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MAGI Scaffolding Molecules Involved in Cancer Cell Signaling

Satoru Matsuda* **and Yasuko Kitagishi**

Department of Food Science and Nutrition, Nara Women's University, Japan

Abstract

PTEN is a tumor suppressor gene inactivated in various human cancers, which antagonizes PI3K activity. The PI3K/AKT pathway is frequently activated in cancer, then, the PTEN tumor suppressor may be the major brake of the pathway. Cells that lack functional PTEN gene have constitutively higher levels of PIP3 and activated downstream targets. The PTEN protein binds to the MAGI proteins (MAGIs), which are scaffolding molecules with PDZ domain involved in the regulation of epithelial cell tight-junction assembly. Studies have revealed the potential relevance of the PDZ interactions to cancer cell behaviors. The molecular mechanisms contributing to cancer invasion are the subject of considerable investigation, as a better understanding of the pathogenesis will lead to the development of novel targeted therapies. We review recent studies on the features of PTEN and MAGIs in the signaling pathways involved in cancer progression.

Keywords: Cancer; MAGI proteins; PI3K; AKT; PTEN; Cell signaling

Abbreviations: ATF2: Activating Transcription Factor 2; GAP: GTPase-Activating Protein; mTOR: Mammalian Target of Rapamycin; MAGI: Membrane Associated Guanylate Kinase Inverted; MAGUK: Membrane-Associated Guanylate Kinase; NF-κB: Nuclear Factor κB;PDK: Phosphoinositide-Dependent Kinase; PH: Plekstrin Homology; PIP2: Phosphatidylinositol 4,5-Bisphosphate; PIP3: Phosphatidylinositol 3,4,5-Triphosphate; PI3K: Phosphatidylinositol-3 Kinase; PTEN: Phosphatase and Tensin Homologue Deleted on Chromosome 10; PTP: Protein Tyrosine Phosphatase; TNF-α: Tumor Necrosis Factor- alpha; TSC: Tuberous Sclerosis Complex

Introduction

The PI3K/AKT pathway has been shown to play a pivotal role on the initiation and progression of malignancies, enhancing cell survival by stimulating cell proliferation, and inhibiting apoptosis [1,2] (Figure 1). PTEN modulates the PI3K/AKT pathway in cancers within a tumor suppressor network. The tumor suppressor *PTEN* (phosphatase and tensin homolog deleted in chromosome 10) is deleted or mutated in a variety of human cancers [3,4]. The implication of PTEN in carcinogenesis has been substantiated by the spontaneous development of tumors in *PTEN* deficient mice [5]. The PTEN interacts with PDZ domain-containing molecules including MAGI proteins (MAGIs), which are scaffolding molecules involved in the regulation of tight-junction assembly and are then involved in diverse regulatory pathways including the control of cell-attachment [6]. PDZ domains are modular protein interaction domains that bind in a sequence-specific manner to peptides that fold in a beta-finger. The PTEN cooperates with MAGIs to block the PI3K/AKT signaling pathway. In addition, PTEN plays a critical role in MAGIs-induced inhibition of cell migration and proliferation in cancers. MAGI stabilizes PTEN [7]. Germ line mutations of *PTEN* are the cause of *PTEN* hamartoma tumor syndromes (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, Proteus-like syndrome) with increased risk for the development of cancers [8]. Loss of Heterozygosity (LOH) studies suggest that PTEN may play the most important role in advanced cancers of particular tissue [9]. Alterations of PTEN in tumors are often associated with a poor prognosis [10], which may be caused by lack of key interaction partners. The PTEN tumor suppressor is recruited to E-cadherin junctional complexes through the binding to the second PDZ domain of the MAGI-1b [11]. The critical role of the MAGI-1b has been shown in stabilization of cell-cell contacts and suppression of cancer cell invasiveness [12]. It is conceivable that the signalosome containing MAGIs/PTEN controls some of its effector systems. In this review, we summarize the current research and our view of how MAGIs and PTEN interact with their binding partners to transduce signals downstream and what are the implications for cancer-associated biology. We also discuss recent data

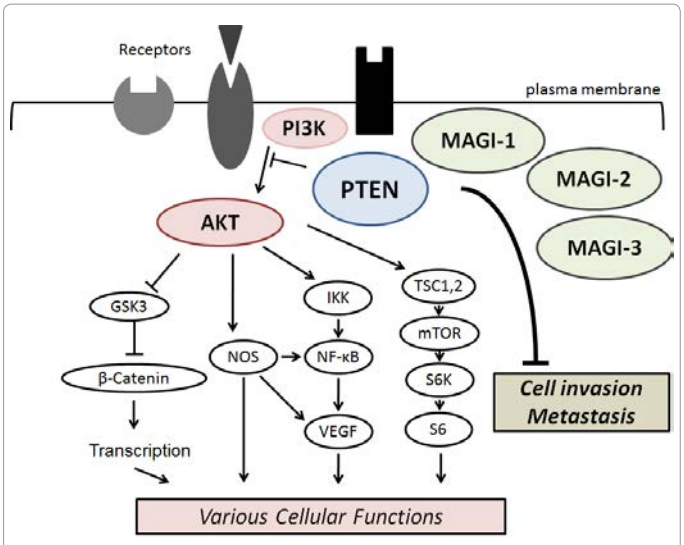

Figure 1: Schematic representation of PI3K/AKT/PTEN signaling. Examples of molecules known to act on the regulatory pathways are shown. Note that some critical pathways have been omitted for clarity.

***Corresponding author:** Satoru Matsuda, Department of Food Science and Nutrition, Nara Women's University, Kita-Uoya Nishimachi, Nara 630-8506, Japan, Tel: +81 742 20 3451; Fax: +81 742 20 3451; E-mail: smatsuda@cc.nara-wu.ac.jp

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which suggests that MAGIs organize a signalosome via PTEN in cell membrane microdomains. Intervention and therapy that modulates those mechanisms may serve to better efficacy of new therapeutic and/or diagnostic approaches against cancer invasion.

MAGIs Involved in Cancer Development

MAGIs contain six PDZ domains, two WW domains, and one guanylate kinase domain (Figure 2). Three closely related MAGI proteins, known as MAGI-1, MAGI-2, and MAGI-3, have distinct expression of tissue distribution. The role of MAGIs as putative tumor suppressor was first suspected since they were the target of some oncoproteins. MAGI-1 was identified in mouse as a protein interacting with K-Ras [13].MAGI-1 has three splice variants, MAGI-1a, MAGI-1b, and MAGI-1c of 1139, 1171, and 1374 amino acids respectively [14]. They diverge primarily in the carboxyl-terminus downstream of the fifth PDZ-domain. Several MAGI-1 binding partners have been found. For example, β-catenin and actin-binding proteins act as binding partners of MAGI-1 [15,16]. In epithelia, MAGI-1 is localized at tight junctions [16]. Interestingly, MAGI-1c is also localized to the nucleus, suggesting that MAGI-1 may participate in the regulatory signal transduction from the cell surface to the nucleus [14]. In overall, MAGIs are multi-PDZ domain proteins implicated into protein complex assembly at cell-cell contacts. PTEN and MAGI-1b plays an important role in stabilization of the cell-cell contacts and suppression of invasiveness [17]. The PTEN tumor suppressor is recruited to E-cadherin junctional complexes through the binding to the second PDZ domain of the MAGI-1b scaffolding molecule, whereas beta-catenin interacts with the fifth PDZ domain [17]. TRIP6 also interacts directly with MAGI-1b by binding to its fifth PDZ domain, whose overexpression in colon tumors suggests its critical role in cancer progression [11].

Membrane-associated guanylate kinase (MAGUK) proteins bind to the MAGI-2 to participate in the assembly of multiprotein complexes at regions of cell-cell contact, which contains potential protein-protein interaction domains and is localized to tight junctions in the membrane of epithelial cells [18]. PTEN binds to the MAGI-2 through an interaction between the PDZ-binding motif of PTEN and the second PDZ domain of MAGI-2 [19]. MAGI-2 suppresses AKT by enhancing PTEN function through assembly of a multiprotein complex, which may affect the efficiency of signaling at the cell membrane. In addition, PTEN is up-regulated after MAGI-2 expression, which is due to the enhancement of PTEN protein stability [7]. Consequently, the MAGI-2-induced inhibition of cell migration and proliferation is attenuated with PTEN silencing. Expression of vinculin mutants that reinstates the disrupted interactions of beta-catenin with MAGI-2 also restores PTEN protein levels [20]. PTEN protein levels are dependent on the maintenance of beta-catenin-MAGI-2 interaction, in which vinculin plays an important role [20]. MAGI-2 is first detected in junctional complexes in podocytes after the migration to the base of the cells [21].

PTEN also binds to the MAGI-3, an inverted MAGUK that localizes to epithelial cell tight junctions. MAGI-3 allows for the juxtaposition of PTEN to phospholipid signaling pathways involved with cell survival. Lysophosphatidic Acid (LPA) is a potent inducer of colon cancer, and LPA receptor type 2 is overexpressed in colon tumors. The LPA receptor type 2 interacts with the MAGI-3 [22]. The LPA receptor type 2 is also regulated by several PDZ proteins via modulation of G-protein coupling and receptor signaling. The MAGI-3 negatively regulates the ability of the LPA-signaling to activate Erk and RhoA [23]. In addition, the MAGI-3 activates JNK in conjunction with frizzled-4, and this activation requires the small GTPase, Rac. The MAGI-3 may function as a scaffold protein for frizzled-4 and several small GTPases to regulate the JNK signaling cascade [24].

Function and Characterization for the PI3K/AKT/PTEN

The PI3K in mammalian cells forms a family that can be divided into three classes based on the structure, distribution, and mechanism of activation [25]. Class I PI3Ks are divided into class IA and class IB based on different associated adaptors. Class IA PI3Ks are activated

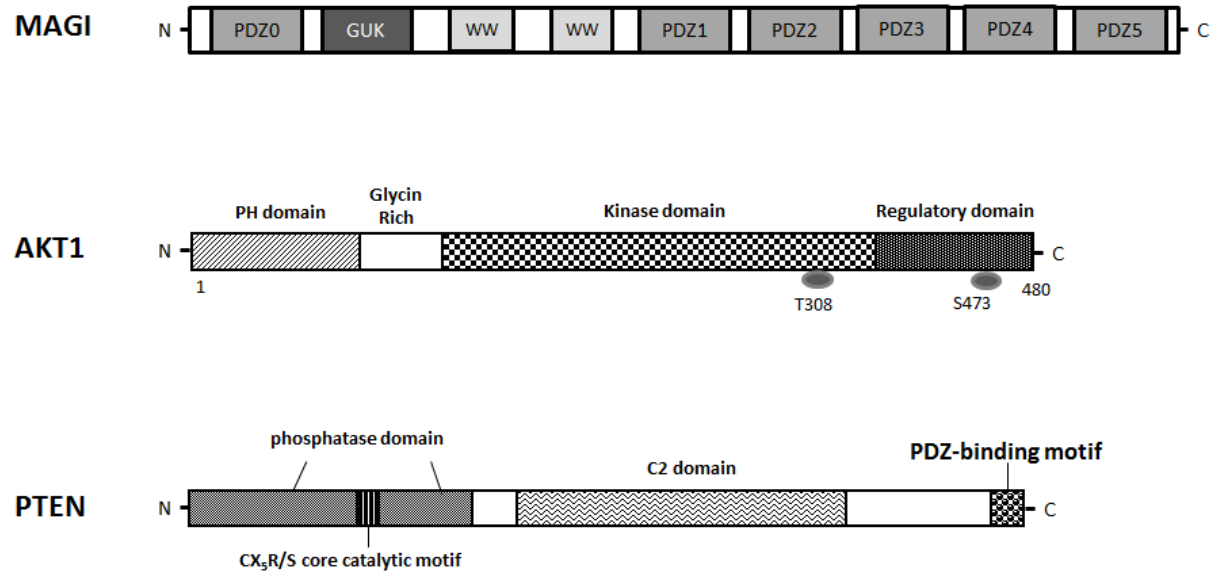

Figure 2: Schematic structures of MAGI, AKT, and PTEN protein. The predicted consensual domain structures for each protein are depicted. The functionally important sites including the sites of protein phosphorylation are also shown. Note that the sizes of protein are modified for clarity. PH domain=pleckstrin homology domain; C2 domain=a protein structural domain involved in targeting proteins to cell membranes; PDZ=a common structural domain in signaling proteins (PSD95, Dlg, ZO-1, etc); WW=WW domain (also known as WWP domain) with two highly conserved tryptophans.

by receptor tyrosine kinases, while class IB PI3Ks are activated by G-protein-coupled receptors. These PI3Ks are heterodimers consisting of a regulatory subunit such as p85, and a catalytic subunit such as p110. The phospholipid second messengers generated by PI3Ks provide a common mechanism for multiple steps during intracellular signal transduction. AKT is a major downstream effector of the PI3Ks. Human AKT has three isoforms: AKT1, AKT2, and AKT3 [26]. The PIP3, a product of the PI3Ks, binds to the AKT, which leads to its membrane recruitment of the AKT. The PIP3 also binds to phosphoinositide-dependent kinase 1 (PDK1) via their plekstrin homology (PH) domains, then PDK1 phosphorylates AKT in the kinase domain (Thr 308 in AKT1). For the full activation of AKT, the phosphorylation within the carboxyl-terminal regulatory domain (Ser 473 in AKT1) of AKT by PDK2 is required [27]. Once activated, AKT moves to the cytoplasm and nucleus, where it phosphorylates, activates, or inhibits many downstream targets to regulate various cellular functions involved in cell survival, cell cycling and metabolism (Figure 1). AKT inhibits the GTPase-activating protein (GAP) activity of the tuberous sclerosis complex 1 (TSC1) and TSC2 complex by phosphorylating TSC2 tuberin protein, leading to the accumulation and activation of the mTOR complex (Figure 1) [28]. The mTOR mediates the phosphorylation of the ribosomal protein S6 kinases and eukaryotic translation initiation factor 4E-binding protein 1 leading to the release of the translation initiation factor eIF4E [29]. Schematic structure of the predicted AKT protein is shown in Figure 2.

PTEN is counteracting one of the most critical cancer-promoting AKT signaling pathways. The PTEN is a dual-specificity phosphatase which has protein phosphatase activity and lipid phosphatase activity that antagonizes PI3K activity [3,30] through converting PIP3 to PIP2. PTEN acts as regulator of maintaining basal levels of PIP3 below a threshold for those signaling activation. PTEN also plays an important role in the induction of apoptotic cell death signals in cells when cells lose contact with the extracellular matrix [31]. The human genomic *PTEN* locus consists of 9 exons on chromosome 10q23.3 encoding a 5.5 kb mRNA that specifies a 403 amino-acid open reading frame [30,32]. The translation product is a 53 kDa protein with homology to tensin and protein tyrosine phosphatases. *PTEN* is ubiquitously expressed throughout early embryogenesis in mammals [33]. *PTEN* gene can be up-regulated by early growth regulated transcription factor 1, peroxisome proliferator activated receptor γ (PPARγ), p53, and activating transcription factor 2 (ATF2) [34-37], while transforming growth factor (TGF)-β, nuclear factor kappaB (NF-κB), and Jun negatively regulate *PTEN* expression [38-40]. Interestingly, rosemary extract represses *PTEN* expression in K562 leukemic culture cells [41]. PTEN activity can be regulated by posttranslational regulation including phosphorylation, methylation, acetylation, and oxidation. PTEN expression may be lost by the posttranslational mechanisms such as methylation. Methylation of the *PTEN* promoter can result in transcriptional silencing of the *PTEN* gene [42]. Schematic structure of the predicted PTEN protein is shown in Figure 2. PTEN protein consists of N-terminal phosphatase, and C-terminal C2, and PDZ (PSD-95, DLG1, and ZO-1) binding domains. The PTEN CX5R(S/T) motif resides within an active site that surrounds the catalytic signature with three basic residues, which are critical for PTEN lipid phosphatase activity. The structure endows PTEN with its preference for acidic phospholipid substrates such as PIP3. Overexpression of PTEN induces growth suppression by promoting cell cycle arrest, which requires lipid phosphatase activity [43,44]. Overexpression of PTEN also correlates with decreased levels and nuclear localization of cyclin D1 [45], a key cell cycle molecule regulated by AKT. One mechanism by which PTEN induces cell cycle arrest is by regulating AKT activity such that levels of the cell cycle inhibitor p27kip1 are increased [46]. Despite the main role of PTEN as a negative regulator of the PI3K/AKT pathway, studies report a lot of tumor suppressive activities for PTEN that are exerted from within the nucleus, where catalysis of PIP3 does not seem to represent a dominant function of this enzyme [47]. The nuclear PTEN activities may include the regulation of genomic stability, cell cycle progression, and gene expression. The C-terminus of PTEN contains two PEST (proline, glutamic acid, serine and threonine) sequences involved in protein degradation [48].

PI3K/AKT/PTEN Pathway Involved in Cancer Development

The PI3K pathways are known as regulating metabolism, cell growth and cell survival [49]. As an active form of PI3K is an oncogene, amplifications and mutations of the PI3K are commonly found in many kinds of human cancers [49,50]. The relevance of the PI3K pathway in cancer is focused by numbers of components within the cascade whose activity is found altered in cancer. Because PTEN protein has been shown to play an important role in regulating proliferation and invasion of many cancer cells, PTEN is considered as an authentic tumor suppressor. Actually, *PTEN* is one of the most mutated and deleted tumor suppressors in human cancer. Loss of heterozygosity studies have also suggested that *PTEN* may play an important role in advanced cancers [51]. In addition, alterations of *PTEN* in tumors are often associated with a poor prognosis [52]. As previously mentioned, germ line mutations of *PTEN* are the cause of *PTEN* hamartoma tumor syndromes with increased risk for the development of various cancers [8,53]. The *PTEN* heterozygous knockout mice are able to complete embryogenesis, which develop multiple organ neoplasms [54]. However, complete inactivation of both copies of the *PTEN* gene results in embryonic death. In contrast, overexpression of *PTEN* induces growth suppression by promoting G1 arrest [55-57]. This cell cycle arrest requires lipid phosphatase activity of PTEN and can be rescued with the introduction of constitutively active forms of PI3K or AKT. Furthermore, PTEN regulates AKT activity so that the cell cycle inhibitor protein p27kip1 is increased [46,58].

Increased proliferation, survival and motility are main cellular effects associated with the increased PIP3 level that contribute to its tumorigenic effects. Actually, dysregulation of the PI3K/PTEN/AKT pathway has been found in many malignant cancers. PTEN exerts its tumor-suppressive effect by dephosphorylating PIP3, thereby negatively regulating AKT activation and the survival pathway. Inactivating mutations in the *PTEN* gene are also common in tumors, indicating that elevated levels of PIP3 confer an advantage to cancer cells. PTEN deficiency leads to increased cell motility. Reintroducing the wild-type PTEN, but not the catalytically inactive PTEN, reduces the enhanced cell motility of PTEN deficient cells, suggesting that PTEN negatively controls the cell motility [59]. Conversely, an absence of PTEN function may allow unregulated cell spreading and invasion, which might contribute to metastasis.

Functional Interplay between MAGIs and PI3K/AKT/PTEN

Interplay between MAGIs and PTEN could be at the important control machinery for switching between cancer cell survival and death (Figure 3). The cross talk may serve as an added regulatory effect on the expression of key genes involved in cancer. Disruption of cadherin junctional complexes is associated with invasiveness and metastasis,

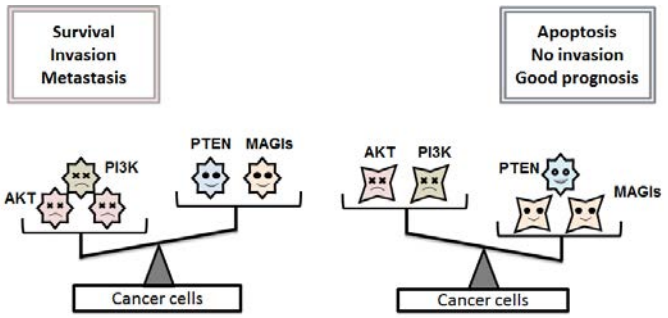

Figure 3: Survival or Apoptosis, that's the problem both in cancer cell fate and for prognosis of patients. The determination either survival or apoptosis may depend on the balance between the PI3K/AKT activity and the MAGIs and PTEN levels in cancer cells.

and is the hallmark of neoplastic progression. The stability of these complexes is under the control of several signaling pathways, including the PTEN tumor suppressor, which antagonizes PI3K activity. PTEN interacts indirectly with β-catenin by binding the MAGI-1b. Ectopic expression of MAGI-1b potentiates the interaction of PTEN with junctional complexes and promotes E-cadherin-dependent cell aggregation, which reduces the Src-induced invasiveness of epithelial cells. Thus, the recruitment of PTEN at adherens junctions by MAGI-1b is a focal point for restraining the disruption of junctional complexes and the tumor cell invasion. So, MAGIs play an important role in stabilization of adherens junctions and suppression of invasiveness and metastasis [22,23]. MAGI-1 expression is decreased in cancers, which correlates with poor prognosis, suggesting MAGI-1 as a novel prognostic marker for cancer. Conversely, overexpression of MAGI-1 induces stabilization of E-cadherin and β-catenin localization at cell-cell junctions, enhances actin stress fiber and focal adhesion formation, increases cell adhesion to matrix proteins and suppresses anchorage-independent growth and migration. Actually, MAGI-1 overexpression suppresses subcutaneous primary tumor growth, attenuates spontaneous lung metastasis, in experimental colon cancer [60]. MAGI-2 gene has been shown to undergo rearrangement in the genome of a melanoma cell line [61]. In principle, genomic rearrangements that disrupt PTEN function might dysregulate the PI3 kinase pathway in cancers. The discovery of MAGI-2 genomic rearrangements in prostate cancer suggests that cross-examining both the PTEN and MAGI-2 loci might improve prognostication [62]. MAGI-3 and AKT3 fusion enriches in triple-negative breast cancer lacking estrogen and progesterone receptors and ErbB2 expression. The MAGI-3 fusion leads to constitutive activation of the AKT kinase, which is abolished by treatment with an ATP-competitive kinase inhibitor.

Perspective

The invasion and metastasis of cancer is a complicated process involving multiple factors, in which the first step is the detachment of cancer cells from a primary site. The intercellular adherence is regulated by a variety of adhesion molecules including MAGIs. It has been proven that MAGIs can recruit PTEN to the junctional complex, stabilize the conjunction, and prevent the cancer cell dissociation. MAGIs scaffolding proteins may play crucial roles in organizing the signaling complexes that control cell growth and dissemination. It has been suggested the MAGIs expression level is closely correlated with the cancer cell invasion (Figure 3). In addition, MAGIs protein expression is decreased in cancers. PTEN is recruited to specific subcellular microenvironments such as adherens junctions via the binding of its PDZ binding motif to scaffolding molecules such as MAGI-1b. The involvement of MAGIs and PI3K/AKT/PTEN in signaling has remained unexplored, however, MAGIs may inhibit several invasion of cancers by regulating PTEN function. The challenge for the future is to elucidate the precise spatiotemporal regulation of these complexes and the mechanisms by which they transmit signals. More understanding of the intracellular mechanisms downstream of MAGIs signaling changes in cancer could provide novel insights into the development of new therapeutic approaches having greater efficacy against cancer invasion and metastasis.

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Competing Interests

The authors declare that they have no competing financial interests.

References

1. Chetram MA, Hinton CV (2012) PTEN regulation of ERK1/2 signaling in cancer. J Recept Signal Transduct Res 32: 190-195.
2. De Luca A, Maiello MR, D'Alessio A, Pergameno M, Normanno N (2012) The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches. Expert Opin Ther Targets 16 Suppl 2: S17-27.
3. Song MS, Salmena L, Pandolfi PP (2012) The functions and regulation of the PTEN tumour suppressor. Nat Rev Mol Cell Biol 13: 283-296.
4. Merritt MA, Cramer DW (2010) Molecular pathogenesis of endometrial and ovarian cancer. Cancer Biomark 9: 287-305.
5. Fraser MM, Zhu X, Kwon CH, Uhlmann EJ, Gutmann DH, et al. (2004) Pten loss causes hypertrophy and increased proliferation of astrocytes in vivo. Cancer Res 64: 7773-7779.
6. Adamsky K, Arnold K, Sabanay H, Peles E (2003) Junctional protein MAGI-3 interacts with receptor tyrosine phosphatase beta (RPTP beta) and tyrosine-phosphorylated proteins. J Cell Sci 116: 1279-1289.
7. Hu Y, Li Z, Guo L, Wang L, Zhang L, et al. (2007) MAGI-2 Inhibits cell migration and proliferation via PTEN in human hepatocarcinoma cells. Arch Biochem Biophys 467: 1-9.
8. Hobert JA, Eng C (2009) PTEN hamartoma tumor syndrome: an overview. Genet Med 11: 687-694.
9. Morgan TM, Koreckij TD, Corey E (2009) Targeted therapy for advanced prostate cancer: inhibition of the PI3K/Akt/mTOR pathway. Curr Cancer Drug Targets 9: 237-249.
10. Knobbe CB, Merlo A, Reifenberger G (2002) Pten signaling in gliomas. Neuro Oncol 4: 196-211.
11. Chastre E, Abdessamad M, Kruglov A, Bruyneel E, Bracke M, et al. (2009) TRIP6, a novel molecular partner of the MAGI-1 scaffolding molecule, promotes invasiveness. FASEB J 23: 916-928.
12. Kotelevets L, van Hengel J, Bruyneel E, Mareel M, van Roy F, et al. (2001) The lipid phosphatase activity of PTEN is critical for stabilizing intercellular junctions and reverting invasiveness. J Cell Biol 155: 1129-1135.
13. Dobrosotskaya I, Guy RK, James GL (1997) MAGI-1, a membrane-associated guanylate kinase with a unique arrangement of protein-protein interaction domains. J Biol Chem 272: 31589-31597.
14. Dobrosotskaya IY, James GL (2000) MAGI-1 interacts with beta-catenin and is associated with cell-cell adhesion structures. Biochem Biophys Res Commun 270: 903-909.
15. Nishimura W, Yao I, Iida J, Tanaka N, Hata Y (2002) Interaction of synaptic scaffolding molecule and Beta -catenin. J Neurosci 22: 757-765.
16. Murata M, Kojima T, Yamamoto T, Go M, Takano K, et al. (2005) Tight junction protein MAGI-1 is up-regulated by transfection with connexin 32 in an immortalized mouse hepatic cell line: cDNA microarray analysis. Cell Tissue Res 319: 341-347.

17. Kotelevets L, van Hengel J, Bruyneel E, Mareel M, van Roy F, et al. (2005) Implication of the MAGI-1b/PTEN signalosome in stabilization of adherens junctions and suppression of invasiveness. FASEB J 19: 115-117.

18. Wapenaar MC, Monsuur AJ, van Bodegraven AA, Weersma RK, Bevova MR, et al. (2008) Associations with tight junction genes PARD3 and MAGI2 in Dutch patients point to a common barrier defect for coeliac disease and ulcerative colitis. Gut 57: 463-467.

19. Tolkacheva T, Boddapati M, Sanfiz A, Tsuchida K, Kimmelman AC, et al. (2001) Regulation of PTEN binding to MAGI-2 by two putative phosphorylation sites at threonine 382 and 383. Cancer Res 61: 4985-4989.

20. Subauste MC, Nalbant P, Adamson ED, Hahn KM (2005) Vinculin controls PTEN protein level by maintaining the interaction of the adherens junction protein beta-catenin with the scaffolding protein MAGI-2. J Biol Chem 280: 5676-5681.

21. Lehtonen S, Ryan JJ, Kudlicka K, Iino N, Zhou H, et al. (2005) Cell junction-associated proteins IQGAP1, MAGI-2, CASK, spectrins, and alpha-actinin are components of the nephrin multiprotein complex. Proc Natl Acad Sci U S A 102: 9814-9819.

22. Lee SJ, Ritter SL, Zhang H, Shim H, Hall RA, et al. (2011) MAGI-3 competes with NHERF-2 to negatively regulate LPA2 receptor signaling in colon cancer cells. Gastroenterology 140: 924-934.

23. Zhang H, Wang D, Sun H, Hall RA, Yun CC (2007) MAGI-3 regulates LPA-induced activation of Erk and RhoA. Cell Signal 19: 261-268.

24. Yao R, Natsume Y, Noda T (2004) MAGI-3 is involved in the regulation of the JNK signaling pathway as a scaffold protein for frizzled and Ltap. Oncogene 23: 6023-6030.

25. Hawkins PT, Stephens LR, Suire S, Wilson M (2010) PI3K signaling in neutrophils. Curr Top Microbiol Immunol 346: 183-202.

26. Hers I, Vincent EE, Tavaré JM (2011) Akt signalling in health and disease. Cell Signal 23: 1515-1527.

27. Chan TO, Tsichlis PN (2001) PDK2: a complex tail in one Akt. Sci STKE 2001: pe1.

28. Kwiatkowski DJ (2003) Rhebbing up mTOR: new insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. Cancer Biol Ther 2: 471-476.

29. Huo Y, Iadevaia V, Proud CG (2011) Differing effects of rapamycin and mTOR kinase inhibitors on protein synthesis. Biochem Soc Trans 39: 446-450.

30. Okumura N, Yoshida H, Kitagishi Y, Murakami M, Nishimura Y, et al. (2012) PI3K/AKT/PTEN Signaling as a Molecular Target in Leukemia Angiogenesis. Adv Hematol 2012: 843085.

31. Fournier MV, Fata JE, Martin KJ, Yaswen P, Bissell MJ (2009) Interaction of E-cadherin and PTEN regulates morphogenesis and growth arrest in human mammary epithelial cells. Cancer Res 69: 4545-4552.

32. Okumura N, Yoshida H, Kitagishi Y, Nishimura Y, Matsuda S (2011) Alternative splicings on p53, BRCA1 and PTEN genes involved in breast cancer. Biochem Biophys Res Commun 413: 395-399.

33. Croushore JA, Blasiole B, Riddle RC, Thisse C, Thisse B, et al. (2005) Ptena and ptenb genes play distinct roles in zebrafish embryogenesis. Dev Dyn 234: 911-921.

34. Teresi RE, Shaiu CW, Chen CS, Chatterjee VK, Waite KA, et al. (2006) Increased PTEN expression due to transcriptional activation of PPARgamma by Lovastatin and Rosiglitazone. Int J Cancer 118: 2390-2398.

35. Shen YH, Zhang L, Gan Y (2006) Up-regulation of PTEN (phosphatase and tensin homolog deleted on chromosome ten) mediates p38 MAPK stress signal-induced inhibition of insulin signaling. A cross-talk between stress signaling and insulin signaling in resistin-treated human endothelial cells. J Biol Chem 281: 7727-7736.

36. Pan L, Lu J, Wang X, Han L, Zhang Y, et al. (2007) Histone deacetylase inhibitor trichostatin a potentiates doxorubicin-induced apoptosis by up-regulating PTEN expression. Cancer 109: 1676-1688.

37. Lee YR, Yu HN, Noh EM, Kim JS, Song EK, et al. (2007) Peroxisome proliferator-activated receptor gamma and retinoic acid receptor synergistically up-regulate the tumor suppressor PTEN in human promyeloid leukemia cells. Int J Hematol 85: 231-237.

38. Yang Y, Zhou F, Fang Z, Wang L, Li Z, et al. (2009) Post-transcriptional and post-translational regulation of PTEN by transforming growth factor-beta1. J Cell Biochem 106: 1102-1112.

39. Han S, Ritzenthaler JD, Zheng Y, Roman J (2008) PPARbeta/delta agonist stimulates human lung carcinoma cell growth through inhibition of PTEN expression: the involvement of PI3K and NF-kappaB signals. Am J Physiol Lung Cell Mol Physiol 294: L1238-1249.

40. Vasudevan KM, Burikhanov R, Goswami A, Rangnekar VM (2007) Suppression of PTEN expression is essential for antiapoptosis and cellular transformation by oncogenic Ras. Cancer Res 67: 10343-10350.

41. Yoshida H, Okumura N, Kitagishi Y, Nishimura Y, Matsuda S (2011) Ethanol extract of Rosemary repressed PTEN expression in K562 culture cells. Int J appl Boil pharm Technol 2: 316-322.

42. Choi Y, Zhang J, Murga C, Yu H, Koller E, et al. (2002) PTEN, but not SHIP and SHIP2, suppresses the PI3K/Akt pathway and induces growth inhibition and apoptosis of myeloma cells. Oncogene 21: 5289-5300.

43. Petrella BL, Brinckerhoff CE (2009) PTEN suppression of YY1 induces HIF-2 activity in von-Hippel-Lindau-null renal-cell carcinoma. Cancer Biol Ther 8: 1389-1401.

44. Yamamoto M, Tamakawa S, Yoshie M, Yaginuma Y, Ogawa K (2006) Neoplastic hepatocyte growth associated with cyclin D1 redistribution from the cytoplasm to the nucleus in mouse hepatocarcinogenesis. Mol Carcinog 45: 901-913.

45. Andrés-Pons A, Gil A, Oliver MD, Sotelo NS, Pulido R (2012) Cytoplasmic p27Kip1 counteracts the pro-apoptotic function of the open conformation of PTEN by retention and destabilization of PTEN outside of the nucleus. Cell Signal 24: 577-587.

46. Planchon SM, Waite KA, Eng C (2008) The nuclear affairs of PTEN. J Cell Sci 121: 249-253.

47. Georgescu MM (2010) PTEN Tumor Suppressor Network in PI3K-Akt Pathway Control. Genes Cancer 1: 1170-1177.

48. Sheppard K, Kinross KM, Solomon B, Pearson RB, Phillips WA (2012) Targeting PI3 kinase/AKT/mTOR signaling in cancer. Crit Rev Oncog 17: 69-95.

49. Aksamitiene E, Kiyatkin A, Kholodenko BN (2012) Cross-talk between mitogenic Ras/MAPK and survival PI3K/Akt pathways: a fine balance. Biochem Soc Trans 40: 139-146.

50. Tysnes BB, Mahesparan R (2001) Biological mechanisms of glioma invasion and potential therapeutic targets. J Neurooncol 53: 129-147.

51. Ohgaki H, Kleihues P (2007) Genetic pathways to primary and secondary glioblastoma. Am J Pathol 170: 1445-1453.

52. Smrkolj S, Sorc L, Sinkovec J, Rakar S (2012) Müllerian papilloma in a patient with Proteus syndrome: case report and review of the literature. Eur J Gynaecol Oncol 33: 428-432.

53. Podsypanina K, Ellenson LH, Nemes A, Gu J, Tamura M, et al. (1999) Mutation of Pten/Mmac1 in mice causes neoplasia in multiple organ systems. Proc Natl Acad Sci U S A 96: 1563-1568.

54. Weng L, Brown J, Eng C (2001) PTEN induces apoptosis and cell cycle arrest through phosphoinositol-3-kinase/Akt-dependent and -independent pathways. Hum Mol Genet 10: 237-242.

55. Weng LP, Brown JL, Eng C (2001) PTEN coordinates G(1) arrest by down-regulating cyclin D1 via its protein phosphatase activity and up-regulating p27 via its lipid phosphatase activity in a breast cancer model. Hum Mol Genet 10: 599-604.

56. Vartanian R, Masri J, Martin J, Cloninger C, Holmes B, et al. (2011) AP-1 regulates cyclin D1 and c-MYC transcription in an AKT-dependent manner in response to mTOR inhibition: role of AIP4/Itch-mediated JUNB degradation. Mol Cancer Res 9: 115-130.

57. Dellas A, Jundt G, Sartorius G, Schneider M, Moch H (2009) Combined PTEN and p27kip1 protein expression patterns are associated with obesity and prognosis in endometrial carcinomas. Clin Cancer Res 15: 2456-2462.

58. Liliental J, Moon SY, Lesche R, Mamillapalli R, Li D, et al. (2000) Genetic deletion of the Pten tumor suppressor gene promotes cell motility by activation of Rac1 and Cdc42 GTPases. Curr Biol 10: 401-404.

59. Zaric J, Joseph JM, Tercier S, Sengstag T, Ponsonnet L, et al. (2012)

Identification of MAGI1 as a tumor-suppressor protein induced by cyclooxygenase-2 inhibitors in colorectal cancer cells. Oncogene 31: 48-59.

60. Pleasance ED, Cheetham RK, Stephens PJ, McBride DJ, Humphray SJ, et al. (2010) A comprehensive catalogue of somatic mutations from a human cancer genome. Nature 463: 191-196.

61. Berger MF, Lawrence MS, Demichelis F, Drier Y, Cibulskis K, et al. (2011) The genomic complexity of primary human prostate cancer. Nature 470: 214-220.

62. Banerji S, Cibulskis K, Rangel-Escareno C, Brown KK, Carter SL, et al. (2012) Sequence analysis of mutations and translocations across breast cancer subtypes. Nature 486: 405-409.

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