Role of four and a half LIM domain protein 1 in tumors (Review)

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Abstract. As a cytoskeletal protein, the four and a half LIM domain protein 1 (FHL1) is widely expressed in various cells, particularly skeletal and cardiac muscle cells. FHL1 is involved in the development of the skeletal muscle and myocardium, regulations of gene transcription and thyroid function, and other physiological processes. Its expression is closely related to numerous diseases, such as skeletal muscle disease and viral infections. With the advances in research, the role of FHL1 in the development of tumors is also being revealed. The mechanism of FHL1 in the regulation of tumor growth is complex and is becoming a research focus. It is also expected to become a potential target for tumor therapy. Therefore, the present article reviewed the progress in research on the role of FHL1 in cancer.

Contents

1. Introduction

The four and a half LIM domain protein 1 (FHL1) belongs to the FHL family and is located in Xq26.3. It is also known as SLIM-1 or KYO-T (1,2).

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As a cytoskeletal protein, FHL1 is widely expressed in humans. Relevant studies have shown that it is mainly expressed in the skeletal muscle and myocardium. FHL1 regulates cell proliferation, differentiation, apoptosis, adhesion, migration, transcription and other cellular processes, and plays an important role in cell growth (3).

FHL1 is composed of four and a half LIM domains and three subtypes have been identified. The LIM domain of FHL1 is responsible for mediating interactions between proteins. Each domain of FHL1 has a different regulatory role in protein function. Mutations in LIM2 and LIM4 cause a loss of function in FHL1, and the function of FHL1 depends on the integrity of its various domains (4).

FHL1 also plays an important regulatory role in the growth of numerous tumors, in addition to affecting the occurrence and development of skeletal muscle and myocardial diseases. In different tumors, the expression of FHL1 is upregulated or downregulated and plays a role in promoting or inhibiting tumor development. Owing to the wide expression of FHL1 in numerous tumors and its different regulatory roles in tumor development, FHL1 has become a hot topic in the field of tumor research. The present article reviewed the role of FHL1 in tumors.

2. Domain architectures of FHL1

A total of 8 exons were found in FHL1 gene and exons 1 and 2 are non-coding. The structure of FHL1 is characterized by the structure of the LIM domain. The N-terminus is a half LIM domain, followed by four complete LIM domains. The LIM domain was first identified during the isolation and identification of the LIN1 gene in *Caenorhabditis elegans*, the ISL-1 gene in rats and the MEC-1 gene in *C. elegans* (5). The consensus amino acid sequence of the LIM domains has been defined as Cys-X_2-Cys-X_{16-23}-His-X_2-Cys-X_2-Cys-X_2-Cys-X_{16-21}-Cys-X_2-Cys/His/Asp, where X represents any amino acid.

The LIM domain is an important sequence mediating interactions between proteins. The structure of the LIM domain is highly conserved. It mediates the interaction between FHL1 and transcriptional regulatory factors, kinases and structural proteins such as receptor-interacting protein140 (RIP140), cytosolic tyrosine kinase Src and α-tubulin.

The alternative splicing results in the existence of three subtypes of FHL1: FHL1A is a complete FHL1 protein; FHL1B lacks the last LIM domain, which includes nuclear

localization, output signal and RBP-J binding domain; and FHL1C lacks the last two LIM domains, which includes the RBP-J binding domain, and has no nuclear location signal. The RBP-J binding domain binds to RBP-J and thus inhibits the binding of RBP-J to DNA and further inhibits its transcriptional activity. The structures of FHL1A, FHL1B and FHL1C are shown in Fig. 1. Studies have indicated that FHL1A is mainly expressed in the skeletal muscle, myocardium and fibroblasts, and FHL1B/FHL1C are mainly expressed in the muscle, brain and testis (6).

The LIM domain, which is composed of ~55 amino acid residues, binds to zinc and is rich in cysteine. It also plays an important role in protein transcription and signal transduction (7). Its cysteine-rich double zinc fingers contain the consensus sequence $X2:CX_2CX_3I\text{-}X_{11\text{-}15}WHX_2CFXCX_2CX_3(I/L)X_4(F/Y)X_8CX_2C$ (8). The consensus sequence facilitates protein-protein interactions. The highly conserved cysteine and histidine residues mediate Zn^{2+} binding, thereby stabilizing the folding and structure of the LIM domain (9,10). LIM domain is able to form homo- or heterodimers via interacting with other domains. It also binds to motifs such as PDZ domains and helix-loop-helix domains and performs its function. Multiple mutations in FHL1 affect its function and are associated with various skeletal and cardiac diseases. Relevant studies have shown that FHL1 mutations mostly occur in the second and fourth LIM domains (11).

The expression of FHL1 is also affected by a variety of post-transcriptional modulations; for example, methylation silences the expression of FHL1. The deubiquitinating enzyme 15 (USP15) stabilizes FHL1 expression by regulating the ubiquitin proteasome (12).

As an important cytoskeletal protein, the structure of FHL1 and the physiological functions of each domain require further study.

3. FHL1 in normal physiology

FHL1 performs its physiological functions by interacting with a variety of molecules. The proteins that interact with FHL1 include structural proteins, signal transduction proteins, transcription regulators, receptors and channels, such as ERK and non-structural protein 3 (Nsp3) (13).

FHL1 plays a role in the regulation of gene transcription, viral infection, thyroid function, blood glucose levels, myoblast differentiation and other physiological processes. Its abnormal expression is closely related to numerous diseases of the skeletal muscle and myocardium (14-17).

FHL1 is closely associated with gene transcription. For instance, FHL1A interacts with Gβγ- and Gαs-dependent guanine nucleotide exchange factor pleckstrin homology and RhoGEF domain containing G2 to enhance its induced serum response element (Ser)-dependent gene transcription (14).

FHL1 interacts with Pol1 transcription factor HMO1 to regulate ribosome synthesis. Interacts with Forkhead 1 (IFH1) is a weak multicopy suppressor with FHL1 deletion, and there is an interaction between FHL1 and the coactivator IFH1. TOR promotes this interaction and inhibits the interaction between FHL1 and the corepressor CRF1 to regulate the expression of ribosomal protein genes (18).

The expression of FHL1 is also associated with viral infections. For instance, FHL1 promotes the development of chikungunya and cashmere virus infection (19). The interaction between Nsp3 (HVD) and FHL1 is important for the proviral function of FHL1 (20). In addition, FHL1 interacts with the viral protein Nsp3 to regulate viral RNA replication. It is also highly expressed in chikungunya virus (CHIKV) target muscle cells and fibroblasts, and plays an important role in CHIKV gene expansion. FHL1 knockdown confers resistance to viral infections (21).

Mutations in FHL1 are associated with skeletal muscle and myocardial diseases. For instance, c.370-375del leads to reductive myopathy and c.763T>c,p.Cys255Arg is associated with hypertrophic cardiomyopathy (22,23).

4. Role of FHL1 in tumors

FHL1 is abnormally expressed in tumors and the expression of FHL1 is not consistent among different tumors. It promotes or inhibits the tumor development by upregulating or downregulating its expression. Simultaneously, the expression of FHL1 in tumors is regulated by epigenetic modifications. Therefore, FHL1 is a potential target in cancer research.

Dysregulation of FHL1 in tumors

Low expression of FHL1 in tumors. The expression of FHL1 is downregulated in cancer types including lung, prostate, breast, ovarian, colon, thyroid, brain, kidney, liver and oral cancers, as well as melanoma (24,25).

In non-small cell lung cancer, a decrease in long intergenic noncoding RNA (LINC)00261, which has a tumor suppressor function, leads to an increased expression of miR-105, which leads to a decrease in FHL1 expression (26,27). The expression level of FHL1 correlates with that of numerous immune cells. For instance, its expression level is positively correlated with the levels of monocytes, eosinophils and neutrophils, and negatively correlated with the level of M0 macrophages (28). Increased FHL1 expression in lung adenocarcinoma predicts a good prognosis (29). In lung adenocarcinoma, the expression of FHL1 is lower than that in normal lung tissue, and patients with relatively high expression have longer overall survival (30). In papillary thyroid microcarcinoma (PTMC), the expression of FHL1 in PTMC is lower than that in normal tissues, and the expression of FHL1 is significantly lower in PTC than in PTMC (31). In gastrointestinal tumors, the FHL1 promoter region is methylated, which silences the expression of FHL1. The expression of FHL1 in gastric cancer tissues is decreased compared to that in normal mucosa. In addition, more invasion and metastasis are found in these patients (24). In liver and colorectal tumors, miR-410 is highly expressed and downregulates the expression of FHL1 to promote tumor growth (27,32,33). In breast cancer, miR-183-5p downregulates the expression of FHL1, resulting in enhanced activity of breast cancer cells (32). In head and neck and esophageal squamous cell carcinomas, FHL1 expression is downregulated, and the prognosis of these patients is poor (2,34). In pediatric acute myelocytic leukemia (AML) with FLT3-ITD mutations, high expression of FHL1 predicts poor prognosis (35).

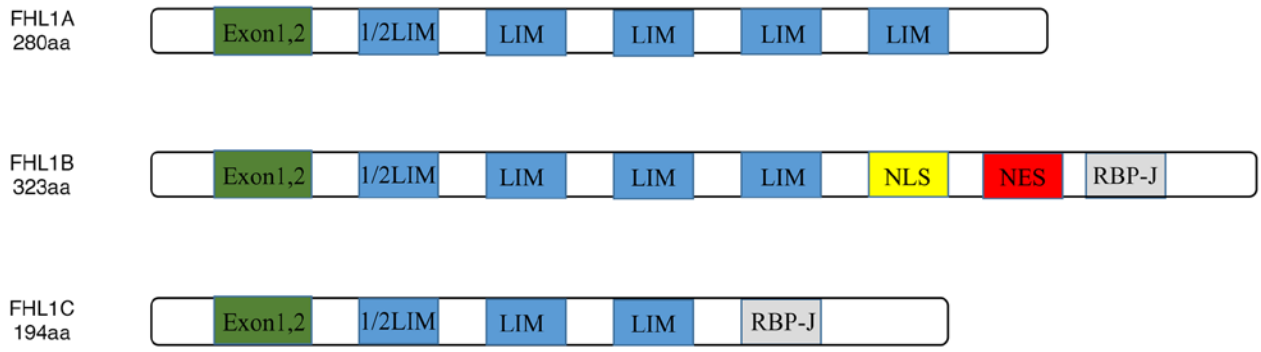

Figure 1. Structure of FHL1A, FHL1B and FHL1C. FHL1, four and a half LIM domain protein 1.

High expression of FHL1 in tumors. The expression of FHL1 is increased in laryngeal carcinomas (36). Increased FHL1 expression has been associated with gastric signet ring cell carcinoma (37). In addition, the expression of FHL1 in patients with acute promyelocytic leukemia and AML without FLT3 mutations or PML/RAR fusion is positively correlated with the expression of Rho-related BTB domain 2, which is an indicator of poor prognosis (38). High FHL1 expression promotes glioblastoma development (39).

FHL1 as a prognostic marker. Significant differences were observed in the expressions of FHL1 between different tumors. Its expression is closely related to the prognosis of patients with various tumors. Via causing the activation of TGF-β and other signaling pathways, promoting or inhibiting the expression of tumor proliferation-related proteins such as putative specific protein 1 (SP1), FHL1 influences the proliferation and migration of tumor cells, thus resembling a prognostic marker in tumors. FHL1 is also regulated by posttranslational modifications, such as phosphorylation and methylation, thus influencing the prognosis of bladder and other tumors (40). FHL1 acts through different pathways in different tumors, thus predicting different prognoses in different tumors. Increased FHL1 expression in lung adenocarcinoma, gastric cancer, colorectal tumors, head and neck squamous cell carcinoma, glioma, liver, breast and papillary thyroid cancers (PTCs), and esophageal squamous cell carcinoma, predicts a good prognosis. A high FHL1 expression in glioblastoma and pediatric AML with FLT3-ITD mutations predicts a poor prognosis. To conclude, the expression of FHL1 is closely related to the prognoses and clinical indicators of different tumors and the role of FHL1 in different tumors is summarized in Table I.

Regulation of FHL1 signaling. The expression of FHL1 is influenced by several factors. Its expression is regulated by miRNA, Src and other proteins, as well as by methylation, ubiquitination and other post-translational modifications.

Interaction with RIP140. In breast cancer, FHL1 interacts with RIP140, in which process all of the domains of FHL1 are required. Overexpression of FHL1 has a synergistic effect on the inhibition of RIP140 in estrogen signal transduction (41).

Mediation by immortalization-upregulated protein (IMUP). IMUP is highly expressed in pancreatic ductal adenocarcinoma and knockdown of IMUP prevents tumor cell growth. IMUP and nucleophosmin (NPMI) are co-localized in the cell nucleus. IMUP inhibits FHL1 transcription via NPMI-induced promoter methylation. Downregulation of IMUP decreases the expression of CyclinA2, cyclinE1 and cyclin-dependent kinase (CDK)2 by upregulating FHL1 expression. FHL1 regulates CyclinA2, cyclinE1 and CDK2 by promoting the degradation of CDC25A through phosphorylation (40).

Mediation by Src. Src is a membrane-bound tyrosine kinase. Src phosphorylates Crk-associated substrate and thus reduces FHL1 expression. In breast, kidney and prostate cancers, the expression of FHL1 is inhibited, possibly owing to gene methylation. FHL1 induces the expression of serum deprivation response factor in Src-transformed cells, whereas the expression of both molecules is inhibited in tumors (2,42).

Silencing by miR-410, enhancer of zeste homolog 2 (EZH2) and methylation. FHL1 may be silenced by miR-410 or EZH2 (30). Methylation of the FHL1 promoter region has been observed in gastrointestinal tumors and oral squamous cell carcinoma-derived cells, which silences the expression of FHL1 (43,44).

FHL1 signaling in cell proliferation and cell cycle. The role of FHL1 in tumor growth is complex and this effect varies among different tumors (Fig. 2). For instance, FHL1 can inhibit the progression of lung, prostate, ovarian, colon, thyroid, brain, kidney, liver and stomach cancers and promote the progression of glioblastoma. High expression of FHL1 is a risk factor for acute glioma and patients with breast cancer undergoing radiotherapy; however, it can inhibit the progression of colorectal cancer through the Wnt/β-catenin signaling pathway (45).

Promotion of tumor proliferation. FHL1 promotes the proliferation of tumor cells via interacting with SP1, Src and other proteins.

Interacting with the transcription factor SP1. FHL1 and SP1 are co-located in the cell and they form a complex. FHL1 interacts with the transcription factor SP1 to upregulate EGFR expression and activate the downstream signaling pathways, including Src, Akt, ERK1/2 and STAT3, thereby causing glioblastoma. When FHL1 is phosphorylated by Src at Y149 and Y272, it is transformed into an oncogene (46).

Mediated by Src and Kindlin-2. Src interacts with FHL1 through its kinase domain and phosphorylates FHL1 via Y149 and Y272 of FHL1. The LIM4 domain is also involved in this interaction. This process makes it a pro-cancer factor that promotes tumor proliferation. Phosphorylated FHL1 is more

Table I. FHL1 as a prognostic marker in tumors.

Tumor type	FHL1 expression	Target	Mechanism	Prognosis	(Refs.)
Glioblastoma	Upregulated	SP1	Promoting cell proliferation	Poor	(46)
Acute myelocytic leukemia	Upregulated	CD14 CD11b	Promoting cell proliferation	Poor	(39)
Gastric cancer	Downregulated	CCDC43	Inhibiting cell proliferation	Good	(51)
Colorectal tumor	Downregulated	GSK3β	Inhibiting cell proliferation	Good	(3)
Glioma	Downregulated	AKT	Inhibiting cell proliferation	Good	(5)
Head and neck squamous cell carcinoma	Downregulated	Cyclin D1 Cyclin E p27	Inhibiting cell proliferation	Good	(2)
Liver cancer	Downregulated	Smad2	Inhibiting cell proliferation	Good	(58)
Breast cancer	Downregulated	VEGF N-cadherin vimentin	Inhibiting migration and invasion	Good	(32)
Lung cancer	Downregulated	RhoGDIβ	Inhibiting migration and invasion	Good	(48)
Papillary thyroid cancer	Downregulated	Wnt/β-catenin	Inhibiting cell proliferation	Good	(59)

FHL1, four and a half LIM domain protein 1; SP1, putative specific protein 1; CCDC43, coiled-coil domain-containing protein 43; GSK3β, glycogen synthase kinase-3β; VEGF, vascular endothelial growth factor; RhoGDIβ, Rho GDP-dissociation inhibitor β.

likely to enter the nucleus and bind to the transcription factor Bcl2 associated transcription factor 1 (BCLAF1) to promote tumor growth. Kindlin2 also interacts with FHL1 via its FERM domain to inhibit cell growth. The last LIM domain is involved in this interaction. Kindlin2 competes with Src to bind FHL1 and inhibits the SRC-mediated phosphorylation of FHL1 (46-48).

Inhibition of tumor proliferation. FHL1 inhibits the growth of colon, bladder and liver tumor cells via mechanisms including blocking hypoxia-inducible factor (HIF)-α-HIF-β dimerization, interacting with coiled-coil domain-containing protein 43 (CCDC43) and regulating the Wnt/β-catenin signaling pathway. For instance, FHL1 knockdown promoted the growth of HeLa and HepG2 cells. Increased FHL1 methylation in bladder and gastrointestinal tumors was observed to lead to decreased FHL1 expression, which promoted tumor cell growth and metastasis (49).

Mediation of HIF-α-HIF-β dimerization. Kruppel-like factor 17 increases the expression of FHL1 by binding to FHL1 promoter and promoting its transcription. This process inhibits the proliferation, invasion and migration of colon tumor cells via influencing the expression of E-cadherin and N-cadherin. In colon cancer, the expression of FHL1 is downregulated, which leads to the proliferation, invasion and migration of tumor cells. As a tumor suppressor gene, FHL1 regulates tumor angiogenesis by blocking HIF-α-HIF-β dimerization and reducing VEGF expression (50).

Interaction with CCDC43. In gastric cancer, CCDC43 and FHL1 are co-localized in perinuclear and nuclear regions and the expression of CCDC43 is negatively correlated with the expression of FHL1. CCDC43 is highly expressed, whereas FHL1 is weakly expressed. There is an interaction between the two molecules. Knocking down CCDC43 improves the stability of FHL1, inhibits the growth and metastasis of gastric cancer cells and promotes apoptosis (51).

Interaction with Smad2, Smad3 and Smad4. FHL1 interacts with Smad2, Smad3 and Smad4 to activate the transcription of p21, inhibit c-Myc transcription and inhibit the growth of liver cancer cells. FHL1 and the tumor suppressor gene Smad4 synergistically inhibit VEGF promoter activity. Furthermore, a reduction in Smad4 abolishes the inhibitory effect of FHL1 on VEGF promoter activity, suggesting that FHL1 inhibits VEGF promoter activity in a Smad4-dependent way (52,53).

Interaction with estrogen receptor (ER)α and ERβ. FHL1 inhibits the growth of breast cancer cells. FHL1 interacts with ERα and ERβ in a 17β-estradiol-independent manner to reduce the transcriptional activity of ERα and ERβ, which is necessary to inhibit estrogen response transcription, resulting in lower expressions of estrogen response genes PS2 and cathepsin D. LIM1, LIM2 and LIM3 of FHL1 are required for this interaction (44,54).

Interaction with OTU domain containing 1 (OTUD1). The ATR inhibitor VE-822 upregulates the expression level of the deubiquitinating enzyme OTUD1 to stabilize FHL1 expression through its OUT domain and inhibits the progression of lung adenocarcinoma. In this process, the deubiquitinase activity of OTUD1 is necessary. The expression of OTUD1 is downregulated in lung cancer. Similarly, the expression of FHL1 is downregulated and OTUD1 has lost its ability to inhibit lung cancer (55)

Interaction with G protein signal regulatory factor 2 (RGS2). In tumors, the expression of RGS2 is lower in cancer than in paracancer cells. High expression of RGS2 can inhibit the invasion and proliferation of tumors. FHL1 competes with damage-specific DNA binding protein 1 to bind to RGS2, thereby reducing its ubiquitination level, stabilizing its expression and playing a role in inhibiting tumor growth.

Inhibition of VEGF promoter activity. FHL1 inhibits the VEGF promoter activity, thereby inhibiting VEGF expression. FHL1 interacts with HIF1α vis its LIM domain. The interaction between FHL1 and HIF1α can inhibit the interaction between HIF1α and HIF1β, thereby inhibiting the dimerization of HIF1α and HIF1β. This can further inhibit the binding of HIF1α and VEGF promoter, thereby inhibiting the expression of HIF1α-dependent VEGF (56).

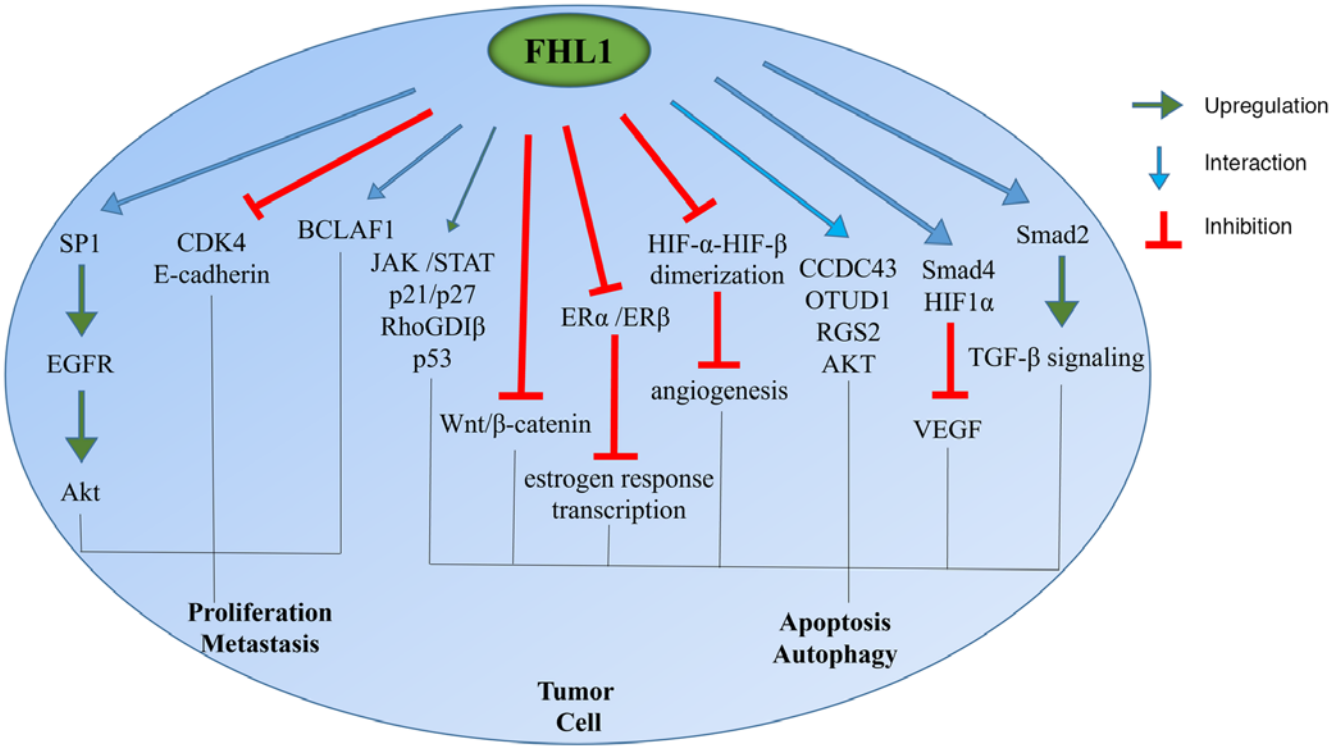

Figure 2. Role of FHL1 in tumor progression. FHL1, four and a half LIM domain protein 1; SP1, putative specific protein 1; EGFR, epidermal growth factor receptor; CDK4, cyclin-dependent kinase 4; BCLAF1, Bcl2-associated transcription factor 1; RhoGDIβ, Rho GDP-dissociation inhibitor β; CCDC43, coiled-coil domain-containing protein 43; OTUD1, OTU domain containing 1; RGS2, G protein signal regulatory factor 2; HIF1, hypoxia-inducible factor 1.

Taking part in the transcription process. Phosphorylated FHL1 binds to the nuclear transcription factor BCLAF1 and takes part in the DNA-binding transcriptional activator activity and transcription factor binding. FHL1 is involved in an IL-15-mediated signaling pathway that activates JAK and STAT family proteins. Its expression is positively correlated with the levels of B, CD8 and CD4 cells and macrophages, and is also correlated with the expression of immune-related genes, such as CD48 and CD80 (57).

Mediation of the Wnt/β-catenin signaling pathway. The expression of FHL1 is downregulated in colorectal tumors and is associated with poor prognosis. FHL1 reduces the phosphorylation of glycogen synthase kinase 3β and activation of β-catenin, thereby negatively regulating the Wnt/β-catenin signaling pathway, causing the downregulation of cyclin D1 and CDK4 and thus inhibiting the proliferation of colon tumor cells (3).

Mediation by miR-410. MiR-410 is highly expressed in liver and colorectal tumors. MiR-410 targets FHL1 via the 3'-UTR of FHL1 and promotes FHL1 methylation, thus negatively regulating FHL1 to promote tumor growth (27,32).

Mediation of Cyclin D1, Cyclin E and p27. In head and neck squamous cell carcinoma, FHL1 expression is downregulated and it promotes tumor cell growth through dysregulation of Cyclin D1, Cyclin E and p27. Decreased FHL1 expression is closely related to poor differentiation. Downregulation of FHL1 expression in head and neck squamous cell carcinoma is usually caused by hypermethylation of its DNA promoter region and EZH2-mediated regulation of histone methylation (2).

Activation of the TGF-β signaling pathway. FHL1 and Smad2 interact in liver cancer cells by phosphorylating Smad2 at Ser465 and Ser467. FHL1 activates the TGF-β signaling pathway in a TGF-β-independent manner, thereby inhibiting tumor growth (58).

Mediation of the cell circle. FHL1 mediates cell cycle in AML and other tumors to influence the development of tumor. The expression of cell cycle-related proteins such as p21 and p27 is regulated in this process.

AML. In AML, FHL1 is highly expressed and promotes the proliferation of AML cells. High FHL1 expression can lead to a decrease in the proportion of cells in G1 phase and a decrease in CDK4. FHL1 knockdown leads to an increase in the proportion of cells in G1 phase. Loss of FHL1 also leads to increased expression of CD11b and CD14. Overexpression of FHL1 prevents all-trans retinoic acid-induced differentiation of HL-60 cells. Consumption of FHL1 inhibits cell proliferation and induces cell differentiation (39).

Lung cancer. The expression of FHL1 in lung tumor tissues is lower than that in normal tissues. FHL1 inhibits the growth of tumor cells by inducing G1 and G2/M phase cell cycle arrest and decreasing the number of cells in S-phase. Overexpression of FHL1 increases the expression of p21 to increase the proportion of cells in G1 and G2/M phases, increases the expression of p27 to promote G1 phase arrest, and decreases the expression of CyclinD1, CyclinB1 and CyclinA (53).

Glioma. FHL1 inhibits the growth of glioma cells and its expression level is negatively associated with prognosis. FHL1 maintains cells in the G0/G1 phase and inhibits tumor growth. When FHL1 is knocked down, cells enter the S phase, which promotes cell growth. FHL1 interacts with AKT and inhibits the binding of AKT and PI3K, thereby inhibiting glioma growth (5).

In conclusion, FHL1 mediates various cellular pathways in tumor progression and mediates tumor growth. FHL1 mainly functions through interacting with proteins, particularly transcription factors such as SP1, to activate downstream signaling pathways. It also affects the transcriptional activity of proteins such as p21 to regulate the growth of tumor cells. Cyclins are also regulated by FHL1 to mediate tumor growth.

FHL1 signaling in tumor invasion and migration. In bladder, breast, lung, papillary thyroid and other cancers, FHL1 inhibits tumor invasion and metastasis by inhibiting the Wnt/β-catenin signaling pathway, and is a good potential therapeutic target. In bladder tumors, the expression of FHL1 is decreased and its methylation level is increased, leading to tumor invasion and migration. Given the complexity of its regulatory mechanisms, the different mechanisms by which FHL1 mediates tumor invasion and migration need to be further explored (49).

Mediation by miR-183-5p. In breast cancer, miR-183-5p downregulates the expression of FHL1 and mediates the upregulation of VEGF, N-cadherin and vimentin, and the downregulation of p53 and E-cadherin, resulting in enhanced activity of breast cancer cells and enhanced invasion and migration abilities (32).

Increase in the expression of RhoGDIβ. The expression of FHL1 is inhibited in lung cancer, thus reducing the expression of RhoGDIβ and leading to tumor invasion (48).

Mediation by miR-96-5p. MiR-96-5p inhibits the expression of FHL1 and promotes the proliferation, invasion and migration of lung adenocarcinomas, resulting in a decrease in the overall survival of patients (27).

Inhibition of the Wnt/β-catenin signaling pathway. FHL1 expression is downregulated in PTC and its expression is negatively associated with T/N staging. Its expression is also related to the progression-free and disease-free intervals. FHL1 inhibits the Wnt/β-catenin signaling pathway, thereby inhibiting the proliferation, invasion and migration of PTC cells (59).

FHL1 signaling in tumor therapy resistance. The comprehensive application of various treatment methods can effectively improve the curative effects in patients with tumors. However, treatment resistance remains an important reason for poor prognosis. FHL1 is abnormally expressed in various tumors and is closely associated with drug resistance during tumor therapy. The mechanism by which it mediates tumor resistance also differs among different tumors.

Induction of radiation resistance. In breast cancer, ionizing radiation can induce the expression of FHL1, thereby inhibiting the activity of CDC25C through its interaction with checkpoint kinase 2 and CDC25, and thus causes radiation resistance (46,60).

Increase of sensitivity to paclitaxel. In hepatocellular carcinoma, knockdown of FHL1 can increase the sensitivity to paclitaxel by inducing the activation of caspase-3 and caspase-9 (46).

Induction of resistance to cytarabin-based induction chemotherapy. High expression of FHL1 is associated with poor prognosis in AML and is an independent prognostic factor. Src phosphorylation of FHL1 promotes cell proliferation. High expression of FHL1 is associated with drug resistance in AML. In patients with AML receiving cytarabin-based induction chemotherapy, high FHL1 predicts a poor prognosis. High FHL1 levels lead to increased expression of ATP-binding cassette, sub-family C (CFTR/MRP), member 1 (ABCC1) and ABCC4, which are associated with the transport of chemotherapy drugs, and which are subsequently excreted into the extracellular system. Simultaneously, the expression of SLC29A1 decreases and the entry of cytarabine into the cell, resulting in drug resistance (61).

Increasing sensitivity to olaparib. In patients with ovarian cancer, tabersonine increases the sensitivity of ovarian cancer cells to the poly ADP-ribose polymerase inhibitor olaparib. In addition, glycyrrhizin increases FHL expression. They act synergistically to decrease epithelial-mesenchymal transformation, thereby inhibiting the invasion and migration of ovarian cancer cells. The combination of tabersonine and olaparib increases the expression of E-cadherin, decreases the expression of N-cadherin and vimentin, and effectively inhibits tumor growth (62).

Inducing resistance to platinum and paclitaxel. In patients with ovarian cancer, low FHL1 expression predicts higher sensitivity to platinum and paclitaxel and a better prognosis. Relevant studies have shown that FHL1 is co-expressed with Filamin C, γ (FLNC), Caveolin-1 and FLNA, and is related to the abundance of macrophages, thus affecting the sensitivity of patients to chemotherapy (45).

In brief, the expression of FHL1 in tumors is complex and the role of FHL1 varies in different tumors, which deserves further study. At the same time, FHL1 has become a potential target in tumor treatment. In different tumors, tumor growth could be inhibited by inducing or inhibiting the expression level of FHL1 or by affecting its post-translational modifications, such as phosphorylation, ubiquitination and methylation (40,44). The expression level of FHL1 could also be used as a reference for estimating the sensitivity to chemoradiotherapy treatment in certain tumors.

However, research on the role of FHL1 in tumor progression and treatment resistance is still limited. The mechanisms of FHL1 affecting tumor cell proliferation and migration have mainly been obtained through the study of cell lines and need to be further verified in clinical samples. There is also a lack of multicenter clinical trials to further increase the reliability of the findings. Furthermore, research methods such as bioinformatics have been rarely used in this field.

5. Conclusions

FHL1 is an important cytoskeletal protein that is expressed in various cells (63-66). It plays a regulatory role in the development of myocardial and skeletal muscle diseases, such as reducing body myopathy and cardiac hypertrophy (67-72). It is also widely expressed in tumor cells, including lung, ovarian and liver cancers. In different tumors, FHL1 functions differently to influence the fate of the tumor (73,74). In numerous tumors such as colon cancer and esophageal cancer, FHL1 functions as a tumor suppressor gene that inhibits tumor growth, while it is also reported that FHL1 promotes the development of glioblastoma and other tumors (75-77). In the process of tumor occurrence and

development, it is regulated by numerous signaling pathways, and it promotes or inhibits tumor occurrence and development by regulating the EGFR and Wnt/β-catenin signaling pathways. Post-transcriptional modifications also affect the function of FHL1. Its expression can be silenced via methylation and it can also be stabilized by deubiquitinating enzymes such as USP15. The regulatory role of FHL1 in tumors is complex and relevant studies suggest that the phosphorylation of FHL1 by Src may play an important regulatory role in the function of FHL1 in tumor growth. When phosphorylated, FHL1 is more likely to be located in the nucleus and facilitates tumor growth.

However, owing to the complexity of its regulatory mechanisms, the role of FHL1 in different tumors has remained to be fully elucidated (78-80). The results of the present study suggest that FHL1 can regulate tumor growth by regulating the cell cycle of tumor cells, as well as other signaling pathways such as Wnt/β-catenin and TGF-β. The different roles of FHL1 in different tumors may be caused by factors including regional differences, tumor differences and small sample size. At the same time, the location of FHL1 and its regulatory mechanism is rarely reported. FHL1 was mainly located in the cytoplasm and whether FHL1 has different functions in the nucleus and cytoplasm, and its regulatory mechanism, still warrant further study. The relationship between the location of FHL1 and its role in tumor progression are also a potential research field.

In addition, the subtype of FHL1 expressed in various tumors deserves further study, and the relationship between the expression of various subtypes and tumor occurrence and development has been rarely reported. This could also be a potential target for treatments against FHL1.

Of note, the abnormal expression of FHL1 is also closely related to tumor resistance to radiotherapy and chemotherapy. Therefore, FHL1 is a promising target for cancer research and may serve as an effective therapeutic target. However, in view of its complex roles in various tumors, its mechanism of action in different tumors requires further study. The relationship between the expression level of FHL1 and sensitivity to chemoradiotherapy has only been studied in a small number of tumors. Whether there is a relationship between FHL1 expression and therapeutic resistance in other tumors deserves further investigation.

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Availability of data and materials

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Authors' contributions

XM and SH contributed to the conceptualization of this study and provided constructive guidance. YT and YW collected relevant studies and wrote the manuscript. RS participated in the study design and completion. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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