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Review

The function and pathogenic mechanism of filamin A

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Filamin A(FLNa) is an actin-binding protein, which participates in the formation of the cytoskeleton, anchors a variety of proteins in the cytoskeleton and regulates cell adhesion and migration. It is involved in signal transduction, cell proliferation and differentiation, pseudopodia formation, vesicle transport, tumor resistance and genetic diseases by binding with interacting proteins. In order to fully elucidate the structure, function and pathogenesis of FLNa, we summarized all substances which directly or indirectly act on FLNa so far, upstream and downstream targets which having effect on it, signaling pathways and their functions. It also recorded the expression and effect of FLNa in different diseases, including hereditary disease and tumors.

FLNa is a homodimer protein (280.739kda), which can integrate cellular mechanics and signal transduction.

FLNa determines the shape and movement of cells by guiding the formation of dynamic actin stress fibers (Hu et al., 2017)

On the other hand, it can also be a scaffold for signal protein (tyrosine kinase, GTPase or phosphatase, *et. al*) and adhesion receptor (such as integrin)

FLNa consists of one actin-binding domain (ABD) and 24 repeat immunoglobulin(Ig) domains, each of Ig contains about 96 amino acids. It can divide into three parts: Rod1 (Rep.1–15), Rod2 (Rep.16–23) and Rep.24(Fig. 1), which are connected by two hinges (Fabrice et al., 2006). Rod1 has a linear structure, including the ABD domain(composed of two calponin homologous regions CH). CH binds to actin. The existence of FLNa Ig10 increases the binding strength of ABD (Xing et al., 2019). Rep.16–23 has a compact structure and consists of some spiral-shaped double domains. Compared with the linear structure of Rep.1–8, it is more flexible and highly variable, and it is involved in a variety of transmembrane transduction and protein interactions (Ruskamo et al., 2012). The domain-domain interactions in FLNa Rep.16–23 lead to compact ge-ometries and alter the pulling direction of each domain, thus regulate the stress of the F-actin network and mechanical sensitivity of FLNa (Xu et al., 2013). When FLNa Rep.20–21 is at a closed conformation, Rep.20 blocks the domain of Rep.21 and prevents integrin from binding. The

Abbreviations: PNH, periventricular nodular heterotopia; ABD, actin-binding domain; Ig, immunoglobulin; SST2, somatostatin receptor 2; D2R, dopamine D2 receptor; D3R, dopamine D3 receptor; Aβ1-42, amyloid-β1–42; α-7nAChR, α 7-nicotinic acetylcholine receptor; TLR4, toll-like receptor 4; IGFBP-5, insulin-like growth factor-binding protein-5; lamc1, laminin gamma 1; PHD2, oxygen-sensing prolyl hydroxylase domain; EMT, epithelial-mesenchymal transition; LSCC, laryngeal squamous cell carcinoma; MMP-9, matrix metallopeptidase 9; ER, endoplasmic reticulum; CRC, colorectal cancer; ADT, Androgen deprivation therapy; CaP, prostate cancer; CRPC, castration-resistant CaP; AR, androgen receptor; GCP, Genistein combined polysaccharide; TNBC, triple-negative breast cancer; CDK1, cyclin dependent kinase 1; Pol I, RNA polymerase I; TIF-IA, transcription initiation factor I; HIF-1α, hypoxia-inducible factor-1α; ECM, extracellular matrix; MVP, mitral valve prolapse; FA, focal adhesion; HCC, hepatocellular carcinoma; AZGP1, Zinc-α2-glycoprotein 1; PrP, prion protein; BSCC, buccal squamous cell carcinoma.

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hidden integrin-binding sites can expose when the mechanical force applied to the domain (Pentikäinen and Ylänne, 2009). Rep.23 binds to RAC-GTPase activator protein FilGAP (Nakamura et al., 2009). FilGAP locates at the site of force transmission of FLNa, which mediates cell lamellae formation under tension and protects cells from apoptosis or necrosis caused by mechanical force (Ohta et al., 2006; Ehrlicher et al., 2011). Rep.24 mediates the formation of homodimers and V-shaped structures, leading to the vertical cross-linking of actin filaments (Nakamura et al., 2007)(Fig. 1).

FLNa is mainly located in the cytoplasm and can affect the orthogonal branching of F-actin.

When calpain cuts the hinge of FLNa, about 90 kDa of rod 2 (rep.16–23) fragment is formed and enters the nucleus to function (Salimi et al., 2018). PKA phosphorylates the Ser2152 site, which increased FLNa's resistance to calpain cleavage (Chen and Stracher, 1989; Jay et al., 2000). Besides, the calpain inhibitor, calpeptin, inhibits the division of FLNa (Bandaru et al., 2019) and reduces the entry of it's fragments into the nucleus. Many studies have shown that FLNa has a dual effect. When it localizes in the cytoplasm, it promotes tumor progression by partici-pating in cell migration, adhesion, and growth signals (Shao et al., 2016). However, when FLNa is hydrolyzed, the C-terminal segment will locate in the nucleus, which can inhibit tumor growth and metastasis by interacting with transcription factors (Savoy and Ghosh, 2013).

Rod 2 is susceptible to the influence of ~ 10pn force, to unwrap the spiral-shaped structure and participating in signal transduction by binding with a variety of transmembrane proteins. In contrast, Rod 1 can withstand greater force (Chen et al., 2011). FLNA also protects cells from force-induced apoptosis by enhancing matrix adhesion (Pinto et al., 2014). We summarized the function and pathway of FLNa, as shown in Table 1. At the same time, we also made the interactive network diagram (Fig. 2) and phylogenetic tree(Supplementary Fig. 1)

2.1. Signal transduction

FLNa is involved in a variety of intracellular signal transduction and transport. One research showed that PKA can induce FLNa Ser2152 phosphorylation, and the phosphorylated FLNa binds to somatostatin receptor 2 (SST2) to inhibit its activity, which hinders the signal transduction of SST2 in pituitary tumor cells (Peverelli et al., 2018). Mei and other researchers found that reducing FLNa increased the activity of RalA, and the activated RalA interacted with GRK2 to separate it from dopamine D2 receptor (D2R). At the same time, active RalA hinders the coupling of D3R and G protein from regulating the transport and signal transduction of D2R and D3R mediated by filamin A (Zheng et al., 2016).

Christine and others found that insulin-like growth factor-binding protein-5 (IGFBP-5) can promote FLNa cracking after dephosphorylation. Then the Smad3/4 was recruited to the C-terminal of FLNa to induce the nuclear shuttle of the fragment. After that, it binds to the promoter re-gion of laminin gamma 1 (lamc1) and participates in signal transduction (Abrass and Hansen, 2010). Also, carcinogenic changes often occur in the PI3K pathway. Najib found that SST2 and p85 can form complex, which can promote tumor development by activating PI3. However FLNA can bind SST2 with p85 competitively to inhibit tumor growth (Najib et al., 2012).

cytoskeleton is mainly composed of microtubules, in-termediate filaments and microfilaments, among which microfilaments are the thinnest.

Microfilaments are synthesized by helical polymerization of actin, which can participate in cell morphology and movement through continuous polymerization and rearrangement. The change of cell adhesion and morphology in the tumor microenvironment is the key to tumor metastasis's occurrence and development. FLNa binding to actin can cause the dynamic change and rearrangement of actin

Table 1
FLNa function and mechanism.

binding sites	Partners	Mechanism / pathway	function	Reference
Ser2152	SST2	cAMP/PKA	SST2 signal transduction	PMID: 30,098,401 (Peverelli et al., 2018)
	STIM1	the distribution of STIM1 in cytoskeleton and Orai1 channel	regulate calcium storage and platelet function	PMID: 29,284,605 (Lopez et al., 2018)
	CCR2B	—	vesicular transport and plasma-membrane circulation	PMID: 27,909,248 (Pons et al., 2017)
	Big2	phosphorylation	migration of neurons	PMID: 22,956,851 (Zhang et al., 2012)
	(ARFGEF2)	—	vesicular transport	PMID: 24,709,996 (Sheen, 2014)
	S6K	PA/S6K/FLNa-actin	cytoskeleton and movement	PMID: 25,512,366 (Henkels et al., 2015)
Ser1084、1459 and 1533	Cdk1	phosphorylation	cell cycle and division	PMID: 25,445,790 (Szeto et al., 2015)
P2309、P2316	PHD2	hydroxylation	controls dendritic spines and synaptic density	PMID: 26,972,007 (Segura et al., 2016)
Rep.1–8	PTPN12	Src、p190RhoGAP	extracellular matrix, focal adhesion and cytoskeleton	PMID: 26,594,644 (Duval et al., 2015)
Rep.3	R-Ras	VE-Cadherin phosphorylation	lose the endothelial barrier function and increase vascular permeability	PMID: 21,660,952 (Griffiths et al., 2011)
		—	regulate the adhesion and migration of melanoma cells	PMID: 20,585,650 (Gawecka et al., 2010)
Rep.5	Syk	ITAM	signal transduction and platelet function	PMID: 20,713,593 (Falet et al., 2010)
Rep.8–15	Integrin α1β1	PKB/AKT/ERK1/2	cell adhesion and migration	PMID: 26,572,583 (Krebs et al., 2015)
	CFTR	—	regulate CFTR surface localization	PMID: 23,636,454 (Smith et al., 2013; Playford et al., 2010)
Rep.9–18	Coronin 1A	—	HL-60 migration and phagocytosis	PMID: 28,595,776 (Roth et al., 2017)
Rep.17	GPIbalpha	—	maintain platelet integrity and shape	PMID: 16,293,600 (Nakamura et al., 2006)
Rep.16–19	Grb7	EGF	cytoskeleton remodeling and migration	PMID: 24,089,360 (Paudyal et al., 2013)
Rep.17–23	SH2B1β	PRL/PAK1	PRL-dependent actin rearrangement	PMID: 21,566,085 (Rider and Diakonova, 2011)
Rep.19	D2R、D3R	—	anchor D2R and D3R to cytoskeleton	PMID: 11,320,256 (Lin et al., 2001)
Rep.20	PACSIN2	—	regulates membrane tubulation in megakaryocytes and platelets	PMID: 25,838,348 (Begonja et al., 2015)
Rep.21	Fimbacin (LUZP1)	—	stable cytoskeleton	PMID: 30,990,684 (Wang and Nakamura, 2019)
	αIIbβ3	—	restrain the integrin in a resting state	PMID: 25,849,143 (Liu et al., 2015)
Rep.22	β-arrestins	MAPK/ERK	cytoskeleton reorganization and membrane ruffle formation	PMID: 16,611,986 (Scott et al., 2006)
	Arl4C	Cdc42	filopodium formation and cell migration	PMID: 28,855,378 (Chiang et al., 2017)
Rep.23	FilGAP	—	cell polarity and movement	PMID: 19,293,932 (Nakamura et al., 2009)
	FilGAP	cell lamellae formation	protect cell against force-induced apoptosis	PMID: 19,144,823 (Shifrin et al., 2009)
	Pak1	phosphorylation	cytoskeleton	PMID: 12,198,493 (Vadlamudi et al., 2002)
	RSK	phosphorylation	cytoskeleton and membrane ruffling	PMID: 15,024,089 (Woo et al., 2004)
Rep.24	MOPr	—	activate MAP kinase p38	PMID: 20,857,334 (Simon and Onoprishvili, 2010)
Rep.20–22	Supervillin	—	cell movement	PMID: 20,309,963 (Smith et al., 2010)
Rep.22–24	TF	increasing cell surface TF activity	Microvesicles transport	PMID: 29,044,292 (Collier et al., 2017)
FLNA C-terminal	PERK	—	regulate the formation of ER-PM contact sites	PMID: 29,290,929 (van Vliet and Agostinis, 2017)
CH1	ASB2α	FLNA degradation	cytoskeleton remodeling, adhesion and diffusion	PMID: 24,052,262 (Razinia et al., 2013)
—	Snail	EMT	cell adhesion and migration	PMID: 28,778,796 (Wieczorek et al., 2017)
	Refilin	EMT	cell phenotype and nuclear morphology	PMID: 22,446,558 (Gay et al., 2011)、PMID: 21,709,252 (Gay et al., 2011)
	smad2	EMT	drug resistance	PMID: 32,195,017 (Cheng et al., 2020)
	ERK	MAPK/ERK	drug resistance	PMID: 26,546,439 (Zhao et al., 2016)
	IR	MAPK	cytoskeleton reorganization and membrane ruffle formation	PMID: 12,734,206 (He et al., 2003)
	Rho A	—	regulate neutrophil uropod retraction during chemotaxis	PMID: 24,205,360 (Sun et al., 2013)
	CCR2B	—	monocyte chemotaxis	PMID: 20,808,917 (Minsaas et al., 2010)
	MKL1	RhoA	promote SRF activity and cell migration	PMID: 26,554,816 (Kircher et al., 2015)
	SphK1	PAK1	mediate cell lamellae formation and migration	PMID: 18,644,866 (Maceyka et al., 2008)
	SMAD2	c-MET/AKT	cell migration	PMID: 20,473,907 (Zhou et al., 2011)
	IRE1α	—	cytoskeleton and migration	PMID: 30,013,108 (Urra et al., 2018)
	RhoA	—	stress fiber formation and fell spreadin	PMID: 28,175,289 (Hu et al., 20172017)
	AR	Rac	regulate AR function and cell movement	PMID: 25,182,765 (Giovannelli et al., 2014)
	P2Y2	—	cytoskeleton and movement、uptake Low Density Lipoprotein	PMID: 27,522,265 (Dissmore et al., 2016)
	PKD2	PC2-FLNa-actin	anchor PC2 to cytoskeleton	PMID: 25,861,040 (Wang et al., 2015)
	BRCA1	—	DNA damage repair	PMID: 20,305,393 (Velkova et al., 2010)
	Ndr2	phosphorylate Ser2152	regulate lymphocyte differentiation and proliferation	PMID: 30,568,657 (Waldt et al., 2018)
	Sam68	enhance NF-κB signal transduction	inflammatory response to vascular injury	PMID: 31,639,388 (Han et al., 2019)

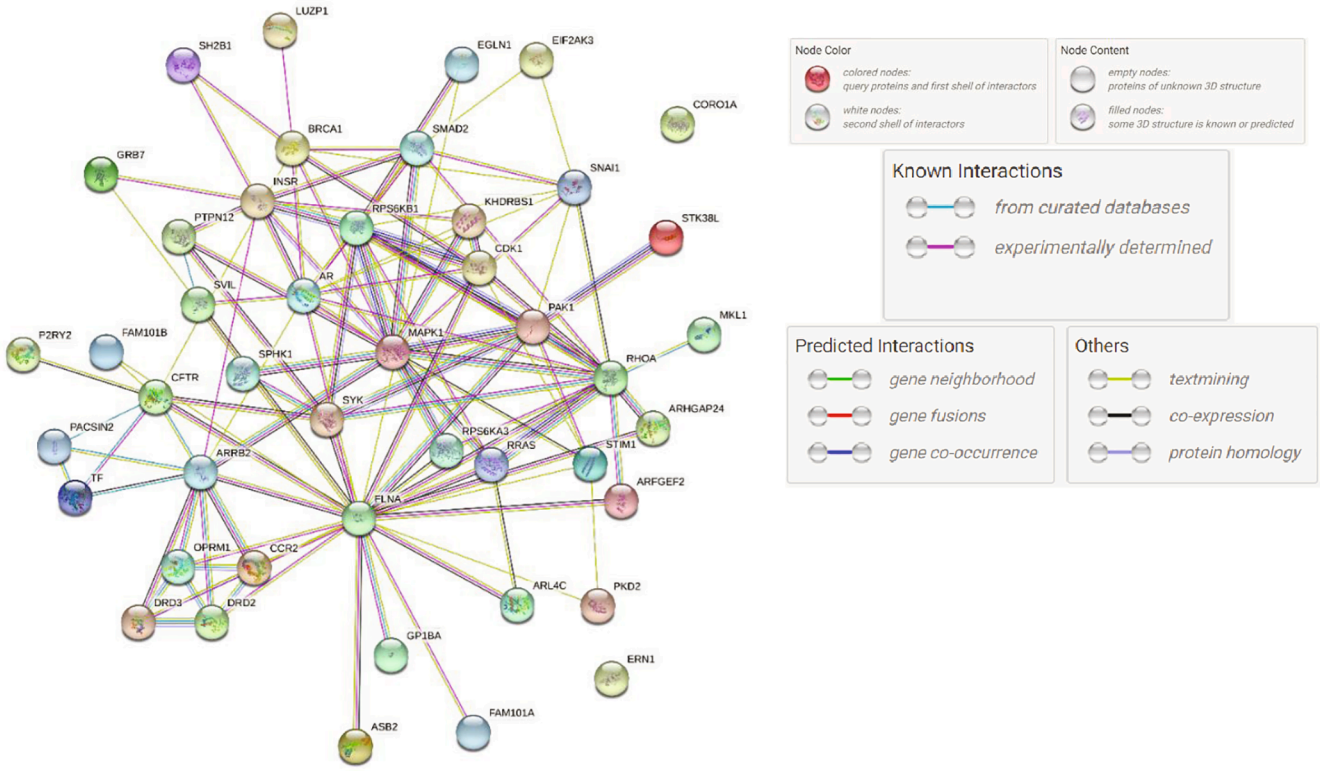

Fig. 2. Interactive Network Diagram of FLNa.

filaments, which is the primary physical force leading to the change of cytoskeleton and cell migration (Kumar et al., 2019).

Segura found that under normal oxygen conditions, oxygen-sensing prolyl hydroxylase domain (PHD2) hydroxylates FLNa proline residues P2309 and P2316 to reduceit. During hypoxia, PHD2 inactivation blocks the degradation of FLNa , which induces the formation of many immature dendrites, de-creases the density of synapses and affecting the function of neurons (Segura et al., 2016). RefilinA and RefilinB belong to the actin regula-tory factor family. In epithelial cells, TGF–β up-regulates RefilinB, and then RefilinB stabilizes the perinuclear actin fiber bundle by binding with FLNa (Gay et al., 2011). RefilinB/FLNa complex controls the for-mation of the actin network around the nucleus and changes the nuclear morphology during epithelial-mesenchymal transition (EMT) (Gay et al., 2011). Another research finds that FilGAP binds to FLNa and suppresses Rac-dependent lamellae formation and cell spreading. Although ARHGAP22 is a member of the FilGAP family, it does not directly bind to FLNa but controls cell morphology by inactivating Rac (Mori et al., 2014).

Because circFLNA can sponge miR-486-3p to relieve its effect, then through upregulating FLNa protein expression to urge the migration of cancer cells and reducing the sur-vival rate of patients (Wang et al., 2019). R-Ras is one of the small GTPases, which can combine with FLNa rep.3 to regulate the adhesion and migration of melanoma cells (Gawecka et al., 2010). FLNa regulates the activation of the Ras/ERK pathway through Ras-GRF1 and then regulates the production of matrix metallopeptidase 9(MMP-9) (Zhu et al., 2007). One study showed that the expression of FLNa in gastric cancer was significantly lower than in healthy tissue.Overexpression of FLNa, the survival rate of SGC-7901 cells decreased, the expression of MMP-9 protein decreased, and the migration and invasion ability of gastric cancer cells decreased significantly well (Sun et al., 2014).

migration of neurons. The transition of newborn neurons from multipolar to bipolar precise channel coupling is called radial migration. The radial migration of LPA4 deficient neurons is impaired. Nobuhiro et al. have shown that overexpression of FLNa can restore the morphology and migration function of defective neurons (Kurabayashi et al., 2018).

In addition, FLNa regulates neutrophil chemotaxis through RhoA. Although neutrophils lacking FLNa can show normal polarization and pseudopodia extension, they can not retract uropod and affect cell migration (Sun et al., 2013).

When the ER Ca^{2+} store is depletion, PERK interacts with FLNa C-terminal to regulate the ER-plasma membrane contact site formation by regulating the actin cytoskeleton (van Vliet and Agostinis, 2017; van Vliet et al., 2017). Planagumà found that after CCL2 ligands were activated, FLNa interacted with chemokine receptor CCR2B in endocytic vesicles, making CCR2B receptor in Rab5 positive vesicles move along FLNa-positive fiber (Planagumà et al., 2012). CCR2B and β2-AR can promote endocytosis and plasma membrane cir-culation by inducing phosphorylation of FLNa Ser2152. Decrease FLNa can reduce the connection between CCR2B and endoplasmic reticulum, thus limiting vesicle transport and slowing down the speed (Pons et al., 2017). Some studies found that FLNa regulates neuronal migration through Big2-dependent ARF1 activation: when FLNa reduce, Big2 up-regulates and subcellular localization is changed. Then the ARF1 located in the cell membrane is activated, after that ,vesicle transport and neuronal migration are promoted (Zhang et al., 2013), which can maintain the adhesion and cortical development of nerve cells (Sheen, 2014). Also, caveolae are membrane invagination and closely associated

with actin fibers. Muriel found that FLNa is required to maintain the F-actin-dependent linear distribution of caveolin-1, and the linear distribution and anchorage of caveolin-1 vesicles are both required for caveolin-1 inwards trafficking. FLNa can anchor caveolin-1 on the plasma membrane and promote the inward transport of caveolae (Muriel et al., 2011).

2.4. Drug resistance

Chemoresistance is the main reason for the recurrence and treatment failure of colorectal cancer (CRC). A research team found that FLNa enhanced the c-Met promoter activity by interacting with Smad2, which induced EMT and drug resistance in colorectal cancer cells (Cheng et al., 2020). Androgen deprivation therapy(ADT) often uses in the treatment of prostate cancer(CaP), unfortunately, Long-term use of ADT leads to castration-resistant CaP(CRPC). In the sensitive phase of hormone therapy, calpain-2 cleaves the androgen receptor(AR) ligand domain but retains the DNA binding domain, so that cancer cells can adapt to androgen-independent growth and proliferation during ADT. However, long-term androgen deficiency promotes the overexpression and activity of calpain 2, increasing the FLNa fragment division (Liu et al., 2014). It has been found that FLNa fragment nuclear localization can induce apoptosis of CRPC cells during ADT (Bedolla et al., 2009). Genistein combined polysaccharide(GCP) can inhibit the phosphorylation of FLNa, which can promote FLNa to divide and locate in the nucleus, and then enhance the sensitivity of androgen therapy in CRPC patients (Mooso et al., 2012). Wang put forward that FLNa was cut into 90 kDa fragments (Rep.16–23) and entered the nucleus to bind with AR, which reduced Akt phosphorylation and restored the sensitivity of C4-2 cells to Casodex (Wang et al., 2007). Besides, FLNa overexpresses in docetaxel resistant triple-negative breast cancer (TNBC) and regulates drug sensitivity through the MAPK/ERK pathway (Zhao et al., 2016). If ERK activity decreased, FLNa also decreased, resulting in cell re-sensitizati on, which can be used as a new target for TNBC chemotherapy.

2.5. Cell proliferation and differentiation

FLNa regulates cell proliferation by regulating cyclins such as cyclin dependent kinase 1(CDK1) in the G2/M phase. Inhibition of FLNa can elengthen cell cycle (mainly in G2/M) and reduce the number of cell division (Lian et al., 2012). Lian found that FLNa and RhoA can interact in the G2/M phase, and inhibiting them would damage the degradation of Aurkb, which is related to cytokinesis. It can not only change the length of the cell cycle but also lead to the neural progenitor differentiation defect and remain in proliferative states (Lian et al., 2019). Besides that, the study found that FLNa can interact with actin-nucleating protein formin 2 and Wnt co-receptor Lrp6, which affects the neuroepithelial proliferation by affecting the activity of LRP6 and its downstream GSK3β and the accumulation of β-Catenin in the nucleus (Lian et al., 2016). FLNa can also regulate cell division involved in the recombination of actin mediated by rock cofilin. Decrease FLNa can reduce the phosphorylation of cofilin and Rho kinase (ROCK) near the spindle, and affects the asymmetric division of cells during meiosis and spindle migration of mouse oocytes (Wang et al., 2017).

FLNa binds to different proteins in the nucleus and plays a corresponding role. FLNa, as a nuclear protein to some extent, binds with RNA polymerase I (PolI) to inhibit ribosomal RNA (rRNA) transcription. After FLNa expression is reduced, rDNA promoter activity and rRNA transcription increase, and cell proliferation is promoted (Deng et al., 2012). Nguyen found that the transcription initiation factor I (TIF-IA) combined with RNA polymerase I (Pol I) promotes rRNA synthesis by activating the PI3K/Akt pathway. Simultaneously, the splicing isoform (TIF-90) of TIF-IA preferentially binds to FLNa 90 kDa fragment and inhibits rRNA synthesis (Nguyen le et al., 2014). However, with the increase of TIF-90 expression and Akt activation, FLNa division was reduced, thus promot the proliferation of leukemia cells.It provides evidence for Akt direct targeted treatment of acute leukemia.

2.6. Angiogenesis

Hypoxia can induce calpain-dependent cleavage of FLNa, then the 90 kDa fragment enters the nucleus and interacts with the N-terminal of hypoxia-inducible factor-1α (HIF-1α), up-regulating HIF-1α, promoting angiogenesis and tumor progression (Zheng et al., 2014). Another study found that after reducing FLNa in adult mouse smooth muscle cells (SM), the blood pressure significantly reduces, indicating that FLNa is the primary determinant of arterial structure and function (Retailleau et al., 2016). Besides, the decrease of FLNa significantly reduced the formation of lung tumors and fibroblast proliferation, decreased the activation of downstream signal molecules ERK and Akt, finally reduced angiogenesis in tumors (Nallapalli et al., 2012).

In heterozygous women, the abnormal expression of FLNa often lead to Periventricular nodular heterotopia(PVNH or PNH), in which children show neuronal differen-tiation or migration disorders.

Cardiac valvular dysplasia (Duval et al., 2015), congenital short bowel syndrome (van der Werf et al., 2013), frontometaphyseal dysplasia (FMD) (Zenker et al., 2006), PNH (Clap-ham et al., 2012), Melnick-Needles Syndrome (Albuquerque do Nasci-mento et al., 2016), otopalatodigital spectrum disorders types 1 and type 2(OPD1, OPD2) (Naudion et al., 2016), Osseous Dysplasia With Pigmentary Defects (TODPD) (Azakli et al., 2019), isolated thrombo-cytopenia syndrome (Nurden et al., 2011), keloid scarring and joint contracture (Atwal et al., 2016). Tyrosine phosphatase PTPN12 (PTP-PEST) combines with FLNa Rep.1–8 to activate two substrates of PTPN12: focal adhesion associated kinase Srcand RhoA specific activating protein p190RhoGAP, which can regulate extracellular matrix (ECM), focal adhesion and actin cytoskeleton. What's more, they also participate in the pathophysiological process of FLNa related mitral valve prolapse (MVP) (Duval et al., 2015; Jenkins et al., 2018). By measuring the crystal of FLNa-Ig10, they found that Melnick's needle syndrome and frontometaphyseal dysplasia were related to the mutation of Ig10 (Page et al., 2011). FLNa deficient megakaryocytes (MKS) pre-maturely release large and vulnerable platelets, which are rapidly removed from the circulation by macrophages leading to thrombocy-topenia (Jurak Begonja et al., 2011). In addition, a newborn boy with septo optic dysplasia found a new hemizygous deletion(c.6355 + 4_+5delAG)in FLNA gene inherited from his mother, which is charac-terized by hypoplasia of optic nerve and hypophysis, has expanded the phenotypic spectrum of the FLNa (Fernández-Marmiesse et al., 2019). The role and pathway of FLNa in diseases show in Table 2.

Table 2
FLNa and Hereditary Disease.

diseases	mechanism/ pathway	effect	reference
PNH	Rcan1	neuronal migration	PMID: 25,589,755 (Li et al., 2015)
tuberous sclerosis (TS)	MEK-ERK1/2	abnormal dendritic structure of neurons	PMID: 25,277,454 (Zhang et al., 2014)
TS and focal cortical dysplasia type II (FCDII)	PI3K-Rheb	control seizure	PMID: 32,075,941 (Zhang et al., 2020)

Table 3
FLNA expression, function and mechanism in tumor.

FLNA expression	tumor	mechanism/pathway	function	reference
FLNA overexpression	breast cancer	Cyclin D1/D4, regulate G1/S	migration and invasion	PMID: 20179208 (Zhong et al., 2010)
		calpain/FA/turnover	migration and invasion, degradation of FA	PMID: 20937704 (Xu et al., 2010)
		down regulate 14–3-3σ	migration and invasion	PMID: 30074213 (Ji et al., 2018)
	pulmonary neuroendocrine tumor	enhance VEGF and cyclin D1	promote cell proliferation and colony formation	PMID: 29100390 (Vitali et al., 2017)
	melanoma	pro-PrP promote FLNa bind with integrinβ1	cell migration	PMID: 20650901 (Li et al., 2010)
	ovarian serous carcinoma	—	Cisplatin-resistance	PMID: 31681605 (Zeng et al., 2019)
	glioblastoma	mTORC2-FLNa	movement and aggression	PMID: 26134617 (Chantaravisoot et al., 2015)
	GH-secreting pituitary tumors	Rab5 and Rab4 sorting endosomes traffic SST2	SST2 internalization and recycling	PMID: 31574507 (Treppiedi et al., 2019)
FLNA low expression	colorectal cancer	calpain-1 negatively regulate FLNa	calpain-1 decrease, the overall survival rate increase	PMID: 31002357 (Xu et al., 2019)
		EGFR/ERK/Akt	cell proliferation and migration	PMID: 31485594 (Wang et al., 2019)
		EGF/ERK/p90RSK/Rho	regulate the activation of α5β1 integrin	PMID: 23007402 (Vial and McKeown-Longo, 2012)
	bladder cancer	—	cell proliferation and migration	PMID: 29288417 (Wang et al., 2018)
	prostatic cancer	MMP-9	cell migration and invasion	PMID: 24390612 (Sun et al., 2014)
	gastric cancer	MMP-9	cell survival and migration	PMID: 24241900 (Sun et al., 2014)
	parathyroid tumors	ERK	regulate cell sensitivity to calcium	PMID: 27872158 (Mingione et al., 2017)

Xu found that FLNa regulated the turnover of focal adhesion (FA) of breast cancer cells, down-regulation of FLNa enhanced calpain activity, stim-ulated the cleavage of FA protein, and promoted the invasion and migration of breast cancer cells (Xu et al., 2010). We summarized the expression, function, and mechanism of FLNa in the tumor, as shown in Table 3.

3.2.2. Prognostic marker of disease

The later the cancer is found, the worse the prognosis is. So early prediction and intervention are the most effective ways to improve the clinical efficacy of patients. It was found that the phosphorylation of FLNa Ser2152 in high metastatic hepatocellular carcinoma(HCC) cells was significantly up-regulated compared with low metastasis cells, which may be a potential prognostic marker for primary liver cancer (Xing et al., 2019). Ji et al. found that Zinc-α2-glycoprotein 1(AZGP1) is highly expressed in colorectal cancer liver metastases. Down regulation of AZGP1 inhibits PAK2 kinase mediated FLNa phosphorylation and promotes it hydrolysis, then through affects its subcellular localization to regulate EMT and local adhesion, which is related to poor prognosis. It may be one of the candidate biomarkers for the diagnosis and prog-nosis of colorectal cancer prognosis (Ji et al., 2019). In addition, about 40% of pancreatic cancer patients express prion protein (PrP). FLNa combines with prion protein in Pro PrP form, which changes FLNa signal transduction mechanism and skeleton rearrangement, and makes tumor cells grow more actively (Sy et al., 2010). So the pro-PrP can be used as a target for pancreatic cancer treatment and intervention.What's more, most buccal squamous cell carcinoma(BSCC) are caused by oral sub-mucous fibrosis. It often occurs local recurrence which caused by can not be completely removed. By absolute quantitative marker (quantitative proteomic iTRAQ) method for determining the pathological group found that FLNa raised obviously, and can be used as a BSCC prognosis of candidate biomarkers and potential therapeutic targets (Liu et al., 2016).

3.3. Pathogenic microorganism

FLNa not only participates in the occurrence of genetic diseases and the progress of tumors but also plays an essential role in the host's microbial infection. When Vibrio vulnificus infects the host cells, it produces Rtxa1 toxin. Rtxa1 and FLNa interact to activate PAK1 and induce JNK and p38 MAPKs phosphorylation, causing cytoskeleton rearrangement and cell death (Guo et al., 2019). Listeria is a foodborne bacterium that can induce its internalization into cells through interaction of the bacterial surface protein InlB with its host receptor, the Met tyrosine kinase. PKC-α-dependent phosphorylation of FLNA Ser2152 contributes to InlB mediated uptake and Listeria infection (Bhalla et al., 2018). Tetherin, also known as bone marrow stromal antigen 2 (BST-2), can contain viruses on the cell surface and inhibit the release of various envelope viruses. HIV-1 helper protein Vpu can resist frenulum restriction and assist virus budding through isolation, down-regulation or replacement mechanism. Also, FLNa overexpression can downregulate tetherin, thus avoiding host restriction and promoting Vpu mediated HIV release (Dotson et al., 2016).

4. Conclusion and outlook

In summary, FLNa can combine with a variety of proteins, through direct or indirect interaction to effect downstream target proteins, which is the junction and intersection of multiple pathways. So FLNa changes will lead to signal transduction changes, cytoskeleton reconstruction, vesicle transport disorders, neovascularization and so on. That is to say, FLNa plays a vital role in the occurrence of genetic diseases, the development of tumors and the infection of pathogenic microorganisms, as well as the process of cell life.

In recent years, many researchers have found that the expression of FLNa is related to the average overall survival rate of patients in a variety of tumors. However, the role of FLNa in different tumors is different, and even appears contradictory results. High expression of FLNa may promote the proliferation or metastasis of some tumors, but in other tumors, this maybe has an inhibitory effect. This contradictory phenomenon not only related to the cell types and states, but also the activation form and cellular localization of FLNa. The posttranslational modification of FLNa is an important form of its function, mainly

phosphorylation. PKA (Jay et al., 2000)、PAK1 (Vadlamudi et al., 2002)、RSK (Woo et al., 2004)、Ndr2 (Waldt et al., 2018)、cyclin D1 (Zhong et al., 2010)、PAK2 (Ji et al., 2019)、PKC (Jay et al., 2004 May) can phosphorylate FLNA at Serine 2152(Rep.20), which could resist calpain cleavage the hinge. Then the phosphorylation FLNa regulates cytoskeletal assembly (Vadlamudi et al., 2002), formation of membrane ruffling (Woo et al., 2004), migration and invasion of cancer cells (Zhong et al., 2010), EMT and local adhesion (Ji et al., 2019). Contrarily, Genistein dephosphorylates FLNa and promotes its hydrolysis to produce 90 kDa fragment into the nucleus, which improves the sensitivity of castration-resistant prostate cancer patients to androgen (Mooso et al., 2012). Therefore, it is of great significance to find out the key driving mechanism of FLNa on tumor metastasis and take early intervention measures to improve the survival rate and life quality of patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2021.145575.

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