds axons of the peripheral nervous system. Expression of MPZ is dependent on axonal signals that stimulate the binding of transcriptional regulators EGR2 and SOX10 to response elements in intron 1, where they recruit SMARCA4 to the gene (Le Blanc et al, 2006; Le Blanc et al, 2007; Jones et al, 2007; Marathe et al, 2013). SOX10 additionally binds to elements in the promoter of MPZ, where it regulates both basal and upregulated MPZ expression (Peirano et al, 2000).

Preceded by: EGR2, SOX10 and SMARCA4 bind the MPZ gene

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PMP22 gene expression is regulated during peripheral nerve myelination by the binding of EGR2 and SOX10 to upstream and intronic enhancer elements (Nagarajan et al, 2001; Maier et al, 2002; Maier et al, 2003; Jones et al, 2011; Srinivasan et al, 2012). Hippo signaling also influences PMP22 expression during peripheral nerve myelination by modulating the binding of the TEAD1, WWTR1 (also known as TAZ) and YAP1 to cognate sites in the PMP22 gene (Lopez-Anido et al, 2016; reviewed in Castelnovo et al, 2017).

Followed by: PMP22 gene expression

Literature references


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The PMP22 gene encodes a peripheral myelin protein that is a component of the myelin sheath surrounding axons in the peripheral nervous system (reviewed in Garbay et al, 2000; Svaren and Meijer, 2008). Point mutations and duplications in the PMP22 gene cause the most prevalent form of the demyelinating peripheral neuropathy, Charcot-Marie-Tooth disease, while deletions lead to Hereditary Neuropathy with liability to Pressure Palsies (HNPP) (reviewed in van Passen et al, 2014).

PMP22 expression is controlled by a number of upstream and intronic enhancer elements that are bound by EGR2 and SOX10, master regulators of peripheral nerve myelination (Nagarajan et al, 2001; Maier et al, 2002; Maier et al, 2003; Jones et al, 2011; Jones et al, 2012; Srinivasan et al, 2012). In addition, PMP22 enhancers contain binding sites for the Hippo pathway transcription factor TEAD1, and TEAD1 and co-activators WWTR1 (also known as TAZ) and YAP1 are required for PMP22 expression (Lopez-Anido et al, 2016).

**Preceded by:** EGR2, SOX10 and TEAD1 bind enhancers in the PMP22 gene

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SOX10, EGR2 and NAB proteins bind the GJB1 promoter

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9618725

**Type:** binding

**Compartments:** nucleoplasm

GJB1 expression is regulated by two alternate promoters in a tissue specific manner. In Schwann cells, expression is driven by the P2 promoter and depends on binding by SOX10, EGR2 and NAB1 or NAB2 (Neuhaus et al, 1996; Bondurand et al, 2001; Le et al, 2005; Lopez-Arido et al, 2015).

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https://reactome.org
EGR2 and SOX10 bind the PRX gene

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9619657

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** Egr2 and Sox10 bind the Prx promoter (Rattus norvegicus)

Periaxin (PRX) is a scaffolding protein that is part of a dystrophin:dystroglycan complex required for maintenance of the myelin sheath in Schwann cells. PRX homodimers interact with DRP2 to form a complex with dystroglycan at the basal lamina, anchoring the complex in the plasma membrane (Sherman et al, 2001; Han and Kursala, 2014). Mutations in PRX are associated with severe demyelinating peripheral neuropathies (Boerkoel et al, 2001; Guilbot et al, 2001).

Expression of PRX initiates earlier than EGR2 during peripheral nerve cell myelination, indicating an EGR2-independent mechanism early during myelination (Parkinson et al, 2003). Candidate regulators of this early expression include SOX10 and EGR1, which is expressed in embryonic Schwann cells and with EGR2 at postnatal day 1 (Topilko et al, 1997). Sustained, upregulated expression of PRX during myelination depends on the binding of EGR2 and SOX10 to a binding site within the first intron, 4.5 kb from the transcription start site (Jones et al, 2007; Srinivasan et al, 2012). Consistent with this, expression of PRX is decreased in EGR2 null mice (Nagarajan et al, 2001; Boerkoel et al, 2001).

**Followed by:** PRX gene expression

**Literature references**


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**Preceded by:** EGR2 and SOX10 bind the PRX gene

**Followed by:** L-PRX dimer binds DRP2

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L-Periaxin (L-PRX) is a membrane protein that is expressed in Schwann cells of the peripheral nervous system where it acts as a key component of the dystrophin glycoprotein complex (DGC). PRX is required for the proper localization of a dystrophin-related protein DRP2 to sites of apposition between the Schwann cell plasma membrane and the abaxonal surface of the myelin sheath (Sherman et al, 2001; Sherman et al, 2012; Court et al, 2004; Court et al, 2009; reviewed in Masaki and Matsumura, 2010). The spectrin repeats of DRP2 and the basic subdomains of L-PRZ mediate direct interaction between the two proteins. S-PRZ, an alternate isofom that lacks the basic subdomains of L-PRZ, does not interact with DRP2 (Sherman et al, 2001). The complex of L-PRX and DRP2 also interact with other dystrophin-related proteins such as utrophin, as well as dystroglycan and components of the basal lumina, such as laminin-211 (Yamada et al, 1994; Yamada et al, 1996; Sherman et al, 2001).

PRZ and DRP2 have partially overlapping but distinct roles in myelin sheath formation. Both are required for the formation of appositions between the plasma membrane and the myelin sheath and for the formation of Cajal bodies. PRX also contributes to normal Schwann cell elongation and regulation of internode space along the axon, which is required for nerve conduction, while DRP2 is dispensable for these activities (Court et al, 2009; Sherman et al, 2012;)

**Preceded by:** PRX gene expression

**Followed by:** L-PRX:DRP2 binds dystroglycan and laminin-211

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L-PRX:DRP2 binds dystroglycan and laminin-211

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9619666

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** L:Prx:Drp2 binds dystroglycan (Mus musculus), alpha-dystroglycan binds laminin-211 (Bos taurus)

The DRP2:L-PRX complex interacts with dystroglycan in the plasma membrane as part of the dystrophin glycoprotein complex (DGC) (Sherman et al, 2001; Court et al 2009; Sherman et al, 2012). DGC complexes have structural and signaling roles and provide a connection between the abaxonal Schwann cell plasma membrane and the adjacent basal lamina through interaction with laminin complexes, including laminin-211 (Ervasti et al, 1993; Yamada et al, 1994; Yamada et al, 1996; Imamura et al, 2000; reviewed in Wrabetz and Feltri, 2001; Masaki and Matsumura, 2010).

**Preceded by:** L-PRX dimer binds DRP2

**Followed by:** L-PRX:DRP:DGC:laminin-211 interacts with UTRN

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**L-PRX:DRP:DGC:laminin-211 interacts with UTRN**

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9619668

**Type:** omitted

**Compartments:** plasma membrane, extracellular region, cytosol

**Inferred from:** Utrn interacts with a complex purified with an anti-periaxin antibody (Mus musculus)

Based on studies in mouse cells, L-PRX co-immunoprecipitates in a complex that includes DRP2, alpha- and beta-dystroglycan and dystrophin family utrophin (UTRN) (Sherman et al, 2001; reviewed in Wrabetz and Feltri, 2001; Masaki and Matsumura, 2010). Because UTRN does not interact directly with L-PRX, it is possible they are recruited indirectly through as part of alternate DGC complexes with varied dystrophin family members. This model remains to be validated, however (Sherman et al, 2001).

**Preceded by:** L-PRX:DRP2 binds dystroglycan and laminin-211

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EGR2 and SREBF2(1-484) dimer bind HMGCR gene

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9621411

**Type:** binding

**Compartments:** nucleoplasm

HMG coenzyme A reductase catalyzes a rate-limiting step in cholesterol biosynthesis and is expressed in a SREBF2- and EGR2-dependent manner during Schwann cell myelination. Cognate binding sites for both SREBF2 and EGR2 have been identified in the promoter of HMGCR, and the transcription factors act synergistically to promote transcription (Pai et al, 1998; Nagarajan et al, 2001; Verheijen et al, 2003; LeBlanc et al, 2005; Jang et al, 2010).

**Followed by:** HMGCR gene expression

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HMGCR gene expression

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9621410

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, nucleoplasm

Cholesterol is highly enriched in the Schwann cell membrane and it plays an essential role in the maturation of MPZ, a key protein component of the compact myelin sheath (Saher and Simons, 2010). The cholesterol of the myelin sheath is synthesized within the Schwann cells, rather than being absorbed from the blood (Jurevics and Morell, 1994; Jurevics et al, 1998). Consistent with this, a number of genes involved in the cholesterol biosynthesis pathway are upregulated during the myelination program, including HMG synthase and HMG coenzyme-A reductase (HMGCR) (Nagarjan et al, 2001; Verheijen et al, 2003; Le Blanc et al, 2005; Jang et al, 2010; Kim et al, 2016; reviewed in Camargo et al, 2009).

Myelin-specific expression of HMGCR depends on binding of sterol response binding factor 2 (SREBF2) to its cognate SRE site in the HMGCR promoter (Vallett et al, 1996; Pai et al, 1998; LeBlanc et al, 2005). SREBF2-dependent expression of HMGCR is increased with co-expression of EGR2, suggesting that the transcription factors synergistically activate expression (LeBlanc et al, 2005).

**Preceded by:** EGR2 and SREBF2(1-484) dimer bind HMGCR gene

**Literature references**


EGR2 and SREBF2 dimer bind SCD5 gene

**Location:** EGR2 and SOX10-mediated initiation of Schwann cell myelination

**Stable identifier:** R-HSA-9621400

**Type:** binding

**Compartments:** nucleoplasm

SCD5 expression is upregulated during Schwann cell myelination in an EGR2- and SREBF2 dependent manner (LeBlanc et al, 2005; Jang et al, 2010). SCD5 encodes a stearyl-CoA desaturase involved in long chain fatty acid biosynthesis (Wang et al, 2005; Zhang et al, 2005).

**Followed by:** SCD5 gene expression

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SCD5 gene expression

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9621399

Type: omitted

Compartments: endoplasmic reticulum membrane, nucleoplasm

Stearoyl-CoA desaturase 5 (SCD5, also known as acyl-CoA desaturase 4 or SCD2) is a ER-membrane protein involved in the desaturation of fatty acyl-CoA substrates (Wang et al, 2005; Zhang et al, 2005). SCD5 gene expression is upregulated in an SREBF2- and EGR2-dependent manner during Schwann cell myelination (Tabor et al, 1998; Tabor et al, 1999; Horton et al, 2003; LeBlanc et al, 2004; Jang et al, 2010).

Preceded by: EGR2 and SREBF2 dimer bind SCD5 gene

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EGR2 and SREBF2 dimer bind CYP51A1 gene

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9621406

Type: binding

Compartments: nucleoplasm


Followed by: CYP51A1 gene expression

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CYP51A1 gene expression

Location: EGR2 and SOX10-mediated initiation of Schwann cell myelination

Stable identifier: R-HSA-9621404

Type: omitted

Compartments: endoplasmic reticulum membrane, nucleoplasm

CYP51A1 encodes lanosterol 14 alpha-demethylase, an enzyme involved in steroid biosynthesis (Stroemstedt et al, 1996; Strushkevich et al, 2010). CYP51A1 is upregulated during Schwann cell myelination in an EGR2- and SREBF2-dependent manner, and sites for these factors have been identified in the upstream promoter region (Nagarajan et al, 2001; Halder et al, 2002; LeBlanc et al, 2005; Jang et al, 2010).

Preceded by: EGR2 and SREBF2 dimer bind CYP51A1 gene

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