Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

NUMB (numb homolog (Drosophila))

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Identity

Other names: S171

HGNC (Hugo): NUMB

Location: 14q24.2

DNA/RNA

Description

The NUMB locus spans 183368 bp on the minus (-) strand of the long arm of chromosome 14 and is composed of 13 exons.

Transcription

As a result of three alternative splicing events the NUMB locus can generate six different transcripts of 3647 bp (isoform 1), 3503 bp (isoform 2), 3614 bp (isoform 3) and of 3470 bp (isoform 4); isoforms 5 and 6 are only partial and cover only the coding sequence and their representation* is putative.

Pseudogene

No known pseudogenes.

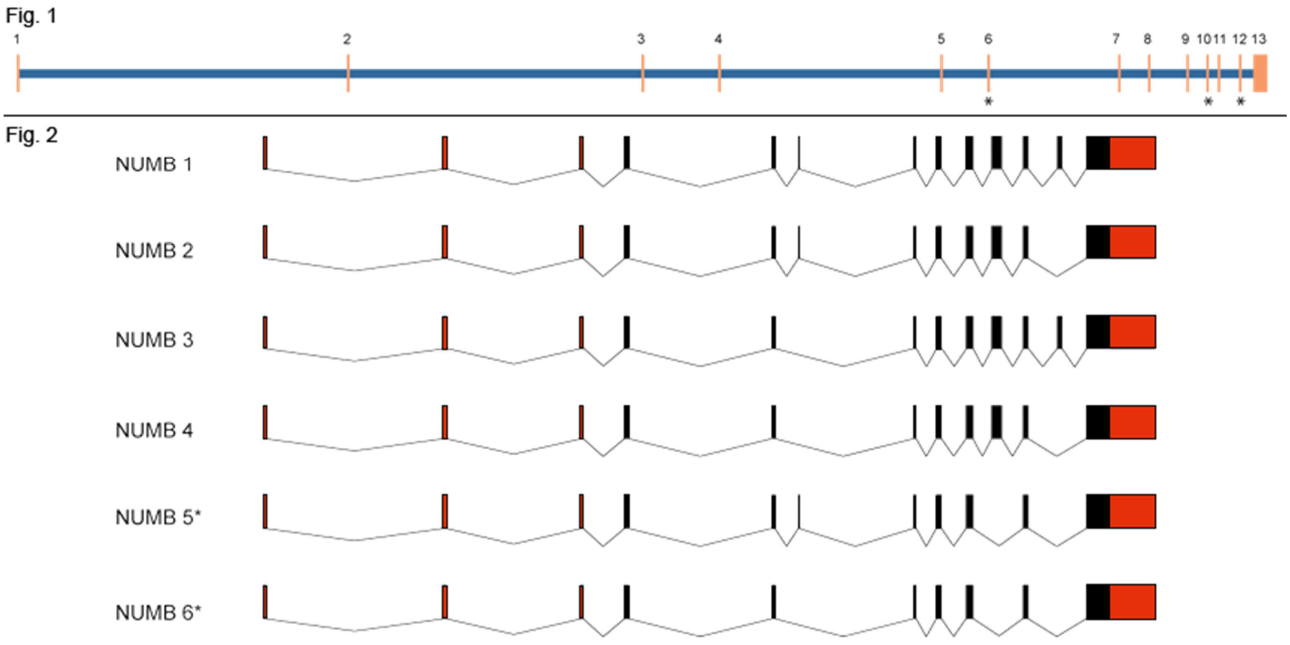
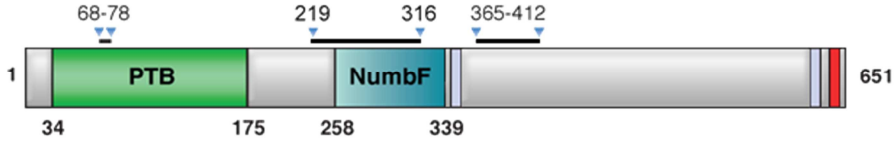


Figure 1: Structure of NUMB gene. Asterisks indicate exons that undergo alternative splicing during NUMB transcript maturation.



The modular structure of the longest human Numb isoform is shown.

Protein

Description

The human Numb gene is transcribed in 6 different splicing variants (see above), due to the alternate skipping of three exons. Arrowheads indicate the boundaries of the protein sequences encoded by the three alternative exons. The PTB (Phospho-Tyrosine Binding) domain and the NumbF domain (domain found in the Numb family of proteins adjacent to the PTB domain) are indicated. The position of the DPF (responsible for binding to alpha-adaptin) and NPF motifs (responsible for binding to the EH domain of endocytic proteins) are indicated as gray and red boxes respectively.

Expression

From an in-silico analysis Numb RNA messenger seems broadly expressed in human tissues. However in mouse and drosophila it has been demonstrated that isoforms 1 to 4 are expressed in a tissue-specific and developmental stage-specific manner.

Localisation

Mostly cytosolic partially associated to the plasma membrane and vesicles; may be found also in the nucleus.

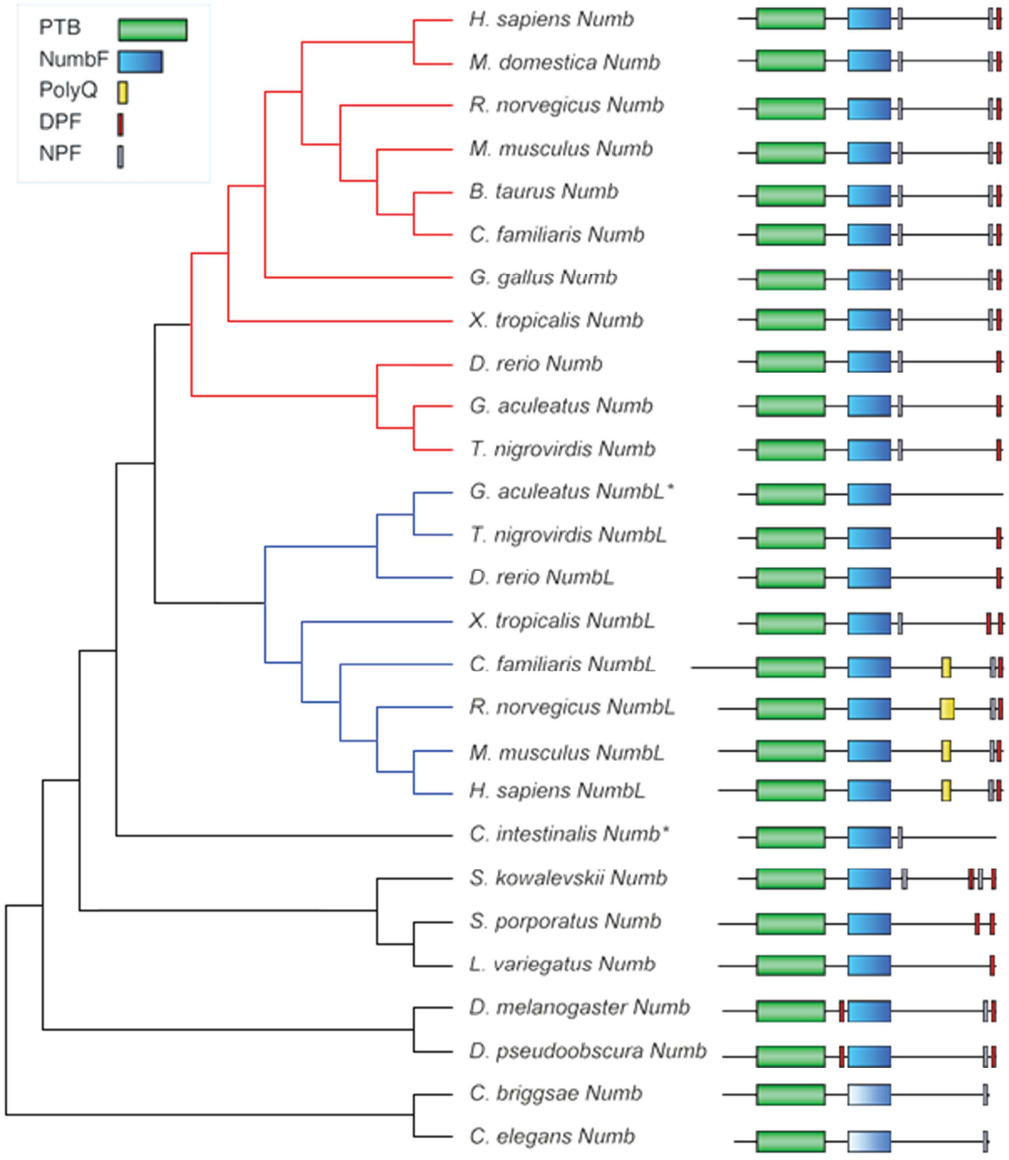
Function

Numb plays a multifaceted role in cellular homeostasis and is implicated in a variety of biochemical pathways connected with signaling, endocytosis, determination of polarity and ubiquitination. The pleiotropic biochemical functions of Numb lie at the heart of its involvement in diverse physiological processes, including cell fate developmental decisions, maintenance of the homeostasis of stem cell compartments, regulation of cell polarity, adhesion and migration. Loss of Numb is implicated in different types of human cancers, underscoring its complex function as a tumor suppressor in normal tissue homeostasis. The role of Numb as an intrinsic molecular determinant of cell fate during developmental programs is inextricably intertwined with the execution of asymmetric mitotic divisions, that is the mechanism through which a mother cell generates two daughter cells with different fates. The unequal distribution of Numb between two daughter cells causes a biochemical asymmetry of pathways epistatically regulated by Numb, a condition epitomized by the differential regulation of the Notch circuitry in the two daughter cells derived from the asymmetric mitotic division of the sensory organ precursor (SOP) in drosophila neurogenesis. This mechanism appears to be conserved between flies and mammals. Numb is involved at different levels in the process of endocytosis and intracellular trafficking. It interacts with the EH domain of several endocytic proteins, such as Eps15 and Eps15R, and with the major clathrin adaptor AP-2, and is subcellularly localized in endocytic/recycling organelles. Numb is also required for the internalization and recycling of transmembrane proteins, such as Sanpodo in drosophila, and different types of integrins or other transmembrane molecules in mammals.The role of Numb in the regulation of cell polarity is exerted through its interaction with core components of the evolutionary conserved Par3/Par6/aPKC (PAR) complex, and through the regulation of adherens and tight junctions. At the biochemical level, Numb is endowed with pleiotropic signaling functions. In fact, besides intersecting the Notch pathway, Numb also modulates the Hedgehog and the p53 circuitry. In general terms, the role of Numb in the regulation of specific molecular pathways is a function of a number of liaisons between Numb itself and components of the ubiquitin/proteasomal machinery. For instance, the interaction of Numb with the E3-ubiquitin ligase Itch is required for the Itch-dependent ubiquitination and ensuing proteasomal degradation of Notch. Likewise, the Numb/Itch interaction is a prerequisite for targeting Itch to the transcription factor Gli1, which ultimately affects Gli1 stability and therefore suppresses Hedgehog signaling. Furthermore, the ability of Numb to bind and inhibit the E3-ligase Hdm2 (Mdm2 in mouse) protects p53 from Hdm2-mediated ubiquitination and consequent proteasomal degradation, thus resulting in a positive regulation of the cellular levels of p53 and of its tumor suppressor activity. The downregulatory function of Numb over Hdm2 occurs in the context of a Numb/p53/Hdm2 tricomplex. Loss of this regulatory circuitry results in impaired p53-mediated cellular responses, such as apoptosis, DNA-damage and cell cycle checkpoint activation response, and is relevant to the intrinsic resistance of Numb-defective breast cancers to genotoxic agents. The networking of Numb into ubiquitin-based circuitries appears also to be at the heart of the regulation of cellular Numb levels in homeostasis. E3-ubiquitin ligases, such as Siah1 and LNX, have been implicated in targeting Numb for ubiquitin-dependent degradation. Ubiquitin-based biochemical pathways that regulate Numb levels under physiological conditions are likely relevant to cancer as

well since, both in breast and in lung Numb-defective tumors, loss of Numb is due to its exaggerated ubiquitination and degradation. Considering its pleiotropic functions in many critical cellular processes, subversion of Numb has been linked to important human pathologies, and in particular to cancer.

Homology

Numb appears in evolution roughly with bilateral animals. Mammalian Numb homologues evolved from a common ancestral gene, possibly owing to gene duplication followed by the divergence of two gene families, Numb and Numbl. In the tree, mammalian Numb and NumbL formed two distinct clusters. A gene duplication of the ancestral Numb gene may be occurred prior to the appearance and the divergence of the major vertebrate clades, since one Numb gene is present in the chordate Ciona intestinalis, and one of the two duplicated genes evolved into NumbL via the acquisition of two Numbl unique motifs. Two of the known cellular functions to which Numb participates, endocytosis and ubiquitination, have ancient origins. Endocytosis is widely held to represent one of the distinguishing features between eukaryotes and prokaryotes. There is evidence that endocytosis is present as far back as the last eukaryotic common ancestor. In actual fact, endocytosis might be even older than this, as recent evidence demonstrates that: i) bacteria of the phyla Planctomycetes and Verrucomicrobia display intracellular membranous compartmentalization, and have membrane coat-like proteins; ii) the planctomycete Gemmata obscuriglobus exhibits endocytic-like protein uptake. Similarly, while ubiquitination is certainly one of the distinctive, and highly conserved, features of eukaryotes, its ancestry can now be traced back to bacteria,



Numb in evolution. The phylogenesis of Numb in bilateral animals is shown.

both in terms of ubiquitin-like molecules and of enzymatic molecular machinery. By the time Numb appears in phylogenesis, endocytosis and ubiquitination are already cornerstones of the eukaryotic make-up that are deeply interconnected. It is unlikely, therefore, that Numb might have evolved in direct conjunction with these processes. At the same time, the appearance of Numb roughly coincides with the appearance of the PAR complex. While polarity is perhaps as old as cellular life, a clear existence of proteins of the PAR complex can be traced back in animals only until roughly 500 million years ago, probably with the emergence of ancestors of bilateral animals (e.g., nematodes, flies and mammals). It is possible therefore that Numb evolved (or co-evolved) together with the PAR complex. Regardless, Numb might represent (and might have evolved to be) a critical connector between polarization and endocytosis. Thus, Numb might have evolved with an original role in polarity, but because of its membrane location might have subsequently acquired additional roles in the connected endocytic/ubiquitin networks: acting as a go-between between these networks and the hardware of polarity, as well as participating in them in a polarity-independent fashion.

Mutations

Germinal

None found.

Somatic

Two mutations are reported in the COSMIC database, both of them are silent mutations:
- c.1452G>T (Substitution), p.G484G (Substitution - coding silent) in one out of 447 glioma samples screened.
- c.354C>T (Substitution), p.A118A (Substitution - coding silent) in one out of 6 malignant melanoma samples screened.

Implicated in

Breast cancer

Prognosis

Loss of Numb in breast cancer correlates with poor prognosis and with clinico/pathological parameters of biological aggressiveness, such as a poorly differentiated tumor phenotype (high grade), high proliferative index (Ki67 expression), a basal-like phenotype and expression of cancer stem cell markers.

Oncogenesis

Numb is a tumor suppressor in the human mammary gland and its expression is frequently lost in breast cancer. Numb-defective breast tumors are addicted to loss of Numb, as witnessed by the loss of their proliferative advantage caused by re-expression of Numb. In these tumors, loss of Numb results in overactivation of oncogenic Notch signaling and impaired tumor suppression function of p53, two molecular events that are causal for transformation. Loss of Numb expression in breast cancer is due to its exaggerated ubiquitination and ensuing proteasomal degradation.

Lung cancer

Oncogenesis

The expression of Numb is frequently lost in non-small cell lung cancer (NSCLC). In NSCLC, loss of Numb results in enhanced activation of the Notch pathway, and addiction of these tumors to deregulated Notch activity. Likewise breast cancer, loss of Numb in NSCLCs is due to enhanced destruction of this protein through the proteasomal machinery.

Salivary gland cancer

Prognosis

Reduced Numb levels correlate with poor prognosis and with clinico/pathological parameters of biological aggressiveness (high grade and proliferative index) in salivary gland carcinomas. The molecular mechanism underlying loss of Numb in these tumors are not yet defined.

Chronic myelogenous leukemia

Oncogenesis

In a mouse model of chronic myelogenous leukemia (CML), Ito et al. found that reduced Numb expression is necessary for the establishment of blast crisis. A molecular mechanism different from enhanced proteasomal degradation appears to be involved in reduced Numb expression during CML progression, which is represented by the high levels of Musashi2, a repressor of Numb translation. An upregulation of Musashi2 expression was found in human CML patients during disease progression towards blast crisis, concomitant to downregulation of numb expression.

References

Uemura T, Shepherd S, Ackerman L, Jan LY, Jan YN. numb, a gene required in determination of cell fate during sensory organ formation in Drosophila embryos. Cell. 1989 Jul 28;58(2):349-60

Rhyu MS, Jan LY, Jan YN. Asymmetric distribution of numb protein during division of the sensory organ precursor cell confers distinct fates to daughter cells. Cell. 1994 Feb 11;76(3):477-91

Spana EP, Kopczynski C, Goodman CS, Doe CQ. Asymmetric localization of numb autonomously determines sibling neuron identity in the Drosophila CNS. Development. 1995 Nov;121(11):3489-94

Guo M, Jan LY, Jan YN. Control of daughter cell fates during asymmetric division: interaction of Numb and Notch. Neuron. 1996 Jul;17(1):27-41

Spana EP, Doe CQ. Numb antagonizes Notch signaling to specify sibling neuron cell fates. Neuron. 1996 Jul;17(1):21-6

Verdi JM, Schmandt R, Bashirullah A, Jacob S, Salvino R, Craig CG, Program AE, Lipshitz HD, McGlade CJ. Mammalian

NUMB is an evolutionarily conserved signaling adapter protein that specifies cell fate. Curr Biol. 1996 Sep 1;6(9):1134-45

Ruiz Gómez M, Bate M. Segregation of myogenic lineages in Drosophila requires numb. Development. 1997 Dec;124(23):4857-66

Salcini AE, Confalonieri S, Doria M, Santolini E, Tassi E, Minenkova O, Cesareni G, Pelicci PG, Di Fiore PP. Binding specificity and in vivo targets of the EH domain, a novel protein-protein interaction module. Genes Dev. 1997 Sep 1;11(17):2239-49

Zhong W, Jiang MM, Weinmaster G, Jan LY, Jan YN. Differential expression of mammalian Numb, Numblike and Notch1 suggests distinct roles during mouse cortical neurogenesis. Development. 1997 May;124(10):1887-97

Juven-Gershon T, Shifman O, Unger T, Elkeles A, Haupt Y, Oren M. The Mdm2 oncoprotein interacts with the cell fate regulator Numb. Mol Cell Biol. 1998 Jul;18(7):3974-82

Park M, Yaich LE, Bodmer R. Mesodermal cell fate decisions in Drosophila are under the control of the lineage genes numb, Notch, and sanpodo. Mech Dev. 1998 Jul;75(1-2):117-26

Dho SE, French MB, Woods SA, McGlade CJ. Characterization of four mammalian numb protein isoforms. Identification of cytoplasmic and membrane-associated variants of the phosphotyrosine binding domain. J Biol Chem. 1999 Nov 12;274(46):33097-104

Verdi JM, Bashirullah A, Goldhawk DE, Kubu CJ, Jamali M, Meakin SO, Lipshitz HD. Distinct human NUMB isoforms regulate differentiation vs. proliferation in the neuronal lineage. Proc Natl Acad Sci U S A. 1999 Aug 31;96(18):10472-6

Wakamatsu Y, Maynard TM, Jones SU, Weston JA. NUMB localizes in the basal cortex of mitotic avian neuroepithelial cells and modulates neuronal differentiation by binding to NOTCH-1. Neuron. 1999 May;23(1):71-81

Santolini E, Puri C, Salcini AE, Gagliani MC, Pelicci PG, Tacchetti C, Di Fiore PP. Numb is an endocytic protein. J Cell Biol. 2000 Dec 11;151(6):1345-52

Zhong W, Jiang MM, Schonemann MD, Meneses JJ, Pedersen RA, Jan LY, Jan YN. Mouse numb is an essential gene involved in cortical neurogenesis. Proc Natl Acad Sci U S A. 2000 Jun 6;97(12):6844-9

Susini L, Passer BJ, Amzallag-Elbaz N, Juven-Gershon T, Prieur S, Privat N, Tuynder M, Gendron MC, Israël A, Amson R, Oren M, Telerman A. Siah-1 binds and regulates the function of Numb. Proc Natl Acad Sci U S A. 2001 Dec 18;98(26):15067-72

Vecchi M, Polo S, Poupon V, van de Loo JW, Benmerah A, Di Fiore PP. Nucleocytoplasmic shuttling of endocytic proteins. J Cell Biol. 2001 Jun 25;153(7):1511-7

Berdnik D, Török T, González-Gaitán M, Knoblich JA. The endocytic protein alpha-Adaptin is required for numb-mediated asymmetric cell division in Drosophila. Dev Cell. 2002 Aug;3(2):221-31

Nie J, McGill MA, Dermer M, Dho SE, Wolting CD, McGlade CJ. LNX functions as a RING type E3 ubiquitin ligase that targets the cell fate determinant Numb for ubiquitin-dependent degradation. EMBO J. 2002 Jan 15;21(1-2):93-102

Shen Q, Zhong W, Jan YN, Temple S. Asymmetric Numb distribution is critical for asymmetric cell division of mouse cerebral cortical stem cells and neuroblasts. Development. 2002 Oct;129(20):4843-53

Li HS, Wang D, Shen Q, Schonemann MD, Gorski JA, Jones KR, Temple S, Jan LY, Jan YN. Inactivation of Numb and Numblike in embryonic dorsal forebrain impairs neurogenesis and disrupts cortical morphogenesis. Neuron. 2003 Dec 18;40(6):1105-18

McGill MA, McGlade CJ. Mammalian numb proteins promote Notch1 receptor ubiquitination and degradation of the Notch1 intracellular domain. J Biol Chem. 2003 Jun 20;278(25):23196-203

O'Connor-Giles KM, Skeath JB. Numb inhibits membrane localization of Sanpodo, a four-pass transmembrane protein, to promote asymmetric divisions in Drosophila. Dev Cell. 2003 Aug;5(2):231-43

Yogosawa S, Miyauchi Y, Honda R, Tanaka H, Yasuda H. Mammalian Numb is a target protein of Mdm2, ubiquitin ligase. Biochem Biophys Res Commun. 2003 Mar 21;302(4):869-72

Yoshida T, Tokunaga A, Nakao K, Okano H. Distinct expression patterns of splicing isoforms of mNumb in the endocrine lineage of developing pancreas. Differentiation. 2003 Oct;71(8):486-95

Pece S, Serresi M, Santolini E, Capra M, Hulleman E, Galimberti V, Zurrida S, Maisonneuve P, Viale G, Di Fiore PP. Loss of negative regulation by Numb over Notch is relevant to human breast carcinogenesis. J Cell Biol. 2004 Oct 25;167(2):215-21

Bhalerao S, Berdnik D, Török T, Knoblich JA. Localization-dependent and -independent roles of numb contribute to cell-fate specification in Drosophila. Curr Biol. 2005 Sep 6;15(17):1583-90

Huang EJ, Li H, Tang AA, Wiggins AK, Neve RL, Zhong W, Jan LY, Jan YN. Targeted deletion of numb and numblike in sensory neurons reveals their essential functions in axon arborization. Genes Dev. 2005 Jan 1;19(1):138-51

Di Marcotullio L, Ferretti E, Greco A, De Smaele E, Po A, Sico MA, Alimandi M, Giannini G, Maroder M, Screpanti I, Gulino A. Numb is a suppressor of Hedgehog signalling and targets Gli1 for Itch-dependent ubiquitination. Nat Cell Biol. 2006 Dec;8(12):1415-23

Toriya M, Tokunaga A, Sawamoto K, Nakao K, Okano H. Distinct functions of human numb isoforms revealed by misexpression in the neural stem cell lineage in the Drosophila larval brain. Dev Neurosci. 2006;28(1-2):142-55

Bani-Yaghoub M, Kubu CJ, Cowling R, Rochira J, Nikopoulos GN, Bellum S, Verdi JM. A switch in numb isoforms is a critical step in cortical development. Dev Dyn. 2007 Mar;236(3):696-705

Maiorano E, Favia G, Pece S, Resta L, Maisonneuve P, Di Fiore PP, Capodiferro S, Urbani U, Viale G. Prognostic implications of NUMB immunoreactivity in salivary gland carcinomas. Int J Immunopathol Pharmacol. 2007 Oct-Dec;20(4):779-89

Nishimura T, Kaibuchi K. Numb controls integrin endocytosis for directional cell migration with aPKC and PAR-3. Dev Cell. 2007 Jul;13(1):15-28

Wang H, Ouyang Y, Somers WG, Chia W, Lu B. Polo inhibits progenitor self-renewal and regulates Numb asymmetry by phosphorylating Pon. Nature. 2007 Sep 6;449(7158):96-100

Colaluca IN, Tosoni D, Nuciforo P, Senic-Matuglia F, Galimberti V, Viale G, Pece S, Di Fiore PP. NUMB controls p53 tumour suppressor activity. Nature. 2008 Jan 3;451(7174):76-80

Nilsson L, Conradt B, Ruaud AF, Chen CC, Hatzold J, Bessereau JL, Grant BD, Tuck S. Caenorhabditis elegans num-1 negatively regulates endocytic recycling. Genetics. 2008 May;179(1):375-87

Sorensen EB, Conner SD. AAK1 regulates Numb function at an early step in clathrin-mediated endocytosis. Traffic. 2008 Sep;9(10):1791-800

Jory A, Le Roux I, Gayraud-Morel B, Rocheteau P, Cohen-Tannoudji M, Cumano A, Tajbakhsh S. Numb promotes an increase in skeletal muscle progenitor cells in the embryonic somite. Stem Cells. 2009 Nov;27(11):2769-80

Westhoff B, Colaluca IN, D'Ario G, Donzelli M, Tosoni D, Volorio S, Pelosi G, Spaggiari L, Mazzarol G, Viale G, Pece S, Di Fiore PP. Alterations of the Notch pathway in lung cancer. Proc Natl Acad Sci U S A. 2009 Dec 29;106(52):22293-8

Bresciani E, Confalonieri S, Cermenati S, Cimbro S, Foglia E, Beltrame M, Di Fiore PP, Cotelli F. Zebrafish numb and numblike are involved in primitive erythrocyte differentiation. PLoS One. 2010 Dec 13;5(12):e14296

Gulino A, Di Marcotullio L, Screpanti I. The multiple functions of Numb. Exp Cell Res. 2010 Apr 1;316(6):900-6

Ito T, Kwon HY, Zimdahl B, Congdon KL, Blum J, Lento WE, Zhao C, Lagoo A, Gerrard G, Foroni L, Goldman J, Goh H, Kim SH, Kim DW, Chuah C, Oehler VG, Radich JP, Jordan CT, Reya T. Regulation of myeloid leukaemia by the cell-fate determinant Musashi. Nature. 2010 Aug 5;466(7307):765-8

Kyriazis GA, Belal C, Madan M, Taylor DG, Wang J, Wei Z, Pattisapu JV, Chan SL. Stress-induced switch in Numb isoforms enhances Notch-dependent expression of subtype-specific transient receptor potential channel. J Biol Chem. 2010 Feb 26;285(9):6811-25

Rennstam K, McMichael N, Berglund P, Honeth G, Hegardt C, Rydén L, Luts L, Bendahl PO, Hedenfalk I. Numb protein expression correlates with a basal-like phenotype and cancer stem cell markers in primary breast cancer. Breast Cancer Res Treat. 2010 Jul;122(2):315-24

Pece S, Confalonieri S, R Romano P, Di Fiore PP. NUMB-ing down cancer by more than just a NOTCH. Biochim Biophys Acta. 2011 Jan;1815(1):26-43

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