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MAGI Scaffolding Molecules Involved in Cancer Cell Signaling

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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.

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
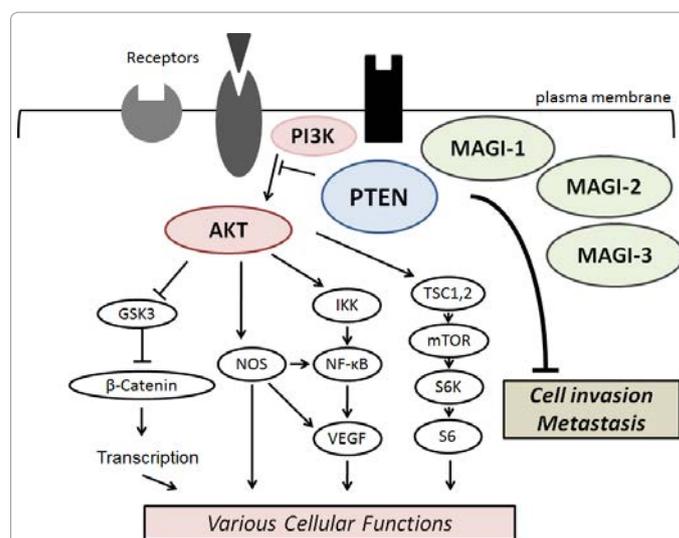

Figure 1: Schematic representation of PI3K/AKT/PTEN signaling. Examples of molecules known to act on the regulatory pathways are shown. Note that some critical pathways have been omitted for clarity.

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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
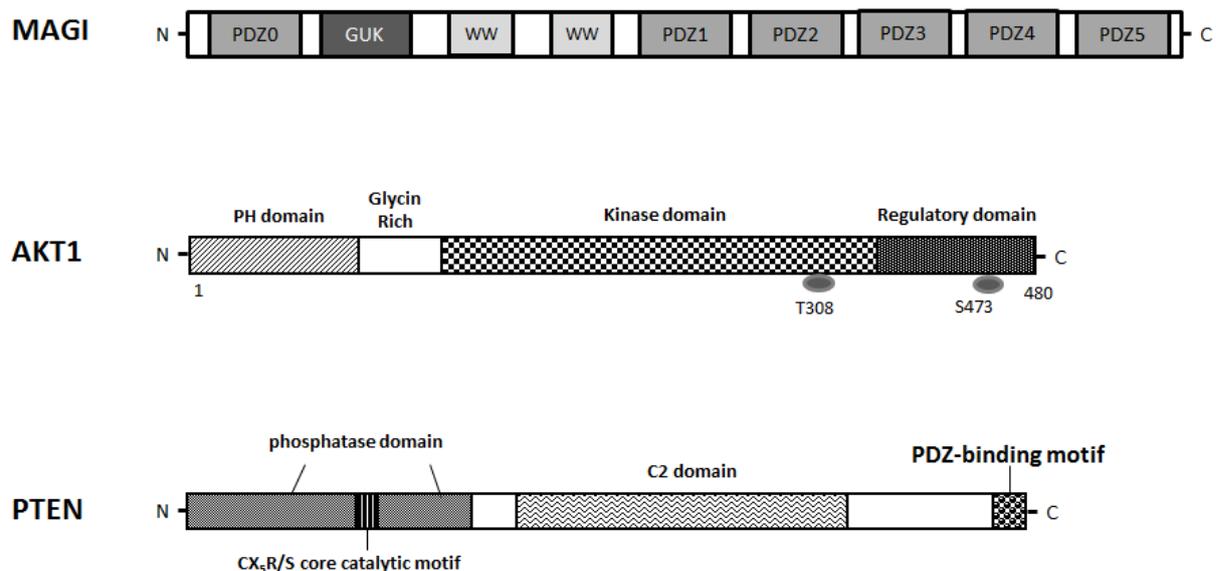
Figure 2: Schematic structures of MAGI, AKT, and PTEN protein. The predicted consensual domain structures for each protein are depicted. The functionally important sites including the sites of protein phosphorylation are also shown. Note that the sizes of protein are modified for clarity. PH domain=pleckstrin 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].
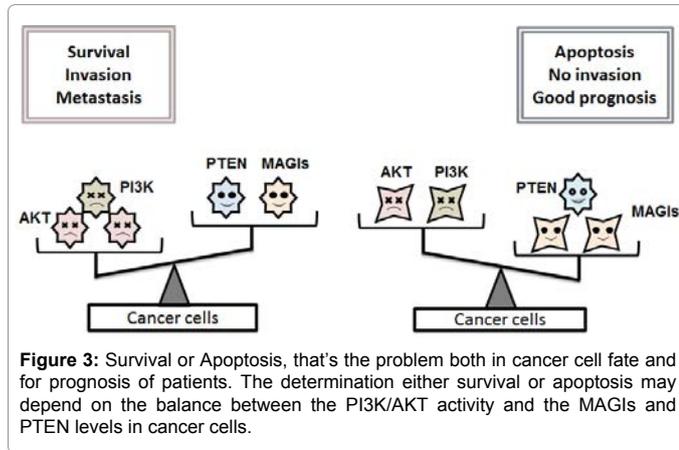
PI3K/AKT/PTEN Pathway Involved in Cancer Development

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.

Competing Interests

The authors declare that they have no competing financial interests.

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