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REVIEW

Filamin A: Insights into its Exact Role in Cancers

Qian-Qian Shao[1] · Tai-Ping Zhang[1] · Wen-Jing Zhao[1] · Zi-Wen Liu[1] · Lei You[1] · Li Zhou[1] · Jun-Chao Guo[1] · Yu-Pei Zhao[1]

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Abstract Filamin A (FlnA) is a well-known actin cross-linking protein. It serves as a scaffold for over 90 binding partners and involves in multiple cell functions, of which cell migration and adhesion is especially critical. Recently, its role in the cell has come under scrutiny for FlnA's involvement in cancer development. Originally revealed as a cancer-promoting protein, FlnA actually plays a dual role in cancers. When localized to the cytoplasm, FlnA has a tumor-promoting effect by interacting with signaling molecules. While once localized to the nucleus, it may act to suppress tumor growth and inhibit metastasis by interacting with transcription factors. Thus drugs that can cause FlnA to transpose from cytoplasm to nucleus could be a promising treatment for cancers. Study to this end is on the way in prostate cancer and the results are encouraging. FlnA has been studied in large categories of cancers, such as prostate cancer, breast cancer, melanoma, lung cancer, etc. However, most studies did not evaluate the differences that arise from the localization of the protein, which was a great pity! What's more, although FlnA's is undoubtedly important in cancer invasion and metastasis, both preclinical and clinical researches are very rare in some highly metastatic cancers, such as pancreatic cancer. In this mini-review, we give a comprehensive summary of FlnA' s expression in cancers. Where available, we also indicate the correlation of FlnA with cancer stages and patient prognosis, and clarify its localization (nucleus/cytoplasm) and its dual role (promote/suppress) in different cancers.

Keywords Filamin A · Cancer metastasis · Localization · Nucleus · Cytoplasm

Abbreviations

FlnA	Filamin A
ABD	Actin-binding domain
MK	Megakaryocyte
PMSA	Prostate-specific membrane antigen
hAR	Human androgen receptor
ADT	Androgen deprivation therapy
CRPC	Castration-resistant prostate cancer
GCP	Genistein-combined-polysaccharide
RCC	Renal cell carcinoma
PrP	Prion protein
EGFR	Epidermal growth factor receptor

Introduction

Filamin A (FLnA) was first identified as a non-muscle actin filament cross-linking protein or gelation factor in 1975 [1]. It is the most abundant and widely distributed member of the filamin family (FLnB and FLnC) and is known to serve as a scaffold for over 90 binding partners, including channels, receptors, intracellular signaling molecules, and even transcription factors [2]. Because of this diversity, mutations in human FlnA gene are associated with a wide range of diseases [3, 4].

Recently, FlnA has drawn a lot of attentions because of its involvement in cancers. Originally revealed as a cancer-promoting protein, FlnA actually plays a dual role in cancers,

Qian-Qian Shao and Tai-Ping Zhang contributed equally to this work.

✉ Jun-Chao Guo
gjcpumch@163.com

✉ Yu-Pei Zhao
zhao8028@263.net

[1] Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences/Peking Union Medical College, 1 Shuaifuyuan Wangfujing, Beijing 100730, China

depending on its subcellular localization and the corresponding binding partners [5]. In this review, we give a summary of FlnA's role in diverse cancers and the possible underlying mechanisms.

FlnA's Function in Cell Motility

FlnA is associated with a lot of cell functions, like cell signaling, cell motility, phosphorylation, proteolysis, ion channel regulation, transcription regulation, receptor activation, muscle development, etc. [2]. Among them, cell motility is especially important and is directly related to tumor invasion and metastasis.

Cell motility inevitably relies on active and reversible changes in the mechanical properties of cells, and FlnA plays a fundamental role in cell mechanics. It is one of the best-studied F-actin crosslinking proteins. Each monomer chain of FlnA comprises an actin-binding domain (ABD) and a rod segment. In human filamins, the rod region consists of 24 highly homologous repeats of ~96 amino acid residues [6] (Fig. 1a). The last repeat of the rod is responsible for dimerization, enabling Filamins to crosslink filaments. And the two hinges in the rod segment account for the intrinsic flexibility of the actin networks generated by filamins [4]. Due to this flexible nature, actin-FlnA networks show weak elasticity under low shear stress, yet can support large shear stresses and have pronounced nonlinear strain-stiffening behaviors [7–9]. FlnA can crosslink actin filaments to form orthogonal networks to parallel bundles [10]. And the orthogonal branching can help to stabilize the cytoskeleton network and is the most efficient way to form the largest volume of actin gel with a minimal of material to support cellular integrity [2]. In conclusion, FlnA's unique structure and its special interaction with F-actin confer cell skeletons mechanical and dynamical properties.

FlnA is critical in organogenesis during development, and large numbers of pre-clinical studies have provided direct evidences showing that FlnA is crucial in cell migration and adhesion. Cultured FlnA-deficient melanoma cells fail to polarize and move because they have highly unstable surfaces [11–13]. Restoring normal levels of FlnA in these deficient cells rescue motility. In human cells, null mutations in FlnA gene disrupt long-range directed neuronal migration within the cerebral cortex in X-linked periventricular heterotopia [14]. On the other hand, overexpression of FlnA also inhibits neuronal migration [15]. FlnA (loxP) PF4-Cre mice that lack FlnA in the megakaryocyte lineage have a severe macrothrombocytopenia in bone marrows and spleens because of accelerated platelet clearance, and FlnA-null proplatelets release platelets more readily than controls in vitro [16]. In FlnA-null Dilp2 mice, absence of FlnA results in male lethality because of incomplete septation of the outflow tract of the heart. In addition, carrier females exhibit misshapen pupils while part of male and female mutant mice have other cardiac defects [17].

Meanwhile, some human developmental disorders due to mutations of FlnA have also highlighted its importance in cell migration [2]. Periventricular heterotopia results from neurons' failure to migration, and this disease has been linked to various mutations in FlnA [18–21]. Heterozygous loss of function of human FlnA causes periventricular nodular heterotopia in females and is generally lethal in hemizygous males [20]. FlnA mutations have also been linked to cardiovascular problems, including familial cardiac valvular dystrophy [22]. However, FlnA's expression is some kind of tissue-specific and its role in cell migration is cell type-dependent [2].

FlnA is of particular importance in facilitating cell adhesion and migration by interacting with binding partners and regulating the corresponding signaling pathways [23]. β1-integrin is of critical importance in cell adhesion. FlnA binds to β1-integrin and promotes cell adhesion and migration by facilitating ligand binding via inside-out signaling [24]. Disruption of this interaction by knockdown of FlnA decreases the amount of β1-integrin. FlnA is often found co-localized with vimentin and both are found at sites of cell protrusions [25]. In addition, FlnA acts at these sites to bring multiple proteins to the sites of lamellipodia formation to promote cell migration [23, 26, 27]. FlnA anchors the GTPases to the cell membrane, acting as a scaffolding protein for downstream targets to remodel the actin cytoskeleton and allow cell motility [23].

FlnA's Function in Cancer Invasion and Metastasis

FlnA is originally revealed as a cancer-promoting protein, and its vital importance in cell migration and adhesion makes it closely involved in cancer invasion and metastasis. However, recent studies have also found that under certain conditions, it prevents tumor progression, confusing the precise function of FlnA in cancer development [5]. FlnA's dual role in cancer invasion and metastasis could be explained as below.

Cancer is very rarely caused by the deregulation of one growth pathway alone. FlnA likely plays a role in cancer metastasis because of its involvement in multiple regulatory pathways [23, 28]. FlnA is highly susceptible to proteolysis. While full-length (280 kDa) FlnA is mainly localized to the cytoplasm, the active cleaved form of FlnA (90 kDa) localizes to the nucleus rather than the cytoplasm [29, 30]. Rosalinda et al. [5] proposed that when FlnA is localized to the cytoplasm or plasma membrane, it has a tumor-promoting effect by interacting with signaling molecules. On the other hand, if FlnA is localized to the nucleus, then they may act to suppress tumor growth and inhibit metastasis by interacting with transcription factors (see Fig. 1b). This view perfectly explains

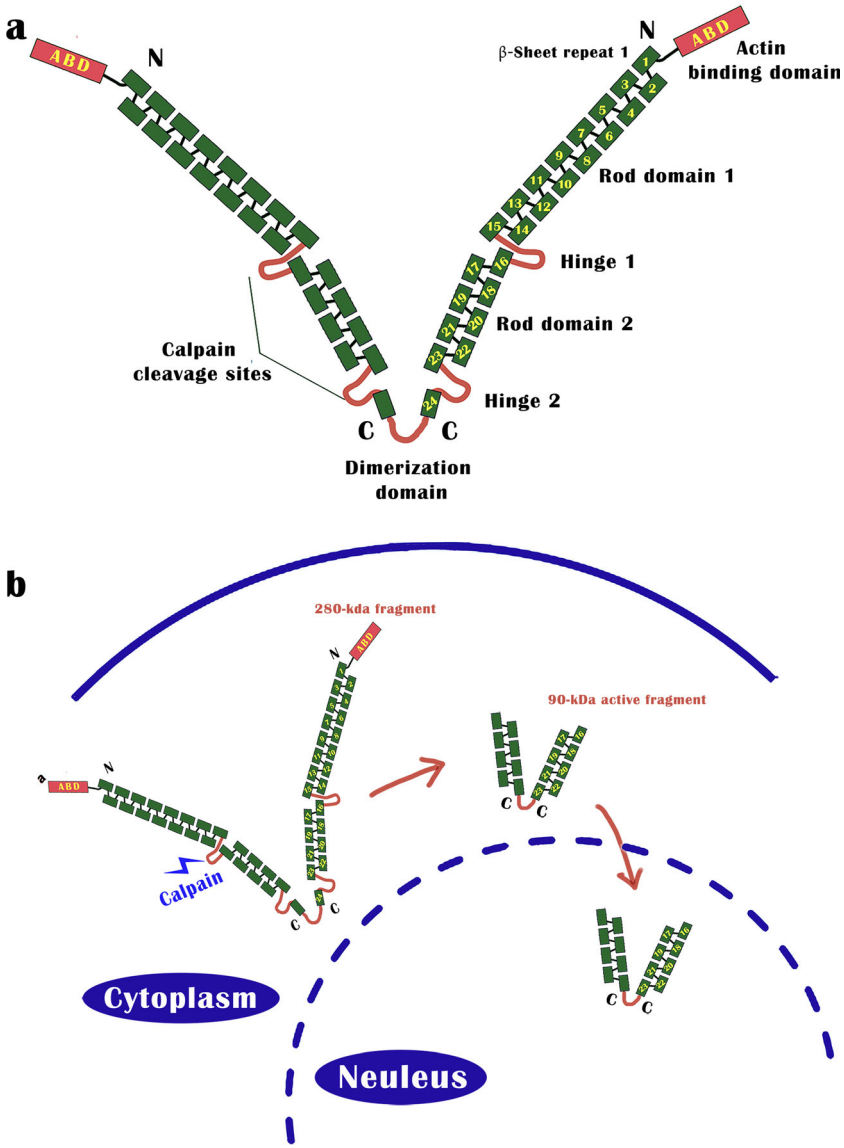

Fig. 1 a | The structure of human FlnA| The amino-terminal actin-binding domain contains sequence motifs found in many actin-filament-binding proteins. The rest of the protein is made of 24 repeats of ~96 amino acids each. Dimerization occurs through the twenty-fourth repeat. All vertebrate filamins have a stretch of 35 amino acids between repeats 23 and 24 designated 'hinge 2'. Some filamins also have a second hinge designated 'hinge 1' between repeats 15 and 16. The subunits have straight segments corresponding to the β-sheet rods interrupted by bends corresponding to sites susceptible to proteolysis by calpain. **b | FlnA's subcellular localization|** When FlnA is localized to the cytoplasm or plasma membrane, it has the ability to promote tumor metastasis through interaction with signaling molecules. If FlnA undergoes proteolysis and the proteolysed fragments localize to the nucleus, where they regulate transcription, then they may act to suppress tumor growth and inhibit metastasis

why FlnA plays an opposite role in cancer invasion and metastasis. Just as Rosalinda and colleagues put it, as a scaffolding protein, FlnA's function in the cell depends on the binding partners, not on itself. That is to say, FlnA only acts to bring proteins together and promote the interaction of these proteins to either promote or prevent cancer [5].

In the following, we comprehensively summarize available findings on FlnA's expression in human cancers. Where possible, we also indicate the correlation of FlnA expression with cancer stages and patient prognosis, and clarify its localization and its dual role in different cancers (see Table 1).

Prostate Cancer

FlnA is seen to be overexpressed in prostate cancer [29, 31], and a role of FlnA is identified in prostate-specific membrane antigen (PMSA) enzymatic activity. PMSA is an integral membrane protein highly expressed in high-grade prostate cancers, metastatic diseases, and hormone-regractory prostate carcinoma [32]. It has an important role in prostate cancer's metastasis and progression [33, 34]. Early study showed that filamin can bind PMSA and reduce the internalization rate of PSMA and its NAALADase activity, which will repress PMSA' metastatic capacity [35].

FlnA can also improve or repress prostate cancer by regulating the human androgen receptor (hAR). Most prostate cancers are androgen dependent and hAR can promote the progression of prostate cancer [36]. An in vitro model showed that nuclear expression of FlnA correlated with androgen dependence [37]. And when colocalized with hAR to the nucleus, FlnA will repress AR transactivation and inhibit the progression of prostate cancer [29, 38]. And the AR/FlnA complex specially regulates AR extranuclear functions leading to consequent cell motility [39]. Whereas cytoplasmic located

Table 1 FlnA's involvement in human cancers

Cancer	Cell experiments			Animal studies	IHC studies			Refs.
	Targets/Cells	Localization	Function		Expression level	Localization	Function	
Prostate cancer[a]	PMSA	/	Inhibit	/	Zhou et al.: ↑ Sun et al.: ↓	/ /	/ Inhibit	[29–40]
	hAR	Nucleus Cytoplasm	Inhibit Promote		Bedolla et al.	Nucleus Cytoplasm	Inhibit Promote	
Renal cell carcinoma	Renal 786-0 cells ACHN cells	/ /	Promote Inhibit	/	Sun et al.: ↓	/	Inhibit	[45]
Breast cancer[a]	Caveolin-1 Cyclin D1 PAK1	/ / /	Inhibit Promote Promote	/	Tian et al.: ↑ Jiang et al.: ↑	Cytoplasm /	Promote Promote	[46–53]
Gastric cancer	SGC-7901 cells	/	Inhibit	/	Sun et al.: ↓	/	Inhibit	[54]
Colorectal adenocarcinoma	/	/	/	/	Tian et al.: ↓	/	Inhibit	[55]
Pancreatic cancer	PrP	/	Promote	/	Zhou et al.: ↑	/	/	[31], [56, 57]
Lung cancer	EGFR	/	Promote	/	Zhou et al.: ↑ Uramoto et al.: ↑	/	/	[31] [58–60]
Nasopharyngeal cancer	CNE2 cells	/	Inhibit	/	Sun et al.: ↓	/	Inhibit	[61]
Squamous cell carcinoma	c-Met	/	Promote	/	/	/	/	[31, 62]
Melanoma	R-Ras integrin β1	/ /	Promote Promote	Promote[b]	Zhang et al.: ↓	/	Promote	[50], [28, 56, 63, 64]
Hemangioma[c]	/	/	/	/	Hosaka et al.: ↑	/	/	[65]
Astrocytoma[c]	/	/	/	/	Alper et al.: ↑	/	/	[52]
Neuroblastoma[c]	/	/	/	/	Bachmann et al.: ↑	/	/	[66]
Colon cancer[c]	/	/	/	/	Porter et al.: ↑ Larriba et al.: ↑	/	/	[67, 68]
Liver cancer[c]	/	/	/	/	Guedj et al.: ↑ Zhang et al: ↑	/	/	[50, 69]

Abbreviations: IHC Immunohistochemistry *PMSA* Prostate-specific membrane antigen *hAR* Human androgen receptor *PrP* Prion protein *EGFR* Epidermal growth factor receptor

[a] Only part of researches in prostate cancer and breast cancer evaluate the differences that arise from the localization of the protein

[b] Animal studies of FlnA were only carried out in melanoma. In melanoma cell induced xenograft models, FlnA deficiency is associated with smaller tumors and reduced metastasis

[c] Immunohistochemistry studies show that FlnA overexpresses in hemangioma, neuroblastoma, astrocytoma, colon cancer and liver cancer, but the relationships between FlnA expression and cancer stages as well as patient prognosis are not clarified

FlnA could interact with hAR and promote it to move from cytoplasm to the nucleus, and then induced cell invasion and migration [29, 36].

In immunohistochemistry studies, Bedolla et al. [29] separately scored FlnA staining in nucleus and cytoplasm/cytoplasmic membrane in prostate cancer tissue. Results showed that in normal prostate, prostatic intraepithelial neoplasia and clinically localized prostate cancers, FlnA is mostly nuclear, whereas in metastatic tissue, it is mostly cytoplasmic, indicating that in prostate cancer, metastasis correlates with cytoplasmic localization of FlnA and may be prevented by cleavage and subsequent nuclear translocation of this protein. Sun et al. [40] also confirmed that FlnA expression decreases in prostate cancer and correlates significantly with T stages, lymph node metastasis, clinic stage, and Gleason score, suggesting that FlnA may play important roles as a negative regulator to prostate cancer.

FlnA may also be a promising treatment target for prostate cancer. Since prostate cancer depends on hAR for growth and survival, metastatic prostate cancer is treated with androgen deprivation therapy (ADT) [41]. However, patients on ADT will eventually progress to castration-resistant prostate cancer (CRPC), which is currently incurable [42]. Long-term androgen deprivation will result in increased expression of FlnA [43], but once nuclear localized, FlnA can enhance androgen responsiveness and sensitize CRPC cells to ADT by inducing apoptosis in CRPC cells during ADT, identifying it is a treatment tool in advanced prostate cancer [44]. Mooso et al. [44]

found that genistein-combined-polysaccharide (GCP) can facilitate FlnA's translocation from cytoplasm to nucleus in prostate cancer cells.

Renal Cell Carcinoma

Sun et al. [45] found that FlnA expression is decreased in human renal cell carcinoma (RCC) tissue and correlates significantly with lymph node metastasis, clinic stage, histological grade and poor overall survival. However, different cell lines show conflict results. ACHN cells transfected with FlnA have a lower survival fraction, significant decrease in migration and invasion, higher cell apoptosis, higher percentage of the G0/G1 phases compared with those untransfected with FlnA. While renal 786-0 cells transfected with FlnA siRNA have a higher survival fraction, significant increase in migration and invasion. Subcellular localization of FlnA may be a possible explanation, but unfortunately, Sun et al. did not clarify the localization of FlnA when they carried out the experiments.

Breast Cancer

Pre-clinical studies show that FlnA palys a dual role in breast cancer's metastasis. On the one hand, FlnA regulates focal adhesion disassembly and suppresses breast cancer cell migration and invasion by interacting with Caveolin-1 [46–48]. On the other hand, FlnA deficiency in breast cancer cells significantly reduces their migration and invasion by interacting with Cyclin D1 [49, 50]. Up-regulation of phosphorylated PAK1 can increase breast cancer cell motility through FlnA [51].

Clinical studies showed that FlnA is overexpressed in metastatic breast cancer [50, 52, 53]. Overexpression of *cytoplasmic* FlnA is associated with advanced stage, lymph node metastasis, vascular or neural invasion, menstruation state and other risk stratifications for breast cancer [53]. And low levels of FlnA expression are associated with a better distant metastasis-free survival than those with normal levels of FlnA [50]. What's more, by detecting circulating FlnA in patient plasma samples, Alper et al. [52] found plasma FlnA appears to be a specific and sensitive marker for patients with metastatic breast cancer.

Gastric Cancer

Sun et al. [54] confirmed that FlnA expression is significantly lower in gastric cancer tissue and correlates significantly with lymph node metastasis, clinic stage, histological grade, and poor overall survival. The result of biological function shows that SGC-7901 cell transfected FlnA has a lower survival fraction, significant decrease in migration and invasion compared with SGC-7901 cell untransfected FlnA.

Colorectal Adenocarcinoma

Latest study showed that FlnA may be a new cancer suppressor gene for colorectal adenocarcinoma [55]. By immunohistochemistry, Tian et al. found that the positive expression of FlnA in cancer tissues was significantly lower than that in normal mucosa, and the expression of FlnA correlated with liver metastasis, lymph node metastasis and rectal invasion depth. Moreover, survival analysis showed that the expression level of FlnA was closely related with survival of patients with colorectal adenocarcinoma.

Pancreatic Cancer

FlnA is overexpressed in pancreas adenocaicinoma [31]. It may promote tumor metastasis by the cellular prion protein (PrP), which can interact with FlnA and alter the cytoskeleton. Inhibition of PrP reduces cellular proliferation and invasiveness in PDAC cell lines. PrP expression in tumors correlates with a marked decrease in pancreatic cancer patient survival [56, 57]. FlnA may also interact with c-MET to paly a role in pancreatic cancer invasion and migration [31].

Lung Cancer

TGF-β induced-EMT in human lung cancer cells mediates tumor cell migration and invasion phenotype. Keshamouni et al. [58] found that FlnA is up-regulated during EMT by a global stable isotope labeled profiling strategy. And Targeting FlnA can reduce K-RAS-induced lung adenocarcinomas and endothelial response to tumor growth in mice [59]. Immunohistochemistry analysis showed that FlnA is overexpressed in lung cancer, but no significance was observed between the expression of FlnA and metastatic or prognostic indicators [31, 60]. Uramoto et al. [60] also found a significant positive relationship between FlnA and EGFR (epidermal growth factor receptor) in patients with lung cancer, indicating that FlnA may function with EGFR together to regulate angiogenesis of tumor.

Nasopharyngeal Cancer

Sun et al. [61] confirmed that FlnA expression is significantly lower in nasopharyngeal cancer tissue and correlates significantly with T stage, lymph node metastasis, clinical stage, and histological grade. The result of biological function shows that CNE2 cell-transfected FlnA has a lower survival fraction, significant decrease in migration and invasion compared with CNE2- cell untransfected FlnA.

Squamous Cell Carcinoma

Kamochi et al. [62] found that irradiated fibroblasts overexpressed FlnA and c-Met and promotes invasion and growth of human squamous carcinoma cells. Without FlnA, expression of c-Met is also significantly decreased and the cells exhibit poor migration and invasion ability. This indicates that overexpression of FlnA can promote human squamous carcinoma invasion and metastasis by interacting with c-Met, and FlnA regulates c-Met expression through its interaction with Smad2 [31, 62].

Melanoma

Early preclinical studies showed that the depletion of FlnA significantly reduces the proliferation, migration and invasion of melanoma cell lines in vitro [50, 63]. In UACC647 melanoma cell induced xenograft model, depletion of FlnA is associated with smaller tumors [63]. In C8161 cell induced xenograft model, FlnA deficiency causes significantly reduced lung, splenic and systemic metastasis in nude mice [50]. PrP is highly expressed in invasive melanoma, and binding of pro-PrP enhanced association between FlnA and integrin β1, which then promote cell spreading and migration [56, 64]. In melanoma cells, R-Ras functionally associates with FlnA and promotes metastasis by enhancing integrin-dependent cell migration [28].

In clinical studies, immunohistochemistry analysis shows that lower FlnA expression can significantly improve overall survival in patients with melanoma tumor [63].

Other Cancers

FlnA also overexpresses in other cancers, like hemangioma [65], neuroblastoma [66], astrocytoma [52], colon cancer [67, 68] and liver cancer [50, 69], but studies providing information about the relationships between FlnA expression and cancer stages as well as patient prognosis are very rare. Thus, more researches are needed in the field of these cancers.

Conclusions and Perspectives

After 40 years of research, we now are much clearer of FlnA's properties and functions than before. FlnA plays an especially significant role in cell adhesion and migration, thus it is undoubtedly that FlnA is closely associated with cancer metastasis and invasion. Originally revealed as a cancer-promoting protein, FlnA actually plays a dual role in cancer metastasis and invasion. In the cytoplasm, FlnA functions in various growth signaling pathways and high cytoplasmic FlnA levels have shown a correlation with invasive cancers. However, cleaved FlnA fragment localizes to the nucleus and interacts with transcription factors to decrease invasiveness of cancer. Therefore, development of drugs to target FlnA and cause cleavage and subsequent localization to the nucleus could be a new and potent field of research in treating cancer. Work toward this end is already in progress in prostate cancer, and hitherto, results are encouraging.

FlnA has been studied in lots of cancers. In different cancers and different cell lines, it presents opposite role in cancer invasion and metastasis. However, the precise underlying mechanism is still a mystery. Different subcellular localization of FlnA may promisingly provide a possible and reasonable explanation. Pitifully, most studies just clarified the relationship between FlnA and a specific cancer, but did not clarify whether FlnA was located in the cytoplasm or nucleus when they carried out experiments. Since FlnA is so deeply involved in cancer metastasis, it has been relatively well studied in several invasive cancers including prostate cancer, breast cancer, colon cancer and melanoma. As for other highly metastatic cancer, like pancreatic cancer and liver cancer, both preclinical and clinical researches are still very scarce! There still remains large amount of work to do and the examination of FlnA in cancer development is still underway.

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