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Authors
Krieger, Jonathan R
McGlade, C J

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Review Article Open Access

Numb

Jonathan R Krieger[1], C J McGlade[2]

Mammalian Numb (Numb) encodes an endocytic adaptor protein first characterized in the *Drosophila* nervous system as an intrinsic cell fate determinant which is asymmetrically localized and preferentially segregates into only one of the two daughter cells upon division (Rhyu *et al*. 1994; Knoblich *et al*. 1995; Spana and Doe 1995). Mammalian Numb homologues have been identified, and homozygous deletion of Numb in mice leads to embryonic lethality, suggesting that Numb plays an essential role in mammalian development (Verdi *et al*. 1996; Zhong *et al*. 1996). In addition to playing a role in asymmetric cell division(ACD), Numb has been shown to function in endocytosis, ubiquitination, cell adhesion, migration, and cancer.

KEYWORDS
M-Numb; Mnb; Numb; Numb gene homolog (Drosophila)

IDENTIFIERS
Molecule Page ID:A002841, Species:Mouse, NCBI Gene ID: 18222, Protein Accession:NP_035079.1, Gene Symbol:Numb

PROTEIN FUNCTION

Numb was identified as a mutation in Drosophila, causing a loss of neurons during development of the peripheral nervous system (Uemura *et al*. 1989). During development, Numb acts as an intrinsic regulator of cell fate decisions in both of the sensory organ precursor (SOP) lineage as well as the central and peripheral nervous systems in Drosophila (Uemura *et al*. 1989; Rhyu *et al*. 1994; Spana and Doe 1995; Ruiz Gomez and Bate 1997). In the SOP lineage, Numb becomes localized to a cortical crescent prior to cell division, and becomes asymmetrically segregated to one of the two daughter cells after division (Uemura *et al*. 1989; Rhyu *et al*. 1994; Knoblich *et al*. 1995; Spana and Doe 1995). The daughter cell acquiring Numb (pIIb) subsequently divides asymmetrically to form a glial cell and a progenitor pIIIb cell, and in doing so adopts a different cell fate than its sister cell, which differentiates into a hair and socket cell (Knoblich *et al*. 1995; Spana and Doe 1995). Loss of Numb causes both daughters to adopt the pIIa cell fate, resulting in the production of support cells without sensory neurons. Similarly, aberrant Numb overexpression causes both daughter cells to adopt the pIIb distinction (Uemura *et al*. 1989; Rhyu *et al*. 1994). Thus, asymmetric distribution of Numb proteins results in the adoption of distinct cell fates.

Studies in Drosophila support a model whereby Numb influences cell fate through negative regulation of the Notch signaling pathway in one of the two daughter cells (Frise *et al*. 1996; Guo *et al*. 1996; Spana and Doe 1996). The inequity of Notch signaling between the two daughter cells allows each of the cells to adopt a distinct cell fate. Notch signaling plays an important role in controlling cell fate decisions and regulation of developmental processes, and abnormalities in Notch signaling have been linked to both developmental disorders and several cancers. Notch loss of function mutations in the developing SOP lineage leads to a phenotype similar to overexpression of Numb in the same lineage (Guo *et al*. 1996; Spana and Doe 1996).

Numb related genes have been identified in C. elegans as well as vertebrates suggesting that Numb has an evolutionarily conserved function (Verdi *et al*. 1996; Zhong *et al*. 1996; Wakamatsu *et al*. 1999; Cayouette and Raff 2002). Numb is essential for mammalian development, and homozygous deletion of Numb in the mouse leads to embryonic lethality at E11.5 with multiple defects in the nervous system, angiogenesis, and placental dysfunction (Zhong *et al*. 2000; Zilian *et al*. 2001). Mammalian Numb has been reported to be asymmetrically distributed in mitotic neural progenitors. Analysis of different mouse knock out models (Petersen *et al*. 2002; Li *et al*. 2003; Rasin *et al*. 2007) suggest that Numb plays a role in regulating neural progenitor cell fate, polarity and adhesion.

Mammalian Numb contains an amino terminal phosphotyrosine binding (PTB) domain, followed by a proline rich region, two DPF (Aspartic Acid-Proline-Phenylalanine) motifs and a NPF (Asparagine-Proline-Phenylalanine) tripeptide endocytic motif (Verdi *et al*. 1996; Santolini *et al*. 2000). Numb is proposed to recognize endocytic signals on specific cargo proteins, and recruit these transmembrane molecules into preexisting sites of clathrin assembly through interaction with AP-2 and/or clathrin (Santolini *et al*. 2000; Dho *et al*. 2006) (reviewed in Polo *et al*. 2003; Mittal and McMahon 2009). Numb also interacts with members of the Eps15 Homology Domain (EHD) containing protein family, RME-1/EHD, that function to promote receptor recycling (Caplan *et al*. 2002; Smith *et al*. 2004; Rapaport *et al*. 2006; George *et al*. 2007). Similar to its Drosophila counterpart, mammalian Numb has been shown to antagonize Notch dependent activation of gene transcription and neural differentiation (Berezovska *et al*. 1999; French *et al*. 2002; McGill and McGlade 2003). Whereas Numb has no effect on the constitutive endocytosis of Notch1 from the plasma membrane, Numb positively regulates late sorting events in the endocytic pathway such that Notch1 is trafficked to the late endosome/lysosomal pathway (McGill *et al*. 2009). This suggests that Numb functions to promote re-routing of specific cargo, including Notch1, from a constitutive recycling pathway, into a late endosomal compartment leading to degradation. In support of this, the C. Elegans Numb orthologue, NUM-1A, also functions to inhibit endosomal recycling (Nilsson *et al*. 2008). Therefore Numb might influence cell fate decisions by suppressing recycling of receptors such as Notch. Integrin based adhesion is also regulated by Numb. Depletion of Numb in cell lines results in increased cell surface integrins consistent with either decreased endocytosis or enhanced recycling (Nishimura and Kaibuchi 2007; Teckchandani *et a*l. 2009). Numb has also

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[1]Department of Medical Biophysics, University of Toronto, Program in Cell Biology, The Hospital for Sick Children, ON M5G 1L7, CA. [2]Program in Cell Biology, The Hospital for Sick Children, and the Department of Medical Biophysics, University of Toronto, ON M5G 1L7, CA.
Correspondence should be addressed to C J McGlade: jmcglade@Sickkids.ca
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been shown to be important for insertion of cadherins and adherans junction integrity in radial glial cells (Rasin *et al*. 2007). Thus Numb regulates the trafficking of multiple trans-membrane proteins involved in adhesion and cell fate.

Several studies have suggested that Numb may act as a tumor suppressor. A study by Pece *et al* (Pece *et al*. 2004) showed that the Numb protein was lost or dramatically reduced in 50% of breast tumor samples compared to normal breast tissue, and increased Notch signaling was observed in Numb deficient tumors. In approximately 30% of non-small cell lung carcinomas, loss of Numb expression was observed, leading to increased Notch activity. This increase in Notch activity was correlated to unfavorable clinical outcomes (Westhoff *et al*. 2009). In addition to activation of Notch signaling, a distinct consequence of Numb loss has also been proposed to explain its involvement in breast tumorigenesis, in which loss of Numb results in enhanced ubiquitylation and degradation of the tumor suppressor p53 (TP53) (Colaluca *et al*. 2008). While these observations are difficult to reconcile with endocytic and trafficking functions of Numb, they may reflect a more general adaptor function for Numb in promoting E3 ligase-substrate interactions.

REGULATION OF ACTIVITY

There is evidence that regulation of Numb activity is accomplished through Numb phosphorylation by several different kinases. aPKC has been shown to phosphorylate Numb at S7 and S295 (Smith *et al*. 2004; Nishimura and Kaibuchi 2007). These phosphorylation events have been shown to regulate Numb localization to the plasma membrane, and to restrict Numb localization to the basolateral membrane in polarized MDCK cells. Mutations of these sites results in a uniform distribution, suggesting that Numb phosphorylation by aPKC regulates its localization in polarized cells, and during asymmetric cell divisions (Smith *et al*. 2004). In addition, S276 was identified as aPKC phosphorylation site (Nishimura and Kaibuchi 2007), and phosphorylation at all three of these sites disrupts Numb interactions with β-integrins and α-adaptin. Thus, a model has been suggested where cell migration is influenced by polarized Numb phosphorylation directing integrin endocytosis to the leading edge of the cell (Nishimura and Kaibuchi 2007).

Numb is also phosphorylated at S276 and S295 by Ca2+/calmodulin-dependent protein kinase 1 (CaM-KI) (Tokumitsu *et al*. 2005; Tokumitsu *et al*. 2006). This phosphorylation also destabilizes the Numb-α-adaptin interaction, and promotes an interaction between Numb and 14-3-3 proteins. The association of Numb with 14-3-3 proteins also inhibited the subsequent dephosphorylation of S264 (Tokumitsu *et al*. 2005). There is little information known about the functional consequence of the Numb-14-3-3 protein interaction, largely due to the diverse roles that 14-3-3 proteins play in the cell.

Regulation of Numb function in endocytic activity may be attributed to the ability of Numb to bind to and be phosphorylated at T102 by Adaptor Associated Kinase 1 (AAK1) (Sorensen and Conner 2008). AAK1 is most active in clathrin coated pits, and overexpression causes Numb to redistribute from the plasma membrane to perinuclear endosomes, near the endosomal recycling compartment and trans-Golgi network. AAK1 depletion, however, causes an accumulation of Numb at the plasma membrane (Sorensen and Conner 2008). Consistently, overexpression of Numb containing a T102A mutation or introduction of a kinase dead AAK1 also results in plasma membrane accumulation of Numb (Sorensen and Conner 2008). Overexpression of T102A mutant Numb also impairs internalization of the transferrin receptor, as well as the low-density lipoprotein receptor, but not EGF receptor suggesting that AAK1 regulation of endocytosis through Numb is limited to a subset of receptors (Sorensen and Conner 2008).

Thus, while there is consistent data suggesting that Numb activity is regulated by phosphorylation at several sites by different kinases, the specific role of individual phosphorylation events in Numb function is still uncertain.

INTERACTIONS

Numb is thought to function as a cargo-specific adaptor protein through interactions with both transmembrane receptors as well as endocytic machinery, and has been shown to regulate the intracellular trafficking of several membrane proteins (Guo *et al*. 1996; Zhong *et al*. 1996; Wakamatsu *et al*. 1999; Nishimura *et al*. 2006; Nishimura and Kaibuchi 2007). Numb contains a PTB domain, a PRR region, two DPF and one NPF tripeptide motif, but lacks domains with enzymatic activity. Several studies to date have identified binding partners of Numb that either regulate or are important in Numb function.

Phosphotyrosine binding domains are structurally conserved domains and are found in proteins that are involved in numerous biological processes such as cellular signaling and receptor trafficking. Generally, PTB domains preferentially bind to specific motifs such as NPXpY, NPXY, NPXF, and NXXF (where X represents any amino acid, p represents phosphorylated). The Numb PTB domain has been shown to interact with an NPXY motif in the integrin β-chain cytoplasmic domain, which has been shown to be important in directing integrin endocytosis at the leading edge of migrating cells. Mutations of Y747 residue in β3 integrin abolish this interaction (Calderwood *et al*. 2003; Nishimura and Kaibuchi 2007). The PTB domain of Numb also mediates an interaction with CRMP2, a mediator of neuronal polarity that regulates axonal growth and branching. The CRMP2-Numb complex has been shown to associate with and regulate the endocytosis and recycling of the neuronal cell adhesion molecule, L1 (Nishimura and Kaibuchi 2007). In *Drosophila*, Numb interacts with Sanpodo, a plasma membrane associated protein that plays a role in the asymmetric cell division (ACD) of sensory organ precursor (SOP) cells by regulating Notch activation (O'Connor-Giles and Skeath 2003; Hutterer and Knoblich 2005). Sanpodo has been shown to interact with Numb through the Numb PTB domain and a NPAF motif in the cytoplasmic tail of Sanpodo (Tong *et al*. 2010; Hutterer and Knoblich 2005). In the presence of Numb, Sanpodo is localized to endocytic vesicles (Tong *et al*. 2010; O'Connor-Giles and Skeath 2003; Hutterer and Knoblich 2005; Roegiers *et al*. 2005). Disruption of the Numb-Sanpodo interaction results in plasma membrane accumulation of Sanpodo (Tong *et al*. 2010; Hutterer and Knoblich 2005). Since no mammalian orthologues for Sanpodo have been identified, this interaction may be specific to *Drosophila* Numb.

Several E3 ubiquitin ligases are known to associate with the PTB domain of Numb, and function in both the endocytic activity of Numb as well as playing a regulatory role in controlling Numb abundance. E3 ubiquitin ligases function as adaptors to transfer ubiquitin to specific protein substrates. A yeast-two hybrid screen identified LNX, a RING finger

containing-E3 ubiquitin ligase that interacts with the PTB domain of Numb through a NPXY motif in a phosphotyrosine independent manner (Dho *et al*. 1998). Although LNX binds to all four mammalian Numb isoforms (Nie *et al*. 2002), only the isoforms containing the eleven amino acid insert region in the PTB domain (mNumbp66, p72) are ubiquitinated and degraded by LNX (Nie *et al*. 2004). Additionally, LNX over-expression has been shown to increase Notch activity, presumably through promoting Numb degradation, thus reducing the ability of mNumb to antagonize Notch (Nie *et al*. 2002). Another E3 ligase, Itch, binds to Numb and promotes the degradation of Notch1 (McGill and McGlade 2003). Notch degradation by Numb-Itch is likely to occur via a mechanism involving endocytic trafficking, as Numb has been shown to inhibit Notch recycling and promote trafficking of Notch to late endocytic compartments, resulting in lysosomal degradation (McGill *et al*. 2009). Siah1 is an E3 ubiquitin ligase that also interacts with the Numb PTB domain and has also been shown to promote the proteosomal degradation of Numb (Susini *et al*. 2001). Finally, the E3 ubiquitin ligase, Mdm2, has been shown to interact with Numb via the PTB domain, although the exact binding site has not been identified (Juven-Gershon *et al*. 1998; Yogosawa *et al*. 2003). Mdm2 is an oncoprotein that has ubiquitin ligase activity towards p53. A recent study suggests that Numb forms a trimeric complex with Mdm2 and p53, subsequently preventing the ubiquitination of p53 and resulting in increased p53 levels (Colaluca *et al*. 2008).

Several protein kinases have also been shown to interact with Numb. The PTB domain is involved in Numb binding to several PKC isozymes and Numb is phosphorylated on several PKC consensus sites (Smith *et al*. 2007). Numb also interacts with AAK1 (Adaptor Associated Kinase) leading to Numb phosphorylation (Sorensen and Conner 2008) although the regions necessary for the interaction have not been mapped (Please see Regulation of Activity section for functional details of this interaction). The *Drosophila* Numb PTB domain binds the AAK1 related serine/threonine kinase, Numb-associated kinase (Nak), which was identified through a yeast-two hybrid screen (Chien *et al*. 1998). dNumb PTB domain binding to Nak is mediated by an 11-amino acid peptide near the carboxy-terminus of Nak that includes an NXXF motif (Chien *et al*. 1998). Numb also interacts with phosphorylated Ca2+/Calmodulin-Dependant Kinase 1 (CaM-KI) (Tokumitsu *et al*. 2005), and while this interaction is not mapped, functional aspects are discussed in the Regulation of Activity section of this review. Phosphorylation of Numb by CaM-KI results in phosphorylation dependent interaction of Numb with multiple 14-3-3 protein isoforms.

The NPF and DPF tripeptide binding motifs at the carboxy-terminal region of all four mNumb isoforms mediate interactions with endocytic proteins. The NPF motif is important for binding of EH domain containing proteins, including Eps15, which help regulate endocytosis and vesicle transport (Salcini *et al*. 1997). A cDNA library screen also identified EHD1 and EHD4 as Numb interactors mediated through the NPF motif (Smith *et al*. 2004). The EHD family of proteins functions to recycle membrane receptors internalized by either clathrin-dependent or clathrin-independent ADP ribosylation factor-6 (Arf6)-mediated endocytic pathway (Caplan *et al*. 2002; D'Souza-Schorey and Chavrier 2006). The carboxy terminal DPF motif of mNumb has been shown to bind the alpha subunit of the AP-2 complex, a major component of clathrin-coated pits (Santolini *et al*. 2000; Dho *et al*. 2006). *Drosophila* Numb has been shown to asymmetrically localize α-adaptin to one pole in dividing SOP cells, and α-adaptin mutants unable to interact with Numb do not asymmetrically localize and show similar cell fate to the Numb mutant phenotype (Berdnik *et al*. 2002). This suggests that Numb may play a role in the localization of endocytic machinery during asymmetric cell divisions or in polarized cells.

PHENOTYPES

Numb was originally identified as a mutation in *Drosophila* causing a loss of neurons during development of the peripheral nervous system (PNS) (Uemura *et al*. 1989). During development of the *Drosophila* sensory organ precursor (SOP) lineage, Numb becomes localized as a cortical crescent prior to cell divisions, and becomes asymmetrically segregated to one daughter cell after division, causing the cell adopting Numb to acquire a different cell fate than its sister cell. Loss of, or ectopic expression of mutant Numb, causes both daughter cells to adopt the same cell fate (Uemura *et al*. 1989; Rhyu *et al*. 1994; Knoblich *et al*. 1995; Spana and Doe 1995).

Studies in *Drosophila* support a model where Numb influences cell fate through the negative regulation of the Notch signaling pathway (Frise *et al*. 1996; Guo *et al*. 1996; Spana and Doe 1996). Although reviewed elsewhere (Artavanis-Tsakonas *et al*. 1999; Allenspach *et al*. 2002; Harper *et al*. 2003; Lai 2004), Notch is an evolutionary conserved cell-surface receptor initially identified in Drosophilia and conserved in vertebrates. Notch signaling plays an important role in controlling cell fate decisions and regulating many developmental processes. Abnormalities in Notch signaling have been linked to both developmental disorders and several cancers. Notch loss-of-function mutations in the developing SOP lineage cause a phenotype similar to overexpression of Numb in the same lineage (Guo *et al*. 1996; Spana and Doe 1996). Thus, evidence in *Drosophila* is suggestive of a model wherein cell fate decisions are influenced by the ability of Numb to antagonize the Notch signaling pathway in one daughter cell. This imbalance of Notch signaling allows the two daughter cells to adopt distinct cell fates, a process critical to normal development (Frise *et al*. 1996; Guo *et al*. 1996; Spana and Doe 1996; Zhong *et al*. 1996; Ruiz Gomez and Bate 1997).

Mammalian orthologues of Numb have been identified, suggesting that Numb has an evolutionarily conserved function (Verdi *et al*. 1996; Zhong *et al*. 1996). Mammalian Numb has been reported to be asymmetrically distributed in mitotic neural progenitors in the mouse forebrain (Zhong *et al*. 1996), retinal precursors (Cayouette *et al*. 2001), dividing T-cells (Chang *et al*. 2007), and isolated cortical progenitor cells (Shen *et al*. 2002). Ectopic overexpression of mammalian Numb in *Drosophila* can rescue the *Drosophila* Numb-/- phenotype, and results in a similar phenotype to overexpression of *Drosophila* Numb (Zhong *et al*. 1996). Additionally, when ectopically expressed in *Drosophila*, mammalian Numb appears asymmetrically localized in PNS progenitor cells, further suggestive of conservation between the species (Zhong *et al*. 1996).

Homozygous deletion of Numb in mice leads to embryonic lethality at E11.5, and although the cause of death is unknown, severe defects in the central nervous system (CNS) have been observed (Zhong *et al*. 2000; Zilian *et al*. 2001). At E9.5, defects in neural tube closure, vascularization, and placental dysfunction are observed (Zhong *et al*. 2000; Zilian *et al*. 2001).

A model generated by Peterson *et al* (Petersen *et al*. 2002), demonstrated that Nbl knockout mice appear normal, however loss of both Nbl and Numb is lethal at E9.5, suggesting that the function of these genes may partially overlap. Peterson *et al* (Petersen *et al*. 2002) conditionally knocked out Numb (on a Nbl-/- background) in neural cells by nestin-Cre-mediated excisions (around E8.5), and observed a significant loss of neural progenitor cells. These observations suggested that Numb plays a role in maintaining the neural progenitor pool during embryogenesis by promoting progenitor over neuronal cell fate. Li *et al* (Li *et al*. 2003) generated a mouse model with restricted inactivation of Numb in the dorsal forebrain (on Nbl-/- background, around E9.5-E12.5), and observed neural progenitor hyper-proliferation, delayed cell cycle exit, and impaired neuronal differentiation. More recently, Rasin *et al* (Rasin *et al*. 2007) showed that Numb associates with adherens junctions and co-localizes and with a cadherin-catenin adhesion complex (E-Cadherin, N-Cadherin , catenin α1, and β-catenin) in the apical end-feet of radial glial cells (RGCs). Inactivation of Numb in RGCs disrupted cell polarity and adhesion junctions that are important for the maintenance of the nuerogenic niche. Thus, Numb appears to play diverse roles in neural development regulating cell adhesion and polarity of neural progenitors, and this role may be distinct from its influence on cell fate presumably by affecting signaling, though this has yet to be demonstrated.

MAJOR SITES OF EXPRESSION

Mammalian Numb proteins are widely expressed during embryogenesis and in most adult tissues (Zhong *et al*. 1996; Verdi *et al*. 1999; Zilian *et al*. 2001). Northern blot analysis has revealed Numb expression in the rat spleen, thymus, prostate, testis, uterus, small intestine, colon, peripheral blood leukocytes, heart, brain, liver, and kidney (Verdi *et al*. 1996; Verdi *et al*. 1999). There are four major isoforms of Numb, and it has been shown that the isoforms are differentially expressed in mouse tissues and cell lines (Dho *et al*. 1999; please see section on splice variants for detailed description of Numb alternative splicing and isoform expression). Briefly, proteins lacking the exon 3 insert are found in all tissues, while proteins including the exon 3 insert are limited to the lung with lesser amounts found in the brain testis, thymus and embryo. In adult tissues, Numb isoforms containing the exon 9 insert were constrained to the testis (Dho *et al*. 1999).

SPLICE VARIANTS

While there are no splice variants in *Drosophila*, mammalian Numb mRNA is alternatively spliced at coding exons 3 and 9 to generate four proteins of distinct molecular mass (72kDa, 71kDa, 66kDa, 65kDa) (Dho *et al*. 1999; Verdi *et al*. 1999). The inclusion of exon 3 results in an insertion of an eleven amino acids within the PTB domain (PTBi), while inclusion of exon 9 results in the insertion of a forty-eight amino acids in the proline-rich region (PRRi) of Numb (Dho *et al*. 1999; Verdi *et al*. 1999). The Numb isoforms are developmentally regulated and appear to have distinct biological effects.

Exon 3 Inclusion:

One difference observed between Numb isoforms containing the 11 amino acid insert and the isoforms lacking it, is subcellular localization. While all isoforms of Numb are able to bind membrane phospholipids, Exon 3 included isoforms bind more efficiently to PI(4)P and localize to the plasma membrane, while proteins that lack this insert are predominantly cytosolic (Dho *et al*. 1999). In addition to localization, inclusion of the PTB insert region has been shown to modulate other signaling events. For example, a Numb interacting protein, Ligand-of-Numb-Protein X (LNX), an E3 ubiquitin ligase has the ability to bind both exon 3 included and excluded isoforms of Numb, but only poly-ubiquitinates the exon 3 included isoform (Dho *et al*. 1998; Nie *et al*. 2002; Nie *et al*. 2004). Another study investigated the effect of Numb isoforms in response to stimulation with nerve growth factor (NGF) in PC12 cells and concluded that Numb protein lacking exon 3 responds to NGF to enhance differentiation and regulated NGF signaling pathways, while Numb protein including the exon 3 insert does not (Pederson *et al*. 2002). Finally, although the biological role of the Numb-amyloid precursor protein (APP) interaction is unknown, a study has shown that cells expressing the Numb isoforms lacking the PTB insert accumulate APP in early endosomes, while expression of Numb isoforms including the PTB insert resulted in reduced amounts of APP compared to control cells (Kyriazis *et al*. 2008).

Exon 9 Inclusion:

In P19 cells, expression of Numb containing the exon 9 insert sharply decreases after cellular differentiation is induced by retinoic-acid (Dho *et al*. 1999). Consistent with these observations, it has been shown in embryonic mouse brain, that exon 9 included isoforms are expressed starting at E7, peaking at E10, and becoming virtually undetectable at E13, the point at which neural progenitors undergo peak differentiation into neurons (Verdi *et al*. 1999). During mouse neurodevelopment, exon 9 included isoforms are predominant in undifferentiated cortical progenitors. However, during differentiation an isoform switch to the exon 9 excluded form occurs (Bani-Yaghoub *et al*. 2007). This expression pattern is consistent with observations by Yoshida *et al* (Yoshida *et al*. 2003). During mouse pancreatic development, both exon 9 included and excluded isoforms are present during early stages of development (E10.5). However, at E12.5 when the endocrine and exocrine pancreas diverge, the exon 9 excluded remains expressed while a decrease in exon 9 included forms is observed. Similarly, during retinal development, p71/p72 (PRRi) isoforms are expressed highly during neurogenesis, but at very low levels during the later stages of development (Dooley *et al*. 2003). Finally, a recent paper (Misquitta-Ali *et al*. 2011) showed that alternative splicing of Numb is significantly increased in human tumour samples, and that exon 9 inclusion is observed in human lung, breast and colon cancers. In comparison, exon 9 is predominantly excluded in normal tissues.

REGULATION OF CONCENTRATION

Regulation of Numb concentration in cells is achieved by ubiquitin-dependant proteolytic degradation. Numb interacts with the Ligand-of-Numb-Protein-X (LNX), a RING finger E3 ubiquitin ligase (Nie *et al*. 2002). LNX, through its interaction with the PTB domain of Numb, targets the p66 and the p72 isoforms for ubiquitination and subsequent proteasomal degradation (Nie *et al*. 2002; Nie *et al*. 2004).

The C-terminal portion of the Numb PTB domain is also responsible for an interaction with another E3 ubiquitin ligase, Siah1 (Susini *et al*. 2001). Siah1 is the mammalian homologue of *Drosophila* Sina (Seven in absentia) and has been shown to promote the proteasomal degradation of Numb (Susini *et al*. 2001).

Finally, a yeast two hybrid screen identified Mdm2 as a Numb

PTB domain interacting protein (Juven-Gershon *et al*. 1998). Mdm 2 is a RING finger ubiquitin ligase that targets p53 for ubiquitin-dependant protein degradation (Fang *et al*. 2000), and has also been shown to also target Numb for proteasomal degradation (Susini *et al*. 2001).

At the translational level, one study has shown that Numb is a target of Musashi 1 (Msi1). Msi1 is an RNA binding protein that acts to repress translation of specific mRNAs (Imai *et al*. 2001). Msi1 has been shown to be stably expressed in fetal and adult neural stem cells, and to play a role in regulation of ACD, likely by promoting Notch signaling though repression of Numb (Okano *et al*. 2005). Msi1 binds Numb mRNA in its 3' untranslated region (UTR) leading to repressed translation (Imai *et al*. 2001). A recent study has shown that the related Musashi 2 (Msi2) also regulates Numb expression in a Chronic Myelogenous Leukemia mouse model, and this loss of Numb promotes a transformation of CML from a chronic stable phase to an aggressive blast phase (Ito *et al*. 2010).

ANTIBODIES

Both monoclonal and polyclonal antibodies to Numb are available from numerous commercial suppliers. Furthermore, a host of antibodies have been generated by research groups, for example: (Verdi *et al*. 1996; Dho *et al*. 1999; Santolini *et al*. 2000, Uemura *et al*., 1989 ; Qin *et al*. 2004)

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
Numb	Unknown	
Numb-PS7	Unknown	Nishimura T and Kaibuchi K 2007; Smith CA *et al.* 2007
Numb-PS295	Unknown	Smith CA *et al.* 2007; Nishimura T and Kaibuchi K 2007; Tokumitsu H *et al.* 2006
Numb-PS276	Unknown	Nishimura T and Kaibuchi K 2007; Tokumitsu H *et al.* 2005
Numb-PT102	Unknown	Sorensen EB and Conner SD 2008
Numb-Ub	Unknown	
Numb/AAK1	Unknown	Sorensen EB and Conner SD 2008
Numb/Eps15	endocytic vesicle	Salcini AE *et al.* 1997
Numb/AP2	endocytic vesicle	Santolini E *et al.* 2000; Dho SE *et al.* 2006
Numb/Lnx1	Unknown	Dho SE *et al.* 1998; Nie J *et al.* 2002
Numb/Lnx2	Unknown	Nie J *et al.* 2002; Rice DS *et al.* 2001
Numb/EHD1	endocytic vesicle	Smith CA *et al.* 2004
Numb/EHD4	endocytic vesicle	Smith CA *et al.* 2004
Numb/Mdm2	Unknown	Juven-Gershon T *et al.* 1998; Yogosawa S *et al.* 2003
Numb/Itch	Unknown	McGill MA and McGlade CJ 2003
Numb/Notch	Unknown	Guo M *et al.* 1996; Zhong W *et al.* 1996
Numb/Siah1	Unknown	Susini L *et al.* 2001
Numb/RalBP1	Unknown	Rossé C *et al.* 2003
Numb/Amyloid Beta Precursor Protein	Unknown	Roncarati R *et al.* 2002
Numb/CRMP-2	growth cone	Nishimura T *et al.* 2003
Numb/Numb Associated Kinase	Unknown	Chien CT *et al.* 1998
Numb/p53/MDM2	Unknown	Colaluca IN *et al.* 2008
Numb/Intersectin	Unknown	Nishimura T *et al.* 2006
Numb/14-3-3	Unknown	Tokumitsu H *et al.* 2005; Tokumitsu H *et al.* 2006
Numb/Camk1	Unknown	Tokumitsu H *et al.* 2005; Tokumitsu H *et al.* 2006
Numb/Beta Integrins	Unknown	Calderwood DA *et al.* 2003; Nishimura T and Kaibuchi K 2007
Numb/aPKC	Unknown	Smith CA *et al.* 2007
Numb/ACBD3	cytosol	Zhou Y *et al.* 2007

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 28 states , has 29 transitions between these states and has 0 enzyme functions.(Please zoom in the pdf file to view details.)