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Review:

Roles of flotillins in tumors*

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Abstract: The identification and use of molecular biomarkers have greatly improved the diagnosis and treatment of malignant tumors. However, a much deeper understanding of oncogenic proteins is needed for the benefit to cancer patients. The lipid raft marker proteins, flotillin-1 and flotillin-2, were first found in goldfish retinal ganglion cells during axon regeneration. They have since been found in a variety of cells, mainly on the inner surface of cell membranes, and not only act as a skeleton to provide a platform for protein–protein interactions, but also are involved in signal transduction, nerve regeneration, endocytosis, and lymphocyte activation. Previous studies have shown that flotillins are closely associated with tumor development, invasion, and metastasis. In this article, we review the functions of flotillins in relevant cell processes, their underlying mechanisms of action in a variety of tumors, and their potential applications to tumor molecular diagnosis and targeted therapy.

Key words: Flotillins; Tumor; Lipid raft protein; Signal transduction
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1 Introduction

Flotillin proteins were discovered by Schulte et al. (1997) in goldfish following optic nerve injury. During the axon regeneration process, two proteins, reggie-1 and reggie-2, were abundantly expressed in retinal ganglion cells (RGCs). Schroeder et al. (1994) isolated and characterized a complementary DNA (cDNA) encoding a novel extracellular epidermal molecule, epidermal surface antigen (*ESA*), which is thought to play a role in intercellular epidermal adhesion. The *ESA* messenger RNA (mRNA) is expressed in cultured keratinocytes, melanocytes, fibroblasts, carcinoma, and melanoma cell lines. The *ESA* gene is conserved in mammalian species and has been localized to human chromosome 17 (M17S1) in the same region as the gene for von Recklinghausen neurofibromatosis. When screening new molecular markers of lipid rafts, Bickel et al. (1997) isolated a protein from membrane extracts of mouse lung tissue, which was called "flotillin" according to its characteristics. Flotillin is a close homologue of *ESA*, and together they define a new family of integral membrane proteins in caveolae. Bickel et al. (1997) proposed that flotillin be known as flotillin-1 and *ESA* as flotillin-2. Subsequently, sequence analysis showed that the sequences of flotillin-2 and reggie-1 are identical, and

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those of flotillin-1 and reggie-2 are the same. Flotillin has now become widely accepted as the official name of the two genes.

Flotillins are widely distributed in bacteria, fungi, multicellular animals, plants, and mammals, but are not expressed in budding yeast or *Caenorhabditis elegans* (Edgar and Polak, 2001; Rivera-Milla et al., 2006). The distribution of flotillins is highly dynamic in subcellular fractions. They appear on the plasma membrane of many cells, and their expression pattern and location partly depend on the type and state of differentiation of cells. In most cell types such as CHO, HePG2, and Hela, flotillins are located mainly on the plasma membrane, but in Malin-Darby canine kidney (MDCK) cells they are found mainly in endosomes and lysosomes (Dermine et al., 2001; de Gassart et al., 2003; Liu et al., 2005). Flotillins are considered to be scaffolding proteins of lipid rafts and are widely used as marker proteins of lipid microdomains.

Previous studies have shown that the consistency of the amino acid sequences of flotillin-1 and flotillin-2 among certain species is around 44% (Schulte et al., 1997), and reaches up to 99% between mouse and human, suggesting that flotillins have been highly conserved in evolution. However, the consistency of flotillin-1 between mouse and fruit fly is only 61% (Galbiati et al., 1998). The human flotillin-1 (reggie-2) gene is a 15-kb single copy housekeeping gene composed of 13 exons and 12 introns, and is located on chromosome 6p21.3 (Edgar and Polak, 2001). The expression of flotillin-1 varies a lot among different tissues. It is highly expressed in brain, heart, and placental tissues, and lowly expressed in pancreatic and liver tissues. With a length of 18 kb, the human flotillin-2 gene is located on chromosome 17q11–12 and is composed of 11 exons and 10 introns. The mRNA of flotillin-2 is widely expressed in all kinds of cells (Edgar and Polak, 2001).

2 Structure of flotillin proteins

Through analysis of its mRNA sequence, investigators found that flotillin-1 has two potential translation initiation sites and the translation products comprise 427 and 417 amino acid residues, respectively (Edgar and Polak, 2001). When expressed from the first initiation site, the protein has a molecular weight of 47 kDa and an isoelectric point (pI) of 7.08. When expressed from the second initiation site, it has a molecular weight of 46 kDa and a pI of 7.69 (Edgar and Polak, 2001). Analysis of the flotillin-2 mRNA sequence showed that the flotillin-2 protein comprises 428 amino acid residues and has a molecular weight of 41 kDa and a pI of 5.23 (Cho et al., 1995) (Fig. 1).

Flotillin-1 and flotillin-2 are interconnected in a heterogeneous oligomeric complex and generate plasma membrane microdomains which are involved in the biological activities of many cells. Decreased expression of one flotillin by small interfering RNA (siRNA) leads to a decrease in that of another (Amaddii et al., 2012; Banning et al., 2014). Knockout of flotillin-2 leads to consumption and instability of flotillin-1 protein. However, when flotillin-1 is knocked out, the change in flotillin-2 level is not significant. Therefore, one is regulated by the other, but the interdependence is more obvious for flotillin-1 (Banning et al., 2014). Liu J et al. (2015) showed that in nasopharyngeal carcinoma (NPC) cells, flotillin-2 overexpression also results in increased flotillin-1 expression, which suggests that flotillin-2 protein may affect the stability of flotillin-1 protein, and that flotillin-1 protein may play an important role in cell cycle changes induced by flotillin-2 protein.

3 Functions of flotillins in relevant cell processes

Flotillin proteins play important roles in many biological processes such as cell proliferation, apoptosis, adhesion, and invasion. Previous studies have shown that flotillins are located on lipid raft microdomains and that the two proteins are involved in the retraction of plasma membrane vesicles (Babuke et al., 2009). Flotillin-1 is widely expressed in the body and may play different roles in different tissues and cells. Recent studies suggested that flotillin-1 not only provides a platform for protein–protein interactions as a tripod protein, but also plays an important role in regulating the regeneration of axons, cell division, endocytosis, T cell activation, and signaling transmission of insulin (Morrow and Parton, 2005; Fecchi et al., 2006; Munderloh et al., 2009; Gómez et al., 2010; Cremona et al., 2011). Flotillin-2 directly interacts with signaling molecules such as receptors,

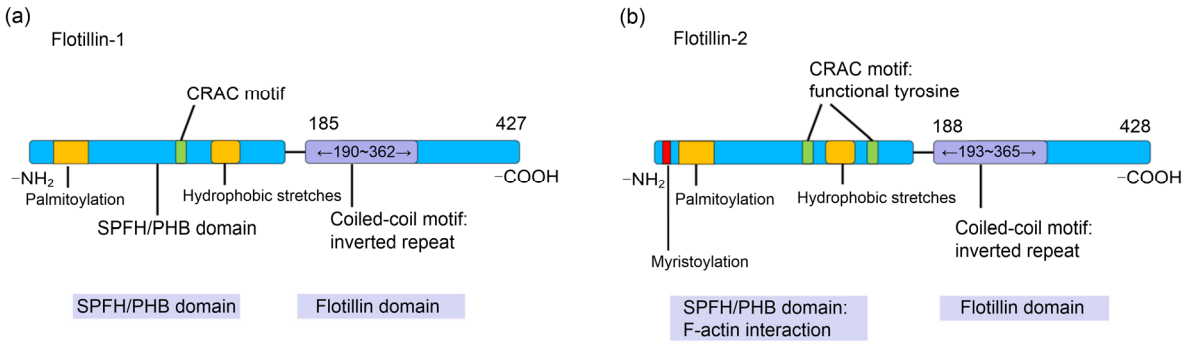

Fig. 1 Structures of flotillin-1 (a) and flotillin-2 (b) proteins

CRAC: cholesterol recognition/interaction amino acid; SPFH: stomatin/prohibitin/flotillin/HflK; PHB: prohibitin homology

kinases, adhesion molecules, and G protein. It also serves as a tumor regulator by regulating cell proliferation, differentiation, apoptosis, adhesion, and invasion (Doherty et al., 2006). It has been reported that flotillin-2 participates in the development of several types of malignant tumors such as breast cancer, melanoma, gastric cancer, cervical cancer (CC), and NPC (Affentranger et al., 2011; Jemal et al., 2011; Zagouri et al., 2012; Li et al., 2013; Liu J et al., 2015). In fact, there are many similarities between the functions of flotillins in the biological processes of cells and in tumor development.

3.1 Roles of flotillins in axon regeneration and neuron differentiation

Flotillin proteins were first found in regenerating nerve cells. In regenerating axons of goldfish, flotillins are up-regulated in RGCs (Schulte et al., 1997), and in zebrafish, down-regulation of flotillins reduces the number of regenerative axons significantly, suggesting that they are necessary for axon regeneration (Munderloh et al., 2009). Decreasing the expression of flotillins suppresses differentiation of nerve cells in mammalian hippocampal neurons (Stuermer, 2010; Koch et al., 2013). Knocking down flotillins by specific siRNA can limit axonal regeneration and division of neuroblastoma cells derived from the mouse hippocampus. The up-regulation of reggie-1 (flotillin-2) is sufficient to promote the regeneration of axons in the injured optic nerve and to improve the intrinsic condition of RGCs. This enables a significant number of regenerative axons to cross the diseased region into the adult distal part of the optic nerve. In mouse hippocampal and N2a neurons, increasing axonal length can be shown to be correlated with flotillin-2-dependent activation of signaling molecules and effectors of actin cytoskeletal dynamics, such as Src, phosphoinosmde-3-kinase (PI3K), Rho-GTPases, Rac1, and TC10, and their downstream effector cofilin (Koch et al., 2013). Thus, up-regulation of reggie (flotillin) activates the cell-intrinsic program that is required for axonal regeneration. Moreover, it apparently provides conditions in neurons for extending axons into the optic nerves.

3.2 Roles of flotillins in endocytosis

Saslowsky et al. (2010) first demonstrated that flotillins participate directly in endocytosis in model organisms. Subsequently, it was reported that flotillins play a key role in the endocytosis of mammalian glutamate and dopamine transporters (DATs) (Cremona et al., 2011). Up-regulation or down-regulation of flotillins may impact endocytosis, indicating that there are relationships between flotillins and specific proteins. Decreasing the expression of flotillin-2 inhibits the endocytosis of glycosylphosphatidylinositol (GPI)-anchored protein in liver cells, which suggests that the endocytosis depends on a flotillin-dependent pathway (Ait-Slimane et al., 2009). Cremona et al. (2011) believe that endocytosis of DATs caused by protein kinase C (PKC) can be found in membrane microdomains where flotillin-1 is abundant. However, flotillin-1 does not participate in epidermal growth factor receptor (EGFR) endocytosis (Amaddii et al., 2012). Moreover, Stuermer (2012) indicated that depletion of flotillin-1 and flotillin-2 proteins by RNA interference does not inhibit PKC-dependent DAT endocytosis in several cultured cell lines. Therefore, further studies are needed to confirm the correct results and the mechanism of flotillin-related endocytosis.

3.3 Roles of flotillins in signal transmission of insulin

Flotillin-1 forms a ternary complex with cb1 and cb1-related proteins, which is recruited to lipid rafts by the first hydrophobic domain of flotillin-1 and the sorbose homology region of cb1-related protein after stimulation by insulin (Baumann et al., 2000). Inhibiting this process can hinder the uptake of glucose by glucose transporter type-4 (GLUT4) (Baumann et al., 2000). Therefore, some researchers consider that flotillin-1 plays a role in the signal transmission process of insulin by interacting with cb1-related proteins (Mitra et al., 2004; Morrow and Parton, 2005). GLUT4 and flotillin-1 are both located in the perinuclear area of skeletal muscle cells. When stimulated by insulin, GLUT4 moves to the muscle fiber membrane to uptake glucose (Fecchi et al., 2006). If the flotillin-1 region is affected by cholesterol-isolated areas, insulin will be unable to stimulate the migration of GLUT4 and the uptake of glucose will be suppressed (Fecchi et al., 2006).

3.4 Roles of flotillins in cell proliferation

Flotillin-1 can migrate to the nucleus and interact with prostate tumor overexpressed-1 (PTOV1) that can shuttle between the nucleus and cytoplasm in human prostate cells and African green monkey kidney cells. In S phase of the cell cycle, flotillin-1 enters the nucleus along with PTOV1. Lack of either can significantly inhibit cell proliferation, and overexpression of either can promote cell proliferation significantly (Santamaria et al., 2005). It was reported that flotillin-1 is critical for maintaining the level of the mitosis regulator aurora kinase B and that they interact with each other directly. When entering the nucleus, flotillin-1 increases the level and activity of aurora kinase B. In contrast, depletion of flotillin-1 reduces the level and activity of aurora kinase B (Gómez et al., 2010). Flotillins are also involved in breast cancer cell proliferation by inhibiting EGFR and mitogen activated protein kinase (MAPK) signaling (Kurrle et al., 2013; Pust et al., 2013; Xie G et al., 2015). In summary, flotillins can participate in and impact cell division and proliferation, but the specific mechanisms involved may not be identical.

3.5 Function of flotillins as signal platforms in T lymphocytes

When T cells are stimulated, flotillin microdomains accumulate in a polar group of cells to form a flotillin cap including thymic antigen 1, T cell receptor (TCR)/CD3 complex, Fyn, tyrosine kinase, and signaling molecules that participate in the activation of T cells (Langhorst et al., 2006). Intervening in the establishment of the flotillin cap, blocking the polarization of rafts and the activation of T cells eventually lead to loss of cytoskeletal reorganization (Langhorst et al., 2006). It was recently demonstrated that flotillins act as scaffolding proteins organizing the uropod and regulating signaling molecules. A study of overexpression of the flotillin-2-G2A mutant highlighted an important role of flotillin-2 in uropod formation and recruitment of P-selectin glycoprotein ligand PSGL-1 (Affentranger et al., 2011).

4 Roles of flotillins in tumors

The dysregulation of flotillins in a variety of tumors, the influence of flotillin up-expression on biological functions in tumor cells, and their molecular mechanisms are summarized in Table 1.

4.1 Flotillins in melanoma

Hazarika et al. (2004) found that flotillin-2, which is highly expressed in melanoma, induced the changes in the phenotypes of SB2 cells from non-tumorigenic and non-metastatic to a highly tumorigenic and metastatic state in a nude mouse xenograft model. It also promoted the formation, proliferation, metastasis, and invasion of melanoma by interacting with protease-activated receptor 1 (PAR-1) (Hazarika et al., 2004), which is in the upstream of the BRAF-MAPK-extracellular signal-regulated kinase (ERK) pathway (Satyamoorthy et al., 2003) and a transmembrane G-protein coupled receptor involved in the development of melanoma. Overexpression of flotillin-2 is related to lymph node metastasis of melanoma (Doherty et al., 2006). Liu R et al. (2015) also demonstrated that flotillin-2 is highly expressed in melanoma and promotes proliferation, migration, and invasion of melanoma cells by a mechanism involving direct targeting by miR-34a. Therefore, overexpression and reduced expression of flotillin-2 can affect the development and metastasis of melanoma. Up to now, there has been no investigation of the role of flotillin-1 in melanoma.

4.2 Flotillins in breast cancer

Breast cancer is the most common and deadly malignancy in women in the world, accounting for

Table 1 Dysregulation and functional roles of flotillins in tumors

Cancer	Dysregulation	Biological function in cancer	Molecular mechanism	Reference
Breast cancer	NA	Potential targets for treatment	Reduced activation of AKT and MAPK signaling cascades	Kurrle et al., 2013
	Up (FLOT-2)	An independent prognostic marker	For further study	Wang et al., 2013
	Up (FLOT-2)	Induce cell proliferation; a potential treatment target	Activate PI3K/AKT signaling pathway	Perou et al., 2000
	Up (FLOT-1)	Promote lymph metastasia, cell proliferation and migration	Targeted by miR-124	Li et al., 2013
	Up (FLOT-1)	Promote cell proliferation and tumorigenicity	Activate FOXO3a transactivity	Lin et al., 2011
Melanoma	Up (FLOT-2)	Promote oncogenicity and metastasis	Upregulated DAR-1 by BRAF-MAPK-ERK	Satyamoorthy et al., 2003; Hazarika et al., 2004
	Up (FLOT-2)	Promote lymph node metastasis	For further study	Doherty et al., 2006
	Up (FLOT-2)	Promote proliferation and metastasis	Targeted by miR-34a	Liu R et al., 2015
Gastric cancer	Up (FLOT-2)	Promote cell proliferation, migration and invasion; independent prognostic factor	For further study	Zhu et al., 2013
	Up (FLOT-2)	An independently prognostic factor; potential novel biomarker for lymph node metastasis	For further study	Cao et al., 2014
	Up (FLOT-1)	Promote cell proliferation, migration, and invasion	Directly targeted by miR-485-5p	Kang et al., 2015
	Up (FLOT-1)	Novel biomarker	For further study	Gao et al., 2015
N0 tongue squamous cell cancer	Up (FLOT-1)	Reduce survival of patients; independent prognostic predictor	For further study	Li et al., 2014
Nasopharyngeal carcinoma	Up (FLOT-2)	Promote NPC metastasis	Activate NF-κB and PI3K/AKT3 signaling pathways	Liu J et al., 2015
	Up (FLOT-2)	Promote cell metastasis; a biomarker for lymphatic and distant metastasis	Involved in TGF-β signaling pathway	Zhao et al., 2015
Cervical carcinoma	Up (FLOT-1)	Promote cell motility, invasion, and pelvic lymph node metastasis	Regulated by the Wnt/β-catenin and NF-κB pathways	Li et al., 2015
	Up (FLOT-2)	Serve as a prognosis biomarker	For further study	Liu Y et al., 2015
Esophageal squamous cell carcinoma	Up (FLOT-1)	Promote proliferation and tumor growth	Activate tumor necrosis factor-α signaling and sustain activation of NF-κB	Song et al., 2012
Non-small cell lung cancer	Up (FLOT-2)	A potential prognostic biomarker	For further study	Wang et al., 2015
	Up (FLOT-1)	Associate with clinical stage and lymph node metastasis	For further study	Zhang et al., 2015
Oral squamous cell carcinoma	Up (FLOT-2)	Independent biomarker for poor prognosis	For further study	Vincent-Chong et al., 2014; Wen et al., 2014; Xie S et al., 2015
Renal cell carcinoma	Up (FLOT-2)	Potential prognostic biomarker and therapeutic target	For further study	Yan et al., 2014
Hepatocellular carcinoma	Up (FLOT-1)	Potential prognostic marker	For further study	Zhang et al., 2013

NA: not analyzed; FLOT-1: flotillin-1; FLOT-2: flotillin-2; NPC: nasopharyngeal carcinoma; MAPK: mitogen activated protein kinase; PI3K: phosphoinosmde-3-kinase; ERK: extracellular signal-regulated kinase; NF-κB: nuclear factor-kappa B; TGF-β: transforming growth factor-β

23% of new cancer cases and 14% of all cancer deaths (Jemal et al., 2011). Flotillin-2 is located in the amplified human chromosome 17q11.2 region in human breast cancer cells (Berger et al., 2013). Wang et al. (2013) have shown that, compared with normal cells and adjacent non-cancerous breast tissues, breast cancer cell lines and tissues exhibit higher expression of flotillin-2, and overexpression of flotillin-2 is related to clinical stage, TNM (tumor, node, and metastasis) classification, tissue differentiation, and the expression of human EGFR. Therefore, flotillin-2 may be an independent biomarker to infer the effect of treatments and make prognoses for breast cancer. As a regulator of lung metastasis, decreased expression of flotillin-2 protein reduces the tumorigenic and metastatic ability of human breast cancer cell lines in vivo (Berger et al., 2013). Therefore, it may be useful to determine the level of flotillin-2 protein in patients at different stages to develop new treatment strategies and establish reasonable treatment methods. Kurrle et al. (2013) found that in MCF7 cells, knockdown of flotillin-1 consistently leads to raised expression of EGFR mRNA and protein and a hyperactive MAPK signaling pathway. The increased EGFR expression and activity, which are dependent on the PI3K signaling pathway, are the cause of the increased MAPK signaling, suggesting that flotillin-1 may be unsuitable as a cancer therapy target in cells that carry certain other oncogenic mutations such as PI3K activating mutations. However, knockdown of flotillin-1 does not affect the expression of ErbB2 or ErbB3. Lin et al. (2011) have shown that the expression of flotillin-1 is significantly associated with clinical stage and survival rate in breast cancer, and that depletion of flotillin-1 inhibits the proliferation and tumorigenicity of breast cancer cells in vivo and in vitro by activating FOXO3a activity. However, Perou et al. (2000) demonstrated that flotillin-2 rather than flotillin-1 can be used as a prognostic indicator for breast cancer patients in stage I/II. Flotillin-2-mediated stabilization of ErbB2 was found to be associated with tumorigenesis in stage I/II breast cancer tissues, which is reflected by reduced p-ErbB2 and p-AKT levels and hyperactivity of the PI3K/AKT/mTOR (mammalian target of rapamycin) pathway. The reason for these contradictory findings may be that estrogen receptor and ErbB2 vary in different types of breast cancer samples. Pust et al. (2013) revealed that flotillin-2 is overexpressed in breast cancer biopsies in which ErbB2 is overexpressed. Also, Li et al. (2013) showed that flotillin-1 is the target of miR-124, which can regulate the translation of flotillin-1 and has a low expression level in breast tumors. This may explain the up-regulated flotillin-1 expression. It was also reported that depletion of flotillin-1 or flotillin-2 may lead to a decline in the migration ability of breast cancer cell line MCF7 (Asp et al., 2014). These results all show that flotillins may participate in the growth, proliferation, metastasis, and oncogenicity of breast cancer cells, and that they may be useful as potential biomarkers and treatment targets for breast cancer.

4.3 Flotillins in gastric cancer

Studies have also shown that flotillin-2 interacts with estrogen receptors that can participate in gastric cancer (Takano et al., 2002; Punyadeera et al., 2005). Also, knockout of flotillin-2 leads to decreased expression of ErbB2 in gastric cancer cells (Zhu et al., 2013). Recent studies have revealed that the expression of flotillin-2 protein is significantly associated with the development and poor prognosis of gastric cancer, which suggests its role in regulating cell proliferation, migration, and invasion in gastric cancer (Zhu et al., 2013; Cao et al., 2014). Flotillin-2 overexpression can promote migration, invasiveness, and lymph node metastasis of gastric cancer cells, suggesting that flotillin-2 may be used as a biomarker for identifying subtypes of gastric cancer and as a molecular target for gastric cancer treatment. Some researchers think that flotillin-1 may also become a potential biomarker for monitoring gastric cancer (Gao et al., 2015). In tumors, microRNA (miRNA) can directly target flotillins. In gastric cancer, flotillin-1 is directly targeted by miR-485-5p, whose low expression is negatively related to the expression of flotillin-1 (Kang et al., 2015), but the mechanism involved is not clear. These findings show that flotillin-1 and flotillin-2 may promote the growth, proliferation, and metastasis of gastric cancer cells, and that they may be useful as potential biomarkers.

4.4 Flotillins in cervical cancer

CC, which is caused mainly by chronic infection of human papilloma virus (HPV) and cervical intraepithelial neoplasia (CIN), is one of the most common malignant cancers in the world (Zagouri

et al., 2012). Molecular mechanisms of CC include abnormal expression of oncogenes, tumor suppressor genes, and alternative signaling pathways such as Wnt/β-catenin, mToR, and Notch signaling pathways (Zagouri et al., 2012). Flotillin-2 mRNA expression is significantly higher in tumor tissues than in adjacent non-tumor tissues (Liu Y et al., 2015). The expression of flotillin-2 is also significantly associated with poor overall and local relapse-free survival, clinical stage, tumor cell differentiation level, and lymph node metastasis (Liu Y et al., 2015). Thus, flotillin-2 may be an oncogene, a prognosis biomarker, and a treatment target for CC. Li et al. (2015) showed that elevated flotillin-1 regulated by the Wnt/β-catenin and nuclear factor-kappa B (NF-κB) pathways is related to lymph node metastasis, and may be a risk factor for early stage cervical cancer patients and a novel predictor for pelvic lymph node metastasis.

4.5 Flotillins in nasopharyngeal carcinoma

An increase of flotillin-2 is a necessary but not sufficient condition for activating the transforming growth factor-β (TGF-β) signal pathway in NPC. Flotillin-2 and Src are associated with a high recurrence rate and mortality in NPC patients. Moreover, inhibiting flotillin-2 may be a new way to hinder epithelial-mesenchymal transition (EMT) induced by TGF-β in NPC (Zhao et al., 2015). Flotillin-2 has a higher expression level in metastatic than in non-metastatic NPC (Yang et al., 2005), which is consistent with the finding that the flotillin-2 protein level is significantly higher in lymph node than in non-lymph node metastatic NPC. These results strongly support the hypothesis that a high expression level of flotillin-2 protein plays a key role in the invasion and metastasis of NPC and may be used as a treatment target and as a biomarker for identifying lymph node metastasis of NPC. Flotillin-2 can participate in the development of NPC, especially in the early stages (Yang et al., 2005). Liu J et al. (2015) demonstrated that flotillin-2 plays a role in development and metastasis in NPC through the NF-κB and AKT3 signaling pathways. Up-regulation of flotillin-2 can activate NF-κB which plays a role in increasing the expression of matrix metalloproteinases (MMPs), reduces the extracellular matrix, and ultimately promotes metastasis of NPC cells. Flotillin-2 can inhibit the activity of FOXO1 to accelerate the cell cycle by affecting the downstream effectors of FOXO1, thereby leading to the proliferation of NPC cells (Liu J et al., 2015). The positive interaction relationships between flotillin-1 and flotillin-2 have also been studied by co-immunoprecipitation.

4.6 Flotillins in lung cancer

Lung cancer is the leading cause of cancer-related death in the world, and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases (Siegel et al., 2013). Flotillins have gradually attracted increasing attention in lung cancer research in recent years. It was reported that flotillin-2 protein expression is positively associated with tumor stage and lymph node metastasis, and is significantly up-regulated in lung cancer cell lines and NSCLC tissues. It was suggested that it may be used as a potential biomarker for prognosis and as a molecular target for the biological treatment of lung cancer (Wang et al., 2015). Zhang et al. (2015) proved that the level of flotillin-1 protein is obviously higher in lung adenocarcinoma tissues than in normal lung tissues adjacent to a carcinoma, and that high expression levels of flotillin-1 are associated with clinical stage and lymph node metastasis.

4.7 Flotillins in other tumors

In 96.1% of tongue squamous cell carcinoma samples, the expression of flotillin-1 protein is significantly associated with pathological grade, T stage, N stage, recurrence, and poor prognosis, and may be used as an independent prognosis indicator for clinically N0 tongue squamous cell cancer (cN0 TSCC) patients (Li et al., 2014). Up-regulation of flotillin-1 leads to poor prognosis and a low survival rate (Li et al., 2014). Thus, flotillin-1 plays an important role in the development of tongue squamous carcinoma and may be an oncogenic protein in this carcinoma. Although the prognosis of oral squamous cell carcinoma is decided mainly by the tumor staging descriptions such as tumor size (T), lymph node metastasis (N), and distant metastasis (M) (Mao et al., 2004; Leemans et al., 2011), biomarkers not only play an important role in accurate diagnosis, but also provide significant prognostic data (Vincent-Chong et al., 2014; Wen et al., 2014; Xie S et al., 2015). Yan et al. (2014) found that flotillin-2 is highly associated with histological grade, tumor stage, lymphoma metastasis, and distant

metastasis of renal cell carcinoma, and that knockout of flotillin-2 inhibits cell proliferation, migration, and invasion. Overexpressed flotillin-2 is associated with a lower overall survival rate and may be an independent factor affecting prognosis in patients with renal cell carcinoma. Flotillin-1 expression markedly increases in cells and patient samples of hepatocellular carcinoma and esophageal squamous cell carcinoma, and high expression positively correlates with disease stage (Song et al., 2012; Zhang et al., 2013). The mechanisms underlying the biological functions of flotillins in tumor cells involve regulating the downstream targets and regulation by miRNAs (Fig. 2).

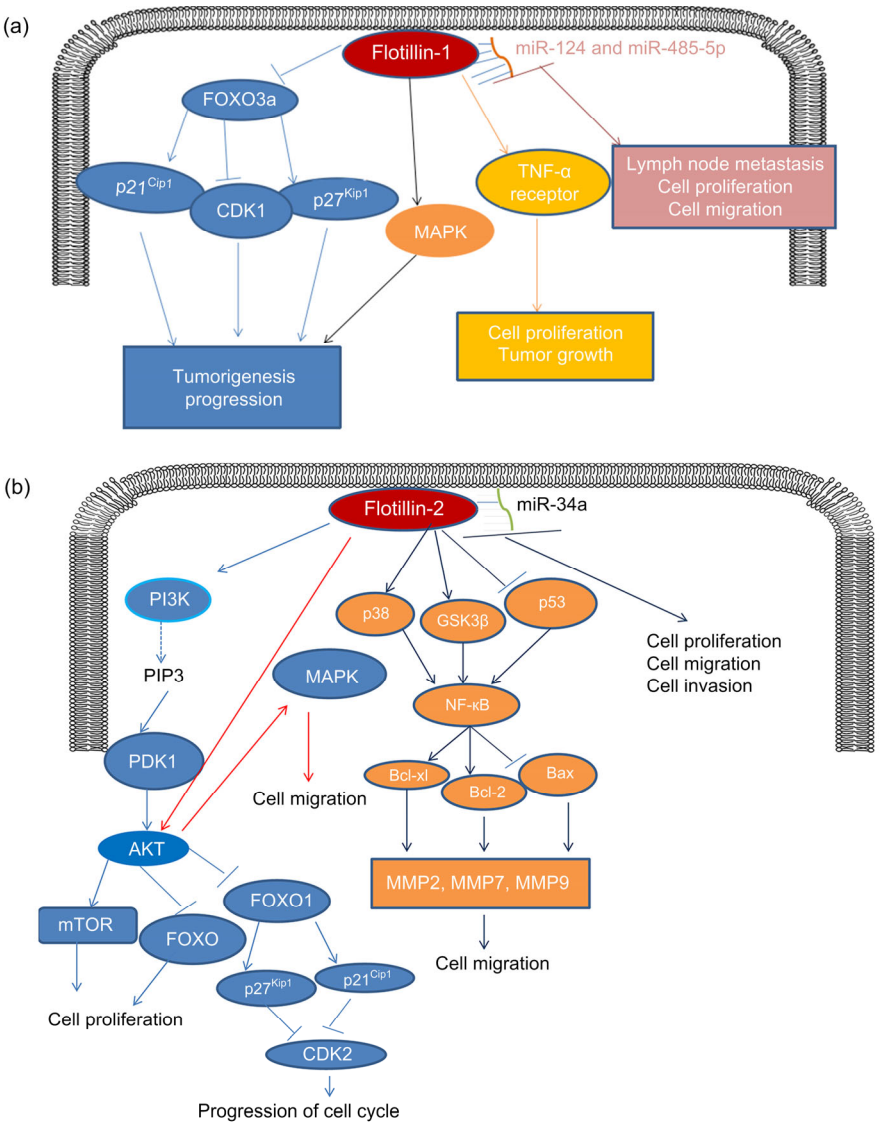

Fig. 2 Mechanisms of flotillin functions in tumors

(a) Flotillin-1 inhibits FOXO3a to down-regulate $p21^{Cip1}$ and $p27^{Kip1}$ and up-regulate CDK1 expression, and subsequently promote tumor progression. It can also up-regulate the expression level of TNF-α receptor and then promote cell proliferation and tumor cell growth. miR-124 and miR-485-5p target flotillin-1 to regulate tumor cell proliferation, migration, and lymph node metastasis. (b) Flotillin-2 activates the PI3K/AKT/mTOR, PI3K/AKT/FOXO, and PI3K/AKT/MAPK pathways to promote cell proliferation, progression of the cell cycle, and cell migration, respectively. It can also activate NF-κB signaling to up-regulate MMP2, MMP7, and MMP9 and then promote cell migration. miR-34a targets flotillin-2 to regulate cell proliferation, migration, and invasion

5 Use of a genetic ablation mouse model

To study the functions of flotillins in detail, genetic ablation models were established. In the mouse embryonic fibroblasts (MEFs) of knockout mice, ablation of the flotillin-2 gene leads to increased activity of ERK and accompanying up-regulation of Egr1, Fos, and Dusp1 in F2-KO mouse tissues (Banning et al., 2014). The increase in ERK activity may be one of the compensatory mechanisms that might operate the following long-term targeting of flotillins. Flotillin-1 knockout mouse exhibited a fertile, normal life span and had no significant developmental defects (Ludwig et al., 2010). Compared with flotillin-1$^{-/-}$ mice, double knockout of flotillin-1 and flotillin-2 did not exhibit a more serious phenotype and provided an important model system for researching the functions of flotillins without the complicating factor of potential functional redundancy between flotillins (Bitsikas et al., 2014). In flotillin-2 knockout mice, the level of flotillin-1 protein was reduced and the flotillin-specific membrane microdomain was absent. After growing an F2-KO mouse with the established breast cancer model, the offspring showed no damage to the primary tumor growth, but metastasis was reduced (Berger et al., 2013), which is convenient for investigating the functions of flotillins.

6 Conclusions

Interactions of flotillins with various proteins and their extensive effects on signaling molecules as lipid raft proteins enable their diverse biological functions in various cells. Many studies have shown that flotillins are overexpressed in a variety of tumors and closely associated with the development, staging, and metastasis of tumors. Metastasis marks the progression of the disease from local development into a systemic, incurable status and is considered to be a major impact factor on prognosis. The mechanisms underlying the roles of flotillins in cancer development, invasion, and metastasis have not been completely elucidated. Further exploration is warranted and will contribute to developing molecular diagnosis, reasonable prognosis, and precise treatment of malignant tumors.

Contributors

Lei WANG and Bin ZHU participated in the design. Xu-xu LIU and Wei-dong LIU wrote this review. Xiao SHI and Zi-xuan PENG draw the structures of flotillin-1 and flotillin-2. He-cheng ZHU, Xing-dong LIU, and Mei-zuo ZHONG collected and screened references. Dan XIE and Mu-sheng ZENG wrote an outline. Cai-ping REN checked and approved the final version.

Compliance with ethics guidelines

Xu-xu LIU, Wei-dong LIU, Lei WANG, Bin ZHU, Xiao SHI, Zi-xuan PENG, He-cheng ZHU, Xing-dong LIU, Mei-zuo ZHONG, Dan XIE, Mu-sheng ZENG, and Cai-ping REN declare that they have no conflict of interest.

This article does not contain studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：脂筏标记蛋白 flotillins 在肿瘤中的研究进展

概　要：本文旨在对 flotillins 在相关细胞进程中的作用、在多种肿瘤中的作用和机制及其在肿瘤分子诊断和靶向治疗等方面的潜在应用价值进行综述。图 1 以示意图的形式直观地展示 flotillin-1 和 flotillin-2 的蛋白结构；表 1 对 flotillin-1 和 flotillin-2 在各种肿瘤中的表达异常情况、发挥的生物学功能及其机制进行汇总；在图 2 中，以模式图的形式展示 flotillin-1 和 flotillin-2 在肿瘤细胞中参与的信号通路及导致肿瘤细胞出现的不同表型。许多研究表明，flotillins 在多种肿瘤中过表达，并且与肿瘤的发生发展、分期和转移密切相关。转移标志着肿瘤由局部病变发展为不可治愈的系统病变，是肿瘤预后的一个重要影响因素，但是其机制尚未完全阐述。因此，对其机制进行进一步探索有助于促进恶性肿瘤分子诊断、预后和精准治疗的发展。

关键词：Flotillins；肿瘤；脂筏标记蛋白；信号传导