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Polarity protein alterations in carcinoma: a focus on emerging roles for polarity regulators

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Abstract

In this review we discuss both gene expression and protein localization changes of polarity proteins in carcinoma. We highlight the importance of protein mislocalization and its possible role in cancer. We also discuss the emerging role of polarity proteins as regulators of proliferation, apoptosis, tissue polarity, epithelial mesenchymal transition, in addition to their known role in cell junction biogenesis.

Carcinomas are malignant cancers of epithelial origins and they occur in many organs of humans, such as liver, lung, breast, colon, prostate, ovary, pancreas, and esophagus. According to American Cancer Society, at least 80% of all cancers are carcinomas. Thus understanding the biology of epithelial cells will not only provide insights into mechanisms that regulate early events of cancer and steps that regulate cancer progression but also help to develop novel strategies for diagnosing and treating malignancy.

Cell and tissue polarity in epithelial organs

Epithelial organs are polarized both at the tissue level and at the cellular level. At the tissue level, epithelial cells organize to form multicellular structures with polarized organization to maintain tissue structure and perform normal physiological functions such as secretion of milk into the lumen, a property referred to as tissue polarity. At the cellular level, epithelial cells have asymmetric distribution of cytoplasmic and membrane proteins to regulate cell structure and transduce signals a property referred to as cell polarity. Both tissue polarity and cell polarity are lost early during the neoplastic process, which is exploited by pathologists for detecting cancer [1]. There are several types of cell polarity. Cells lining ductal structures exhibit apical-basal polarity where proteins asymmetrically distribute along the apical-basal axis [2]; fields of cells in a tissue exhibit planar cell polarity (PCP) which refers to the ability of cells to orient in a predetermined direction [3]; migrating cells exhibit front-back polarity where proteins asymmetrically distribute along the axis of migration and; lastly progenitor cells exhibit asymmetric cell division, a property that facilitates generation of two daughter cells with different cell fates [4]. Thus, the ability of cells to asymmetrically distribute proteins plays important roles during various physiological events. In this article, we will review cancer related changes in gene expression and localization patterns of

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polarity proteins with a focus on the emerging roles for polarity proteins as regulators of biological processes related to tumorigenesis in mammals.

Polarity proteins

Studies in model organisms such as yeast, worms and flies have led to the identification of a set of proteins that regulate various aspects of cell polarity, which includes scaffolding molecules, kinases and GTPases (for review see [5]). Polarity proteins function as multi-protein complexes and their primary function is to generate asymmetry within a cell. In epithelial cells with apical-basal polarity, polarity proteins are asymmetrically distributed along the apical-basal axis (see Figure 1 for localizations of several polarity proteins). For example, members of the Crumbs polarity complex (Crumbs/Protein associated with Lin seven 1(Pals1)/Pals1-associated tight junction protein (PATJ)) and the Partitioning defective (Par) polarity complex (Par3/Par6/atypical protein kinase C (aPKC)) are localized to the apical cortex (for review of those proteins, see [6]), whereas members of the Scribble polarity complex (Scribble/Discs large (Dlg)/Lethal giant Larvae (Lgl)) are localized at the basolateral regions of the cell [7-10].

Crumbs are transmembrane proteins that bind to PDZ domains of Pals1 and PATJ through C-terminal ERLI motif. Pals1 is a member of the membrane-associated guanylate kinase (MAGUK) family, which has a PDZ domain, two L27 domains, a SH3 domain and a guanylate kinase domain. PATJ has ten PDZ domains and one L27N domain. Par3 and Par6 interact with each other via their PDZ domains. Par3, through aPKC and Par6, can also interact with the Crumbs complex (see[11] for a detailed review). There are two aPKC isoforms in mammals: PKC ζ and PKC λ/ι . The two isoforms have 72% sequence similarity and currently functional differences between the two are not well understood. Kinase activities of aPKC are calcium independent and negatively regulated by multiple proteins including Partitioning defective-4 (Par-4) protein (LKB1) kinase, the Par6 scaffolding protein as well as the inhibitory PKC ζ II protein [12].

Scribble, Dlg and Lgl were identified in *Drosophila* as tumor suppressors and their roles in mammalian carcinomas are starting to be revealed [9,13,14]. Scribble is a member of LAP family with leucine rich repeats and PDZ domains, while Dlg is a member of the MAGUK family containing PDZ domains. Lgl does not contain PDZ domains but has WD40 domains, which is thought to mediate interactions with phosphorylated serine and tyrosine [15]. Planar cell polarity (PCP) is orthogonal to apical-basal polarity. The core PCP proteins in vertebrates include transmembrane proteins Frizzled, Vang and Celsr1 as well as cytoplasmic proteins Dishevelled and Prickle [3]. In vertebrates, there are only a few events clearly involving PCP, such as the convergent extension and neurulation during embryonic development and orientation of the stereocilia in cochlea of the inner ear (for review, see [3]).

The apical polarity proteins can cross-regulate basolateral polarity proteins during establishment and maintenance of cell polarity. Lgl is a substrate of aPKC and its cellular localization is regulated by aPKCs in normal epithelia as well as in carcinoma tissues [16,17]. On the other hand, Scribble is required to restrict apical proteins such as Crumbs to the apical region of *Drosophila* epithelia [18]. The localization of Lgl is also regulated by PCP pathway, knockdown of Dishevelled mislocalizes Lgl from cell membrane and downregulates Lgl protein levels in *Xenopus* embryonic ectoderm [19].

A given polarity protein can regulate different types of cell polarity. For example, Scribble, is involved in all the types of cell polarity discussed above [18,20-24]. These common components in different polarity pathways as well as the mutual dependence of different polarity complexes highlight the fact that one needs to be careful in choosing model systems

to study the role played by polarity proteins, because many polarity proteins are likely to function in a context-specific manner.

Alteration of polarity proteins in carcinoma

Tissue transformation in cancer is frequently associated with loss of cell and tissue polarity but the molecular mechanisms are not known. It is likely that the transformation process involves alteration in polarity genes expression and/or their protein subcellular localization resulting in functional inactivation of polarity pathways [25]. There is a significant body of evidence demonstrating that alteration of polarity protein genes are frequently observed in carcinomas (see Table 1 for summary).

Members of apical polarity complex are altered in multiple cancers. The *Par3* gene is deleted in 15% of primary esophageal squamous cell carcinoma (ESCC) and the mRNA levels are downregulated in 23 of 33 ESCC tumor tissues compared to matched normal [26]. *Par6 β* mRNA levels are upregulated in ER-positive primary breast tumors and in ER-positive breast tumor cell lines [27]. In non-small cell lung cancers (NSCLCs), *Par6* is highly expressed in stromal cells and correlates with good prognosis [28]. Downregulation of *Crumbs3* is required for transformation and tumorigenesis of immortalized baby rat kidney (BRK) cells and re-expression of *Crumbs* restores polarity and inhibits invasion of BRK cells [29] demonstrating that loss of *Crumbs3* is causally linked to the transformation process. Cancer genome sequencing efforts are likely to identify additional cancer-associated genetic alterations in polarity proteins. For example, peering into data generated from a transcriptome sequencing study shows the presence of a novel fusion between the transcription factor *ZNF667* and the polarity protein *Par6 β* [30]. Careful mining into the data generated by the cancer genome atlas efforts is likely to identify novel genetic alterations associated with polarity proteins.

It is likely that aPKC isoforms play cell type specific roles in cancer. In androgen insensitive rat prostate cancer lines, *PKC ζ* mRNA is downregulated [31] whereas in human liver cancer, ovarian cancer and non-small cell lung cancers cancer mRNA levels of *PKC λ/ι* are upregulated [32-34]. High levels of *PKC ζ* proteins are observed in hepatocellular carcinomas, bladder transitional carcinomas, dysplastic oral epithelia and squamous cell carcinomas of the head and neck [35-37]. *PKC λ/ι* proteins are increased in breast cancers, ovarian cancer, liver cancer and non-small cell lung cancer [32-34,38]. In breast cancer, overexpression and mislocalization of *PKC ι* from the apical membrane is correlated with invasive disease [38]. *PKC ι* gene is amplified and the protein is mislocalized in ovarian cancers [16,32]. Atypical *PKC* also shows intra-tumor heterogeneity. For example, *PKC ζ* is overexpressed in both ductal and ampullary pancreatic cancers, whereas, *PKC ι* is overexpressed only in major ducts of ductal cancers and ampullary cancers but downregulated in minor ductules. Furthermore, in the stroma, *PKC ζ* , but not *PKC ι* , is overexpressed [39]. Together these studies suggest that the role played by polarity proteins in tumor progression is likely to be context-dependent.

Members of the basolateral polarity complex are also altered at the level of protein localization in cancers. The Scribble polarity protein is altered at multiple levels in human cancers. The mRNA levels are increased in 37.5% and reduced in 53.1% of breast cancer compared to normal tissue samples and the protein is mislocalized in almost 50% of DCIS lesions [14]. In HPV positive cervical high-grade squamous intraepithelial lesions and invasive cancers, Scribble protein levels are reduced and cellular distribution is disrupted [40]. In colon carcinomas, Scribble is mislocalized and expression downregulated in poorly differentiated adenocarcinomas [41]. *Dlg* expression levels and basolateral localizations are altered in colon cancers, high-grade premalignant cervical neoplasias and invasive squamous

carcinomas [41,42]. Lgl-1 transcripts are lost in tumor tissues of the breast (76%), prostate (53%), lung (63%), ovarian (50%) and colon carcinomas (75%) [43]. Re-expression of Lgl-1 in 293 cells increases cell adhesions [44] suggesting that loss of Lgl-1 is causally linked to loss of cell adhesion. Lgl2 is either negative or mainly cytoplasmic in gastric carcinomas [45]. In addition to changes in mRNA levels, polarity protein can also be regulated by alternative splicing. Lu et al report that aberrant splicing of Lgl-1 transcripts is observed in hepatocellular carcinomas [46]. The truncated Lgl-1 forms are correlated with large tumor sizes.

Members of the PCP complex are also altered in human cancers. In several hepatocellular carcinoma cell lines and primary tumors, Prickle-1 mRNA level is downregulated and correlates with increased expression of Dishevelled and β -catenin [47]. Human homolog of *Drosophila* Naked Cuticle (hNkd), an antagonist of the canonical Wnt signaling, is overexpressed in 72% of primary colon tumors [48] and all of 23 hepatocellular carcinoma samples analyzed [49]. Wnt5a, a regulator of PCP [50], is overexpressed in thyroid carcinoma cell lines and tumor tissues [51] but lost in 44% of invasive ductal carcinomas (IDC) and 24% of invasive lobular carcinomas (ILC) of the breast [52]. Moreover, in IDC but not in ILC, loss of Wnt5a is correlated with higher grade of cancer as well as tumor recurrence.

Together the data highlighted above demonstrate that functions of polarity proteins are regulated at several levels. They are amplified or overexpressed, deleted or underexpressed, mRNA alternatively spliced and protein mislocalized from their respective intracellular location. Thus, in addition to assessing genomic alterations and expression changes, monitoring changes in protein subcellular localization should be an important component of the studies aimed at analyzing changes in polarity proteins in cancer.

Cell polarity proteins as regulators of cancer relevant cell biological processes

In this section, we will discuss how polarity pathways can also regulate multiple biological processes related to tumor initiation and progression (see Figure 2), in addition to their known role in cell junction biogenesis.

Proliferation

There is increasing evidence to suggest that polarity proteins can also function as regulators of cell proliferation. Qiu et al discovered that Par6 mediates the interaction between Rac1/Cdc42 and PKC ζ [53]. Par6 and PKC ζ are required for Rac1 and Cdc42, but not Raf, induced transformation of NIH3T3 cells. We have shown that overexpression of Par6 induces growth factor-independent proliferation of human mammary epithelial cells by promoting sustained activation of Mitogen activated protein kinase (MAPK) in an aPKC and Cdc42/Rac-binding domain dependent manner [27]. Furthermore, downregulation of aPKC in MCF-7 breast cancer cell line inhibits cell proliferation demonstrating that the Par6/aPKC module is likely to be an important regulator of cell proliferation in both non-tumorigenic and tumor-derived mammary epithelial cells. Atypical PKCs can regulate cell cycle progression by multiple mechanisms: PKC ζ is required for estrogen-induced nuclear transport of Erk2 and degradation of p27 [54]. The aPKC can also promote tumor growth by stabilizing the Steroid receptor coactivator 3 (SRC-3), known regulator of cell proliferation [55]. Phosphorylation of SRC-3 protein by PKC ζ stabilizes the protein by inhibiting interaction between SRC-3 and the C8 subunit of 20s proteasome [55].

Scribble, *Dlg* and *Lgl* were shown to regulate G1-S transition in a *Drosophila* genetic suppressor screen for novel regulators of G1-S transition [56]. Expression of the PCP gene

Prickle1 inhibits growth of hepatocellular carcinoma cells by promoting degradation of Dishevelled 3, a positive regulator of Wnt signaling [47]. However, further investigation will be necessary to understand if these polarity proteins directly regulate cell cycle.

Apoptosis

Evasion of apoptosis is a critical step during cancer progression [57]. We recently reported a novel role for Scribble as a regulator of apoptosis in mammary epithelial cells. Both downregulation of Scribble protein and mislocalization of Scribble from cell-cell junctions inhibited lumen formation during three-dimensional (3D) morphogenesis of mammary epithelial cells and during Myc-induced transformation and tumorigenesis. Thus, proper localization of Scribble at cell-cell junctions is critical for normal morphogenesis and to resist Myc-induced transformation [14]. However, clonal analysis of cells lacking *Scribble* in *Drosophila* eye imaginal disc demonstrates that loss of Scribble triggers a JNK-dependent cell death [56]. Although these results seem contradictory, they could be explained by differences in cell autonomous (in mammalian studies) versus non-autonomous (*Drosophila* clonal studies) effects of Scribble loss. These observations highlight the need for a better understanding of the relationship between Scribble and regulation of cell death.

Atypical PKC also regulates apoptosis in epithelial cells. We reported that the Par6/aPKC complex was required for ErbB2-induced inhibition of cell death [58] in MCF-10A cells. Inhibition of aPKC significantly increases apoptosis during 3D cysts morphogenesis of MDCK cells by activating GSK3 β [59]. Atypical PKC also inhibits apoptosis by activating the NF κ B pathway either by phosphorylating and activating IKK β kinase or by phosphorylating RelA subunit of NF κ B to activate transcription [60,61]. Atypical PKC can also function downstream of another protein Prostate Apoptosis Response-4 (Par-4, different from the Partitioning Defective proteins that regulate epithelial cell polarity) to regulate apoptosis [62]. Par-4 binds and inhibits aPKC activity resulting in low NF κ B activation. Loss of Par-4 results in activation of aPKC and increased expression of an inhibitor of apoptosis, XIAP, an NF κ B target. Thus polarity proteins are a novel class of regulators of apoptosis in cancer.

Tissue polarity

Changes in cell size, cell shape, and cell organization within the 3D space of tissue lead to a loss in tissue polarity and are known to occur very early and worsen during the progression of carcinoma. Homotypic interactions between epithelial cells and heterotypic interactions between epithelia and stromal cell types and interactions with surrounding extracellular matrix will influence the ability of epithelial cells to organize in a 3D space and develop tissue polarity. The molecular mechanisms that regulate establishment of normal tissue polarity and how they are disrupted in cancer are only beginning to be understood. Culture conditions where epithelial cells grown on 3D matrices to undergo morphogenesis and form cysts or acini are useful platforms to begin to understand how epithelial cells establish the normal multicellular organization and develop tissue polarity. Several studies have identified critical roles for cell junctions and cell-matrix interaction during the 3D morphogenesis of epithelial structures (For detailed reviews on this topic please refer to [6,63,64]). In addition, cell polarity proteins Crumbs, PATJ, Par3, Par6, aPKC, Cdc42, and Scribble have been demonstrated to regulate normal epithelial morphogenesis and establishment of tissue polarity (for details please see [59,65,66]). The precise mechanisms by which cell polarity pathways help regulate development of tissue polarity and how alterations in polarity pathways deregulate 3D tissue organization and polarity remain to be understood.

The mechanisms by which oncogenic events induce disruption of polarized, 3D organized epithelial structures are only beginning to be understood. Here again, use of epithelial cells

grown in 3D matrices is beginning to reveal novel insights that were not apparent from using traditional cell culture platforms. For example, under three dimensional culture conditions, normal mammary epithelia form structures with normal tissue polarity and growth control whereas tumor derived cells grow as unorganized mass with no apparent tissue polarity or growth control [67]. We demonstrated that the oncogene ErbB2 requires an interaction with cell polarity proteins Par6/aPKC to disrupt tissue polarity of acini derived from normal mammary epithelia [58]. The interaction with Par6/aPKC is required for the ability of ErbB2 to disrupt apical-basal polarity but not required for ErbB2-induced cell proliferation [58]. The distinct role for polarity and proliferation is also true when one tries to restore tissue polarity to cancer-derived cell lines. Inhibition of both Rac mediated regulation of cell polarity and Akt mediated cell proliferation is required to make breast cancer-derived cells form normal acini-like structures in 3D matrix [68]. Taken together, the above observations demonstrate that polarity pathways are critical regulators of tissue polarity loss observed in carcinoma. It is likely that a deeper analysis of the mechanisms by which cell and tissue polarity pathways are altered in cancer and how they cooperate with oncogenes to transform polarized epithelia will identify novel diagnostic and therapeutic strategies.

Cell migration and epithelial-mesenchymal transition

Polarity proteins are regulators of front-back polarity in migrating cells. For example, Par6 is required for orienting microtubule organizing centers towards the leading edge in migrating astrocytes [69]. Several polarity proteins including Par3, Par6, aPKC, Scribble, Dlg and Lgl are localized to the leading edge of migrating cells and play critical roles during directional migration (for a detailed review see [70]).

Loss of epithelial characteristics and gain of mesenchymal properties are frequently associated with metastatic progression. Migration/invasion of cells is always associated with dramatic changes in cell architecture suggesting that cell polarity proteins are likely to play important roles during this process. Consistent with this notion, genetic screen in *Drosophila* identified mutation in several polarity proteins including Scribble, Dlg, Lgl, Baz, and Cdc42 that cooperate with RasV12 to promote invasion and metastasis [71]. The role played by polarity proteins during epithelial to mesenchymal transition (EMT) and invasion of mammalian epithelia is beginning to be unraveled. The Par6 polarity protein plays a critical role during TGF β -induced EMT. TGF β type II receptor phosphorylates Par6 to promote assembly of a protein complex containing Par6, Smurf1 (an ubiquitin ligase) and RhoA to promote localized degradation of RhoA [72]. Phosphorylation of Par6 and interaction with Smurf1 are required for TGF β -induced disruption of tight junctions and migration/invasion of NMuMG cells in culture and *in vivo* [72,73] demonstrating a critical role for the polarity protein Par6 in breast cancer metastasis.

Transcriptional regulators of EMT target polarity proteins. In breast and colorectal cancer cells the transcriptional repressor ZEB1 inhibits expression of polarity proteins Crumbs, Lgl2 and PATJ to induce mesenchymal phenotypes [74], and re-expression of Lgl2 restores epithelial cell polarity and inhibits invasion and metastasis [75] in these cells. In addition to breast and colon, loss of Lgl2 is also associated with EMT in melanoma-derived cells and restoration of Lgl2 restores epithelial cell polarity and blocks cell migration [76]. These studies identify polarity proteins as important regulators of the EMT process in cells derived from multiple organs.

Conclusion and Perspective

We have attempted to summarize the changes of polarity protein observed in human carcinomas. As outlined above, polarity proteins are not only targets of genetic and epigenetic changes but are also regulated at the level of subcellular localization. These

findings highlight the need for analyzing subcellular localization, in addition to gene expression changes, when studying polarity proteins in carcinoma. There is an emerging body of evidence implicating polarity proteins as regulators of multiple cell biological properties in addition to cell junction biogenesis. Thus, it is critical to use appropriate biological context for understanding the consequences of polarity protein alterations in cancer. A better and deeper analysis of changes in polarity proteins and the pathways they regulate is likely to identify a new class of biomarkers and drug targets for diagnosing and controlling cancer.

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Figure 1.
Spatial distribution of polarity regulators in epithelial cells polarized along the apical-basal axis.

Figure 2. Emerging roles for polarity proteins: A, polarity pathways regulate cell proliferation [27,54,55]. B, polarity pathways regulate apoptosis [14,59,62]. C, polarity proteins regulate tissue polarity [58,63,64,66,68,77]. D, polarity pathways regulate cell migration and EMT [13,71-73,75].

Table 1

Summary on expression and localization alternations of polarity proteins in carcinomas cell lines and primary tissues.

Protein	Defects	Tissue/Cell line	Functions/Phenotype	Reference
<u>Crumbs</u>	Downregulated	Tumor derived cell lines from in vivo selection in mice	Cell junctions disrupted, increase of metastasis	[29]
<u>Par3</u>	Gene deleted, or downregulated	Esophageal squamous carcinoma cell lines and primary tumor tissues	Cell junctions disrupted	[26]
<u>Par6</u>	Overexpressed	ER positive breast cancer cell lines and primary tumor tissues	Cell hyperproliferation	[27]
	Overexpressed, phosphorylated	Mouse mammary cell lines, BRCA1 associated tumor tissues	Lumen filling, cell junctions disrupted, increase of metastasis	[73]
	Overexpressed	Stromal cells in non small cell lung cancer tissues	Good prognosis	[28]
<u>PKC zeta</u>	Downregulated	Rat prostatic carcinoma cell lines	Prostatic tumor	[31]
	Overexpressed	Hepatocellular carcinoma	Liver cancer	[35]
	Overexpressed	Urinary bladder tumor cell lines and primary tumor tissues	Invasive tumor	[36]
	Overexpressed, Phosphorylated	Dysplastic oral epithelia tissues, squamous cell carcinoma of head and neck tissues and cell lines	Increase in cell proliferation, squamous carcinoma	[37]
	Overexpressed	Normal pancreas, pancreatic cancer tissues	Pancreatic cancers	[39]
	Overexpressed	Hyperplastic enlarged lobular units of precancerous breast lesion	Increase in cell proliferation	[27]
<u>PKC lambda/iota</u>	Gene amplified, protein overexpressed and mislocalized	Ovarian cancer	Ovarian cancer, low survival rate	[16,32]
	Overexpressed, Phosphorylated	Hepatocellular carcinoma tissues	E cadherin reduction, metastasis and invasion	[33]
	Overexpressed	Non small cell lung cancer cell lines, primary tumor tissues	Cell transformation, poor prognosis	[34]
	Overexpressed	Primary breast cancer tissues	Larger tumor, invasion, metastasis	[38]
	Organ structure specific regulation	Normal pancreas, pancreatic cancer tissues	Pancreatic cancers	[39]
<u>Scribble</u>	Mislocalized or downregulated	HPV positive cervical high grade squamous intraepithelial lesions, invasive cervical cancer	Cervical cancers	[40]
	Mislocalized or downregulated	Neoplastic colon mucosa	Colon adenocarcinoma	[41]
	Mislocalized or downregulated	Human breast cancer tissues	Breast cancer	[14]
<u>Dlg</u>	Mislocalized or downregulated	High grade uterine cervical neoplasm	Cervical cancers	[42]
	Mislocalized or downregulated	Neoplastic colon mucosa	Colon adenocarcinoma	[41]
	Upregulated	Progestin treated MCF7 cells	Cell growth inhibition	[78]
<u>Lgl</u>	Downregulated	Tumor tissues of breast, prostate, lung, ovary	Carcinoma	[43]
	Downregulated	Colon cancer lines, colon cancer primary tissues	Colon cancers, adenoma	[44]

Protein	Defects	Tissue/Cell line	Functions/Phenotype	Reference
	Aberrantly spliced tmRNA, truncated protein	Hepatocellular carcinoma cell line and primary tissues	Poor differentiation, larger tumor size	[46]
	Mislocalization, downregulation	Gastric epithelial dysplasia, adenocarcinoma	Tissue disruption, cancers	[45]
<u>Prickle-1</u>	Downregulated	hHepatocellular carcinoma cell line and primary tissues	High β -catenin activity, cell overproliferation	[47]
<u>hNkd</u>	Overexpressed	Colon cancer lines, colon cancer primary tissues	Not determined	[48]
	Overexpressed	Hepatocellular carcinoma primary tissues	Antagonizes Wnt3a activation	[49]
<u>Wnt5a</u>	Overexpressed	Thyroid cancer cell lines and primary tumor tissues	Overexpression inhibits cell proliferation, motility and invasions	[51]
	Downregulated	Invasive ductal carcinoma and invasive lobular carcinoma of the breast	High tumor grade and tumor recurrence of invasive ductal carcinomas	[52]
	Overexpressed	Macrophages in breast cancers,	Increases MMP-7 expression in breast cancer cells, increase invasion	[79]
<u>LKB1 (Par-4)</u>	Mutations (Rare)	Colorectal cancer, testicular tumor, cervical adenocarcinoma, lung adenocarcinoma,	Cancer	[80,81]
	Promoter hypermethylation (Rare)	Colorectal cancer, testicular tumor,	Cancer	[82]
	Downregulation	Breast cancer	Breast cancer, poor prognosis	[83]