introduction browse basic search advanced search my proteins

Protein A000032

Protein Overview
XML
BioPAX3
SBML2

Author-entered Data
V1.0, Peer Reviewed
Published 15 Sep 2010

Abstract
Full Text
Network Map
States
Transitions
Functions
Protein Classes

Automated Data
Not Reviewed
As At Publication

Sequence
Interactions
Pathways
Domains & Motifs
Protein Structure
Orthologs

Automated Data
Not Reviewed
Latest from 6 Dec 2010

Sequence
Interactions
Pathways
Domains & Motifs
Protein Structure
Orthologs
Blast Data

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Laforin

Vikas V Dukhande[1], Amanda R Sherwood[1], Matthew S Gentry[1]

[1]Molecular and Cellular Biochemistry, University of Kentucky, KY 40536-0509, US.

Correspondence should be addressed to Matthew S Gentry: msge222@email.uky.edu

Protein Function

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Domain structure

The epilepsy of progressive myoclonus type 2 gene A (*EPM2A*) encodes laforin (Minassian *et al*. 1998, Serratosa *et al*. 1999). Laforin is a bimodular protein that contains an amino-terminal carbohydrate-binding module (CBM) and a carboxy-terminal dual-specificity phosphatase (DSP) domain (Minassian *et al*. 1998, Serratosa *et al*. 1999, Wang *et al*. 2002). The dual-specificity phosphatases belong to the larger protein tyrosine phosphatases (PTP) family of cysteine-dependent phosphatases that comprise 107 genes in humans (Alonso *et al*. 2004, Tonks 2006). The PTP superfamily uses a conserved CX_5R motif to hydrolyse phosphoester bonds, with DSPs hydrolysing phosphoester bonds in both proteinaceous and non-proteinaceous substrates (Moorhead *et al*. 2009, Tonks 2006, Denu *et al*. 1996, Yuvaniyama *et al*. 1996). Bioinformatic data suggest that the DSP of laforin shares multiple structural characteristics with the non-proteinaceous DSPs (Gentry *et al*. 2009). CBMs are typically found in glycosylhydrolases and glucotransferases in non-vertebrate genomes (Boraston *et al*. 2004, Coutinho and Henrissat 1999, Rodríguez-Sanoja *et al*. 2005). Laforin is one of only 36 proteins in humans that have a CBM (see CAZy, Cantarel *et al*. 2009). Recessive loss of function mutations in either of these two domains results in a neurodegenerative epilepsy called Lafora disease (LD).

Phylogeny

The *EPM2A* gene that encodes laforin has a unique evolutionary lineage. *EPM2A* is conserved in all vertebrates; the invertebrates *Nematostella vectensis* and *Branchiostoma floridae*; and the protozoans *Toxoplasma gondii*, *Paramecium tetraurelia*, *Eimeria tenella*, *Neospora caninum* and *Cyanidioschyzon merolae* (Gentry *et al*. 2007, Gentry and Pace 2009). The genomes of the green alga *Chlamydomonas reinhardtii*, the land plant *Arabidopsis thaliana*, the moss *Physcomitrella patens* and all land plants encode a protein with an N-terminal DSP domain and a C-terminal CBM, similar domains to laforin, but in the opposite orientation (Gentry *et al*. 2007, Gentry and Pace 2009, Kerk *et al*. 2006, Niittylä *et al*. 2006). In *A. thaliana*, this locus is the *Starch Excess 4* gene encoding the protein SEX4 (previously named AtPTPKIS1) (Fordham-Skelton *et al*. 2002, Kerk *et al*. 2006, Niittylä *et al*. 2006). Although laforin and SEX4 have similar activities *in vitro* and *in vivo*, they are not orthologous proteins because their domains are arranged in opposite orientations (Gentry *et al*. 2007). While laforin is conserved in all vertebrates, two invertebrates and five protozoans, a gene encoding a laforin-like protein is not present in any other sequenced genome in Kingdom Animalia (Gentry and Pace 2009). Thus, the genomes of flies, worms, yeast lack a gene that encodes a protein containing a CBM and DSP in any orientation (Gentry *et al*. 2007, Gentry and Pace 2009).

Activity

The CBM of laforin targets laforin to subcellular sites of glycogen synthesis and promotes the

binding of laforin to glycogen *in vitro* and *in vivo* (Wang *et al*. 2002). Recombinant laforin can hydrolyse phosphotyrosine and phosphoserine/threonine substrates *in vitro* and this activity is dependent on the CX_5R motif of the DSP domain (Ganesh *et al*. 2000, Wang *et al*. 2002). Laforin can also hydrolyse the artificial substrates *para*-nitrophenylphosphate (*p*-NPP) and 3-*O*-methylfluorescein phosphate (OMFP) (Ganesh *et al*. 2000, Minassian *et al*. 2001, Wang *et al*. 2002). The addition of glucans, such as glycogen, amylopectin and amylose, to the *p*-NPP reaction cause potent inhibition of laforin activity against *p*-NPP, but this inhibition is dependent on a functional CBM (Wang and Roach 2004). A similar glycogen-dependent inhibition of laforin activity is observed using the exogenous substrate OMFP (Castanheira *et al*. 2010).

Although laforin can dephosphorylate exogenous proteinaceous substrates, its more biologically relevant substrate appears to be non-proteinaceous. Laforin is the founding member of a unique class of DSPs that dephosphorylate phosphorylated complex carbohydrates, a class of phosphatases referred to as glucan phosphatases (Worby *et al*. 2006). Similar to laforin, the *A. thaliana* protein SEX4 can also dephosphorylate phosphorylated glucans (Gentry *et al*. 2007). Human patients with Lafora disease were shown in early studies to have glucan accumulations called Lafora bodies (LBs) that are hyperphosphorylated when compared with glycogen (Sakai *et al*. 1970, Schnabel and Seitelberger 1968). Laforin was later shown to dephosphorylate glycogen and loss of laforin activity in mice was shown to result in the hyperphosphorylated LBs (Tagliabracci *et al*. 2008, Tagliabracci *et al*. 2007). These findings led to the hypotheses that laforin dephosphorylates glycogen during either glycogenolysis or glycogenesis (Worby *et al*. 2006, Gentry *et al*. 2009, Gentry *et al*. 2007, Tagliabracci *et al*. 2008, Tagliabracci *et al*. 2007).

A second proposed substrate of laforin is glycogen synthase kinase 3 β (GSK3β). This finding arose from a mouse expressing simian virus 40 large tumor antigen that was engineered with a transgenic rearranged T-cell receptor (TCR) and in which the TCR transgene had randomly inserted into the *EPM2A* gene locus (Geiger *et al*. 1992, Wang *et al*. 2006). These transgenic mice are immunocompromised and develop an increased rate of lymphoma (Wang *et al*. 2006). Laforin suppressed tumor growth in these immunocompromised mice (Wang *et al*. 2006). In addition, a laforin immunoprecipitation from human embryonic kidney (HEK)293 cells could dephosphorylate a 20-mer peptide containing the proposed GSK3β phospho-site (Wang *et al*. 2006). However, two groups have reported that recombinant laforin does not dephosphorylate purified full-length GSK3β *in vitro* (Tagliabracci *et al*. 2007, Worby *et al*. 2006). In addition, neither group observed an increase in GSK3β phosphorylation in tissue extracts derived from laforin-deficient mice (Tagliabracci *et al*. 2007, Worby *et al*. 2006). Thus, there is currently not a consensus substrate(s) for laforin.

In addition to binding glucans and dephosphorylating glucans and/or GSK3β, laforin is also a scaffold protein. Malin is a single-subunit E3 ubiquitin ligase that binds and ubiquitinates laforin (Gentry *et al*. 2005). In addition to laforin, malin also ubiquitinates glycogen synthase and protein targeting to glycogen (PTG) (Solaz-Fuster *et al*. 2008, Vilchez *et al*. 2007, Worby *et al*. 2008). Laforin is necessary for the ubiquitination of glycogen synthase and PTG in cell culture and it is a necessary component for *in vitro* ubiquitination of PTG (Solaz-Fuster *et al*. 2008, Vilchez *et al*. 2007, Worby *et al*. 2008). Multiple groups have identified and confirmed a direct interaction between laforin and PTG (Fernandez-Sanchez *et al*. 2003, Solaz-Fuster *et al*. 2008, Vernia *et al*. 2009, Worby *et al*. 2008). Similarly, laforin is required for malin to downregulate the protein levels of muscle glycogen synthase (Solaz-Fuster *et al*. 2008, Vilchez *et al*. 2007). Thus, it is postulated that laforin acts as a scaffold to bring malin to its substrates (Solaz-Fuster *et al*. 2008, Vernia *et al*. 2009, Worby *et al*. 2008). One report, however, did not observe a laforin-dependent decrease in PTG or glycogen synthase protein levels (Tagliabracci *et al*. 2008). Thus, a consensus on these proposed events has not yet been reached.

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Regulation of Activity

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The most rigorously demonstrated regulation of laforin activity is by malin-directed ubiquitination. Malin directly binds laforin as determined by *in vitro* protein–protein interaction experiments, yeast two-hybrid analyses and co-immunoprecipitation (Gentry *et al*. 2005, Lohi *et al*. 2005, Solaz-Fuster *et al*. 2008). In addition, malin polyubiquitinates laforin and promotes its degradation in HEK293 cells (Gentry *et al*. 2005). The polyubiquitination of laforin by malin has also been recapitulated *in vitro* (Gentry *et al*. 2005). Malin has also been shown to promote the degradation of laforin in mouse neuronal Neuro-2a (N2a) cells (Vilchez *et al*. 2007) and in rat hepatoma FTO2B cells (Solaz-Fuster *et al*. 2008). Lastly, endogenous laforin is observed only in LD patients who have a mutation in malin and not in non-LD patients, suggesting that the absence of malin results in increased laforin levels (Chan *et al*. 2004).

Although a malin–laforin complex is proposed to regulate the protein levels of PTG and glycogen synthase, it is not entirely clear how these processes are modulated. In the case of PTG, the malin–laforin complex is modulated by AMP-activated protein kinase (AMPK) (Solaz-Fuster *et al*. 2008, Vernia *et al*. 2009). In neurons, the malin–laforin complex may act constitutively on muscle glycogen synthase to keep its levels low (Vilchez *et al*. 2007).

One group reports that dimerization of laforin is required for its maximal phosphatase activity (Liu *et al*. 2006). Dimerization is a common mechanism for regulating receptor protein-tyrosine phosphatases (Jiang *et al*. 1999, Tonks 2006). However, there are only a few examples of non-receptor phosphatases that dimerize under physiological conditions, including alkaline phosphatase, bovine protein tyrosine phosphatase, and *Vaccinia* virus H1 (VH1) phosphatase (Sowadski *et al*. 1985, Stec *et al*. 2000, Schlesinger and Barrett 1965, Koksal *et al*. 2009, Tabernero *et al*. 1999). If correct, laforin dimerization would present a very useful means to control its phosphatase activity.

Interactions with Ligands and Other Proteins

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Laforin is a bimodular protein with an N-terminal carbohydrate-binding module (CBM) and a C-terminal dual-specificity phosphatase (DSP) domain, and as such it binds to carbohydrates and has phosphatase activity. Laforin also acts as a scaffolding protein. Thus, interactions with laforin can be categorized on the basis of the following activities: binding to carbohydrates; dephosphorylation of substrate(s); acting as a scaffolding protein; and other protein–protein interactions.

Binding to carbohydrates

Laforin is the only dual-specificity phosphatase in vertebrate genome containing a CBM, and the CBM belongs to the CBM20 family (Wang *et al*. 2002, Worby *et al*. 2006, Gentry *et al*. 2007, Christiansen *et al*. 2009). The presence of an N-terminal CBM enables laforin to interact with cellular glycogen, and mutations in the CBM abolish this interaction (Wang *et al*. 2002). In addition, laforin colocalizes with LBs in mice overexpressing inactivated laforin (Chan *et al*. 2004) and laforin binds purified LBs *in vitro* (Ganesh *et al*. 2004). Lastly, binding of laforin to complex carbohydrates, such as glycogen and amylopectin, inhibits the phosphatase activity of laforin (Wang and Roach 2004).

Dephosphorylation of substrate(s)

The ability of laforin to dephosphorylate complex carbohydrates established laforin as the first glucan phosphatase (Worby *et al*. 2006). Phosphate levels associated with glycogen are higher in hepatic and skeletal muscle tissue from *EPM2A* knockout mice than in wild type, confirming phosphoglucans as a substrate of laforin (Worby *et al*. 2006, Tagliabracci *et al*. 2007, Tagliabracci *et al*. 2008). Similarly, pathognomonic LBs biochemically characterized from LD patients also have higher phosphate content (Sakai *et al*. 1970, Schnabel and Seitelberger 1968). One group reports that laforin interacts with and dephosphorylates GSK3β (Lohi *et al*. 2005, Liu *et al*. 2008); however, other groups have published conflicting data regarding this interaction (Worby *et al*. 2006, Wang *et al*. 2007). Moreover, laforin is shown to form homodimers in breast cancer cell line 4T1 and this dimerization is needed for dephosphorylation

of GSK3β by laforin (Liu *et al*. 2006). Laforin also interacts with tau by means of its DSP domain and dephosphorylates the microtubule-stabilizing protein tau (Puri *et al*. 2009).

Acting as a scaffolding protein

Laforin interacts with the NHL domain (first identified in NCL-1, HT2A, and LIN-41; Slack and Ruvkun 1998) of malin and the interaction results in ubiquitination and degradation of laforin (Gentry *et al*. 2005). Another study confirmed the interaction of laforin and malin but indicated that full-length malin was needed for this interaction (Lohi *et al*. 2005). The laforin–malin complex has been shown to decrease the expression of several proteins important in glycogen metabolism, such as PTG, amylo-1,6-glucosidase,4-alpha-glucanotransferase (AGL) and muscle glycogen synthase (Cheng *et al*. 2007, Worby *et al*. 2008, Solaz-Fuster *et al*. 2008, Vilchez *et al*. 2007). In addition, the laforin–malin complex physically interacts with the heat shock protein Hsp70 and the resulting complex formed leads to degradation of misfolded proteins through ubiquitin proteasome system (Garyali *et al*. 2009). The interaction of laforin with PTG requires the presence of the glycogen-binding and glycogen synthase-binding site of PTG (Fernandez-Sanchez *et al*. 2003). Interaction of laforin with AMP-activated protein kinase (AMPK) was identified by using yeast two-hybrid analysis in which laforin interacted with the α2 and β2 subunits of AMPK but not with the γ1 subunit (Solaz-Fuster *et al*. 2008).

Other protein–protein interactions

A yeast two-hybrid analysis with laforin as the bait identified EPM2A-interacting protein (EPM2AIP); to date no function has been identified for EPM2AIP (Ianzano *et al*. 2003). In addition, a yeast two-hybrid analysis of laforin identified the iron-sulfur cluster protein HIRA-interacting protein-5 (HIRIP-5, also known as NFU (Nitrogen-Fixing Bacteria Gene U)), but the relevance of HIRIP5 to LD is currently unclear (Ianzano *et al*. 2003, Ganesh *et al*. 2003, Liu *et al*. 2009).

Regulation of Concentration

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We are unaware of any data regarding transcriptional regulation of laforin. Although the physiological concentration of laforin is unknown, laforin levels are modulated under following conditions.

The interaction between laforin and malin, a single-subunit E3 ligase, leads to the ubiquitination and degradation of laforin in HEK293 cells (Gentry *et al*. 2005). This malin-mediated downregulation of laforin is also observed in mouse neuronal Neuro-2a cells (Vilchez *et al*. 2007) and in rat hepatoma FTO2B cells (Solaz-Fuster *et al*. 2008). In mouse models with either high or low muscle glycogen content, the levels of laforin showed direct correlation with muscle glycogen content (Wang *et al*. 2006). Proteasomal inhibition by MG132 resulted in increased level of laforin in COS-7 cells, indicating that laforin levels are regulated by proteasome (Mittal *et al*. 2007).

Subcellular Localization

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Laforin localizes to multiple intracellular sites, such as the rough endoplasmic reticulum (rough ER), glycogen granules in the cytoplasm and the nucleus.

Endoplasmic reticulum

Initial subcellular localization studies for laforin were carried out using mammalian expression vectors that greatly overexpressed laforin. These studies revealed that overexpressed laforin localizes at polyribosomes on the rough ER (Ganesh *et al*. 2000) and at the cytoplasmic membrane (Minassian *et al*. 2001, Ianzano *et al*. 2004). The ER-associated laforin forms aggregates at centrosomes following treatment with proteasomal inhibitors (Mittal *et al*. 2007). A recent study using a transgenic mouse model of Huntington's disease found laforin to be colocalized with aggregated huntingtin protein (Garyali *et al*. 2009).

Glycogen and LBs

The CBM of laforin localizes laforin to the site of glycogen synthesis in the cytoplasm, and the CBM also directs colocalization with glycogen synthase (Wang *et al*. 2002, Girard *et al*. 2006). In a mouse model overexpressing a catalytically inactive phosphatase domain (C266S), laforin preferentially localizes with LBs over glycogen (Chan *et al*. 2004). Another study to determine subcellular localization of endogenous laforin was performed in the protist *Cyanidioschyzon merolae* and used immunogold electron microscopy to demonstrate that *Cyanidioschyzon merolae* laforin is present on the outer surface of starch granules (Gentry *et al*. 2007).

Nucleus

A laforin isoform with alterations in the C-terminal amino acids (310–317) and lacking the final 14 amino acids localizes to both cytosol and nucleus (Ganesh *et al*. 2002). However, another study demonstrated that only the cytoplasmic isoform is associated with LD pathogenesis (Ianzano *et al*. 2004). A third study revealed that the laforin isoform with 317 amino acids forms homodimers and heterodimers with full-length laforin and these dimers lack phosphatase activity and do not bind to glycogen (Dubey and Ganesh 2008). Another study demonstrated that under glycogenolytic conditions, laforin changes its localization from cytoplasm to nucleus in HepG2 cells (Cheng *et al*. 2007).

***EPM2A* Mutations affecting subcellular localization**

Mutations W32G and R108C in *EPM2A* lead to laforin localization in the nucleus and cytoplasm. Mutations R171H, T194I, G279S, Q293L and Y294N all resulted in ubiquitin-positive cytoplasmic clumps (Ganesh *et al*. 2002). In addition, the ability of laforin to bind glycogen was affected by mutations W32G (Wang *et al*. 2002, Ganesh *et al*. 2004), F84L, G279S, Q293L, Y294N and P301L (Fernandez-Sanchez *et al*. 2003). Mutation L310W resulted in formation of perinuclear aggregates of laforin (Singh *et al*. 2008).’

Major Sites of Expression

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Laforin is widely expressed and a laforin transcript was found in all human tissues examined, such as brain, heart, skeletal muscle, lung, liver, placenta, kidney, testis, spleen, thymus, prostate, ovary, small intestine and pancreas (Minassian *et al*. 1998, Ganesh *et al*. 1999, Serratosa *et al*. 1999). Among these tissues the highest transcript expression was observed in heart, brain, liver, skeletal muscle and kidney (Ganesh *et al*. 1999). Expression in brain tissue is also ubiquitous, with the highest level of laforin expression in the adult mouse brain compared with the pre-natal and early post-natal levels (Ganesh *et al*. 2001).

Phenotypes

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A hallmark of LD is cytoplasmic polyglucosan inclusion bodies, LBs, that are present in cells from most tissues (Schwarz and Yanoff 1965, Harriman *et al*. 1955). In addition to these inclusion bodies, LD patients show myoclonus, tonic-clonic seizures, cognitive decline with dementia and neurodegeneration (Minassian 2002, Sakai *et al*. 1970, Delgado-Escueta *et al*. 2001, Ganesh *et al*. 2002, Van Heycop Ten Ham 1975, Lafora 1911, Berkovic *et al*. 1986). The accumulation of LBs as a patient ages is hypothesized to have a role in the increased neural cell death and neurodegeneration observed over time (Yokoi *et al*. 1968). However, the exact role of LBs in the development of neurological symptoms is unclear, as *EPM2A* knockout mice developed epilepsy without LB accumulation (Ganesh *et al*. 2002). Despite the genetic heterogeneity of the laforin disease mutations (Gómez-Garre *et al*. 2000, Minassian *et al*. 1998), the clinical progression of LD is not heterogeneous (Minassian *et al*. 1999). However, the disease can vary in its initial presentation (Berkovic *et al*. 1986) and age of onset (Lohi *et al*. 2007, Gómez-Abad *et al*. 2007).

Missense and nonsense mutations, insertions and deletions in the *EPM2A* gene encoding laforin are evenly distributed across the four exons of the gene and thus also equally spread across the two domains of the protein, the CBM and the dual-specificity phosphatase domain (Ganesh *et al*. 2006, Singh and Ganesh 2009). Mutations in either domain lead to very similar phenotypes

(Ianzano 2005, Gómez-Abad *et al*. 2005, Minassian *et al*. 2000). In addition, mutations in malin lead to a phenotype that is indistinguishable from that caused by mutations in laforin, indicating that both proteins are critical components of a common pathway in glycogen metabolism (Ganesh *et al*. 2006, Gentry *et al*. 2005).

Glycogen is the major carbohydrate energy storage molecule of vertebrates. It is a branched polymer of glucose residues joined by α-1,4-glycosidic linkages, formed by glycogen synthase, with continuous branches occurring every 12–14 residues with α-1,6-glycosidic linkages, formed by branching enzyme (Roach *et al*. 2001). The continuous branching and the placement of the branches make glycogen a water-soluble polymer. Photosynthetic eukaryotes use starch as a functional equivalent of glycogen. Starch is water-insoluble and in *Arabidopsis thaliana* leaves it is a semi-crystalline mixture of <10% w/w amylose and >80% w/w amylopectin (Zeeman *et al*. 2007). Amylose is largely a linear molecule with few α-1,6-glycosidic branches. Amylopectin is more similar to glycogen, but it contains longer branches (12–25 glucose monomers/branch) and the branching occurs in clusters at regular intervals (Buléon *et al*. 1998, Gallant *et al*. 1997). The decreased branching and the crystalline nature of amylopectin render it and thus starch water-insoluble.

LBs are water-insoluble, poorly branched glucans that biochemically more closely resemble plant amylopectin than animal starch (Yokoi *et al*. 1968, Schnabel and Seitelberger 1968, Sakai *et al*. 1970). Laforin has been shown to have carbohydrate phosphatase activity (Worby *et al*. 2006, Gentry *et al*. 2007), and thus it has been proposed that mutations in laforin lead to an increase in glycogen phosphate content that may disrupt glycogen branching required for solubility (Gentry *et al*. 2009). Indeed, early biochemical characterizations of LBs discovered that LBs from human patients contain a higher amount of phosphate than glycogen (Yokoi *et al*. 1968, Schnabel and Seitelberger 1968, Sakai *et al*. 1970). The human results have been recapitulated in mice: mice lacking laforin develop glucan accumulations that have increased phosphate and decreased branching (Tagliabracci *et al*. 2008, Tagliabracci *et al*. 2007).

Transgenic mice overexpressing a catalytically inactivate laforin mutation (C266S) develop symptoms of the pathology of LD (Chan *et al*. 2004). These animals form polyglucosan LBs in skeletal muscle, liver and neurons, but they show no signs of neurodegeneration (Chan *et al*. 2004). An *EPM2A* knockout mouse was also generated by deletion of the phosphatase domain (Ganesh *et al*. 2002). These mice showed many symptoms of LD within 2 months of birth, including development of LBs followed later by myoclonic seizures, epileptic electroencephalographic activity, ataxia, neurodegeneration and altered behavior (Ganesh *et al*. 2002). However, it was unclear whether these mice had altered life spans, as the mice analysed were only a year old. Transcriptional profiling of the *EPM2A* knockout mice revealed changes in the expression of genes involved in transcriptional regulation and translational modification of proteins (Ganesh *et al*. 2005). However, no clear link was derived between the expression of these genes and LD.

In *EPM2A* knockout mice, neurofibrillary tangles incorporating hyperphosphorylated tau protein were also observed (Puri *et al*. 2009). Disruption of the *EPM2A* gene has been implicated in increased tumorigenesis through Wnt signaling in immunocompromised mice (Wang *et al*. 2006). *EPM2A* knockout mice have also been shown to have high expression levels of ER stress markers, implicating laforin as a regulator of ER stress necessary for cell survival (Vernia *et al*. 2009, Liu *et al*. 2009).

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Splice Variants

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The *EPM2A* gene contains four exons and spans 130 kb. There are four proposed gene products of the *EPM2A* gene (transcripts A–D), with isoform A being the most abundant (Minassian *et al*. 1998, Serratosa *et al*. 1999). Two splice variants have been well characterized, each with unique C termini and subcellular localization. The protein encoded by the primary transcript (331 amino acids) localizes to the cytoplasm and ER (Ganesh *et al*. 2000, Minassian *et al*. 2001), whereas the protein encoded by the minor transcript (317 amino acids) localizes to the nucleus (Ganesh *et al*. 2002). The cytoplasmic 331 amino acid isoform has been proposed to retain phosphatase activity, whereas the nuclear 317 amino acid isoform is thought to lack phosphatase activity and instead have a regulatory role by interacting with the cytoplasmic isoform (Dubey and Ganesh 2008).

Antibodies

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Antibodies against the protein product of the EPM2A gene are available from a variety of commercial suppliers. In addition to the following antibodies for the human protein, there are antibodies available for mouse, rat and dog protein. Product information supplied by each company includes references describing applications for which these antibodies have been used.

Abgent

- rabbit polyclonal EPM2A antibody; reacts with C terminus of human protein. Suitable for western blot (catalog number: AP1453b).

- rabbit polyclonal EPM2A antibody; reacts with N terminus of human protein. Suitable for western blot (catalog number: AP1453a).

AbDSerotec

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for western blot (clone 4A12, catalog number: MCA4207Z).

ATGen

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (clone k2A3, catalog number: AEP0911).

Everest Biotech

- goat polyclonal EPM2A antibody; reacts with mouse, dog and human protein, isoform A. Suitable for western blot and ELISA (catalog number: EB08570).

Assay Designs/Stressgen

- mouse monoclonal EPM2A antibody; reacts with mouse and human protein. Suitable for western blot (clone 4A12, catalog number: H00007957-M01).

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (clone 6C6, catalog number: H00007957-M02).

- mouse polyclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (catalog number: H00007957-A01).

Sigma-Aldrich

- rabbit polyclonal EPM2A antibody; reacts with human protein. Suitable for western blot (catalog number: E0158).

- goat polyclonal EPM2A antibody; reacts with mouse, dog and human protein, isoform A. Suitable for western blot and ELISA (catalog number: SAB2500581).

- mouse monoclonal EPM2A antibody; reacts with mouse and human protein. Suitable for western blot and ELISA (clone 6C6, catalog number: WH0007957M2).

R and D Systems

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for western blot (clone 523435, catalog number: MAB5714).

Santa Cruz Biotechnology

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for western blot and immunoprecipitation (catalog number: sc-81309).

- goat polyclonal EPM2A antibody; reacts with mouse and human protein. Suitable for western blot, immunohistochemistry and ELISA (catalog number: sc-70291).

- rabbit polyclonal EPM2A antibody; reacts with human protein. Suitable for western blot, immunohistochemistry, ELISA, immunocytochemistry and immunoprecipitation (catalog number: sc-130799).

Novus Biologicals

- goat polyclonal EPM2A antibody; reacts with mouse, dog and human protein. Suitable for western blot and ELISA (catalog number: NBP1-18846).

- rabbit polyclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (catalog number: H00007957-D01P).

- mouse polyclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (catalog number: H00007957-B01).

LifeSpan Biosciences

- goat polyclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (catalog number: LS-C87285).

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for western blot and ELISA (clone 9C83, catalog number: LS-C90409).

US Biological

- mouse monoclonal EPM2A antibody; reacts with human protein. Suitable for flow cytometry (clone 8C130, catalog number: E3384-75).

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