

FAM83D in cancer: Molecular mechanisms, biomarker potential and future therapeutic perspectives (Review)

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Abstract. Family with sequence similarity 83 member D (FAM83D) is a member of the FAM83 protein family characterized by a conserved domain of unknown function 1669 domain. Initially recognized for its role in mitotic spindle organization and cell-cycle regulation, FAM83D has increasingly emerged as a cancer-associated protein. FAM83D is frequently upregulated in multiple malignancies, including lung, hepatocellular, ovarian, breast, gastric, colorectal, esophageal and pancreatic cancer. Elevated FAM83D expression is associated with tumor progression, lymph node metastasis, epithelial-mesenchymal transition, therapeutic resistance and worse clinical outcomes. Mechanistically, FAM83D may promote malignant phenotypes by regulating cell-cycle progression, interacting with casein kinase 1 isoforms, kinesin family member 22 and F-box/WD repeat-containing protein 7, and modulating oncogenic pathways such as MAPK/ERK, PI3K/AKT/mTOR, Wnt/ β -catenin and TGF- β /SMAD signaling. There may be an association between FAM83D and the tumor immune micro-environment, although direct mechanistic evidence remains limited. Clinically, FAM83D may have value as a diagnostic or prognostic biomarker and as a potential therapeutic target. However, the majority of available evidence comes from public database analyses, retrospective tissue studies and preclinical models, while large-scale prospective validation and standardized detection methods are lacking. The present review

summarizes the biological features, expression patterns, functional roles, regulatory mechanisms, clinical implications, limitations and future research directions for FAM83D in cancer.

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1. Introduction

The incidence and mortality rates of malignant tumors remain high worldwide, and cancer continues to pose a major public health burden (1,2). According to GLOBOCAN 2022 estimates, ~20 million new cancer cases and 9.7 million cancer-related deaths occurred worldwide in 2022 (1). Although surgery, chemotherapy, radiotherapy, molecular targeted therapy and immunotherapy have advanced considerably in recent years, tumor heterogeneity, recurrence, metastasis and multidrug resistance continue to limit treatment efficacy (3,4). Therefore, identifying novel cancer-related molecular biomarkers and elucidating their roles in tumor initiation and progression remain priorities in basic and translational oncology.

Family with sequence similarity 83 member D (FAM83D) was first identified as a spindle-associated protein (also termed CHICA) in 2008, and its oncogenic role has increasingly been recognized in multiple types of cancer (5). The FAM83D gene is located on chromosome 20q11.23 and encodes a member of the FM83 protein family. The FAM83D protein contains a highly conserved domain of unknown function 1669 (DUF1669) domain, which is considered to be involved in protein interactions and signal transduction (6). Studies have indicated that FAM83D participates in cell-cycle regulation and mitosis in normal cells (5,7). With advances in multiomics and functional cancer studies, FAM83D has emerged as a cancer-associated

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Abbreviations: ceRNA, competing endogenous RNA; CK1, casein kinase 1; CDK, cyclin-dependent kinase; EMT, epithelial-mesenchymal transition; FAM83D, family with sequence similarity 83 member D; HCC, hepatocellular carcinoma; HMMR, hyaluronan-mediated motility receptor; miRNA, microRNA; NSCLC, non-small cell lung cancer; OC, ovarian cancer; TF, transcription factor; TNBC, triple-negative breast cancer

Key words: FAM83D, cancer, molecular mechanism, biomarker, therapeutic target, tumor progression

protein of interest in multiple solid tumors (8,9). Previous studies have suggested that high FAM83D expression levels are associated with advanced tumor stage progression, lymph node metastasis, worse survival and therapeutic resistance, and that FAM83D may contribute to abnormal activation of several classical oncogenic signaling pathways (10-12).

Research on FAM83D has expanded from expression profiling to functional validation, mechanistic exploration and preliminary assessment of its clinical relevance. Nevertheless, the biological roles of FAM83D vary across types of tumors, and some conclusions are mainly derived from database analyses or *in vitro* experiments, providing limited levels of evidence (8,9,13). In addition, high-quality clinical evidence supporting FAM83D as a robust and reliable biomarker or establishing its druggability remain lacking (9). Therefore, a systematic review and comprehensive evaluation of the existing evidence is warranted. Unlike previous reviews which primarily examine the FAM83 protein family as a whole or examine specific types of cancer, the present review provides an updated, FAM83D-specific synthesis, with particular emphasis on recently published mechanistic insights (2024-2026), comparisons across different types of cancer and critical evaluation of challenges to clinical translational (14).

FAM83D has functions beyond typical cell-cycle regulation. Unlike conventional cyclins or cyclin-dependent kinases (CDKs), FAM83D functions as a scaffolding protein that anchors casein kinase 1 (CK1) isoforms via its DUF1669 domain (15), thereby coupling cell-cycle regulation to several oncogenic signaling pathways, including Wnt/ β -catenin, MAPK/ERK and PI3K/AKT (6,7). Moreover, its prognostic value has been validated across multiple types of cancer, a feature that distinguishes FAM83D from conventional cyclins and CDKs (8,9). The scaffolding function of FAM83D may also provide opportunities for therapeutic targeting through protein-protein interaction interfaces (12). Together, these features highlight FAM83D as a cancer-associated protein with potential biological and clinical relevance beyond its established role in cell cycle regulation. The present review summarizes the basic biological characteristics of FAM83D as well as its expression patterns and functions across malignancies, its potential regulatory networks and critically evaluates the potential utility and current limitations of FAM83D as a biomarker and therapeutic target.

2. Basic biological characteristics of FAM83D

Gene and protein structural features. The Human FAM83D gene, also referred to as FAM83D/scaffolding CK1 (SACK1) anchoring protein D in some annotations, is located on chromosome 20q11.23 (16). According to the annotation summarized in Fig. 1, the representative RefSeq transcript of FAM83D is NM_030919.3 (17). The FAM83D protein comprises 585 amino acids and has a predicted molecular weight of ~64.4 kDa. The N-terminus of FAM83D contains a conserved DUF1669/SACK1 domain, a characteristic feature of the FAM83 protein family that is involved in anchoring CK1 isoforms and mediating protein-protein interactions (6,15). Similar to other FAM83 family members, FAM83D is not a classical enzyme but is hypothesized to function primarily as a scaffolding or regulatory protein involved in multiple cellular

processes (6,18). A previous study has indicated that FAM83D exhibits dynamic changes in localization and expression during mitosis, supporting its role in cell cycle regulation (7).

Physiological functions and cell-cycle regulation. FAM83D first attracted attention mainly due to its close association with cell-cycle regulation and mitosis (6,7). Studies have suggested that FAM83D can influence the expression of cell cycle-related proteins such as cyclin D1 and cyclin E1, promoting the G₁-to-S phase transition and facilitating cell cycle progression (19,20). FAM83D can also localize to the mitotic spindle and interact with spindle-associated proteins such as kinesin family member 22 (KIF22), facilitating chromosome alignment and segregation and maintaining the stability of cell division (5). In pancreatic cancer, gastric cancer and nasopharyngeal carcinoma models, FAM83D has been reported to affect the activity of the Wnt/ β -catenin pathway and thereby participate in cellular proliferation, migration and other processes (21-23). As cell cycle dysregulation and abnormal proliferation are common features of tumor cells, aberrant FAM83D expression may contribute to sustained tumor growth by promoting cell cycle progression and activation of proliferation-related signals (8,19). The structural features, cellular localization and biological functions of FAM83D are summarized in Fig. 1.

Regulation of FAM83D expression. Aberrant upregulation of FAM83D in malignant tumors may be jointly regulated by multiple molecular mechanisms, including non-coding RNA regulation, abnormal promoter methylation, transcription factor (TF) regulation and m⁶A modification (24-26). First, non-coding RNA networks may participate in the regulation of FAM83D expression. Several microRNAs (miRNAs/miRs) directly target the 3'-untranslated region of FAM83D and suppress its expression, including miR-142-3p and miR-495 (25,27). Downregulation of these miRNAs in tumor tissues may weaken their inhibitory effects on FAM83D (27,28). Conversely, competing endogenous RNA (ceRNA) mechanisms may contribute to FAM83D upregulation. For example, in non-small-cell lung cancer (NSCLC), circFOXMI upregulates FAM83D expression by sponging miR-614 (28). An AC099850.3-miR-101-3p-FAM83D ceRNA regulatory network has also been proposed (29), although this conclusion requires further functional validation.

Second, altered promoter methylation may affect the transcriptional activity of FAM83D. In hepatocellular carcinoma (HCC), high FAM83D expression has been reported to be associated with promoter hypomethylation, suggesting that demethylation may relieve transcriptional repression and promote FAM83D expression (24). Additionally, TFs and RNA modifications may regulate FAM83D expression at different levels. MYB proto-oncogene like-2 has been implicated in the transcriptional activation of FAM83D, whereas FOXMI-related transcriptional networks may also contribute to FAM83D dysregulation in certain cancer contexts (30,31). At the post-transcriptional level, methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3)-mediated m⁶A modification enhances FAM83D expression (26), whereas YTH N6-methyladenosine RNA binding protein F2 (YTHDF2) negatively regulates FAM83D (32). Overall, aberrant FAM83D upregulation is

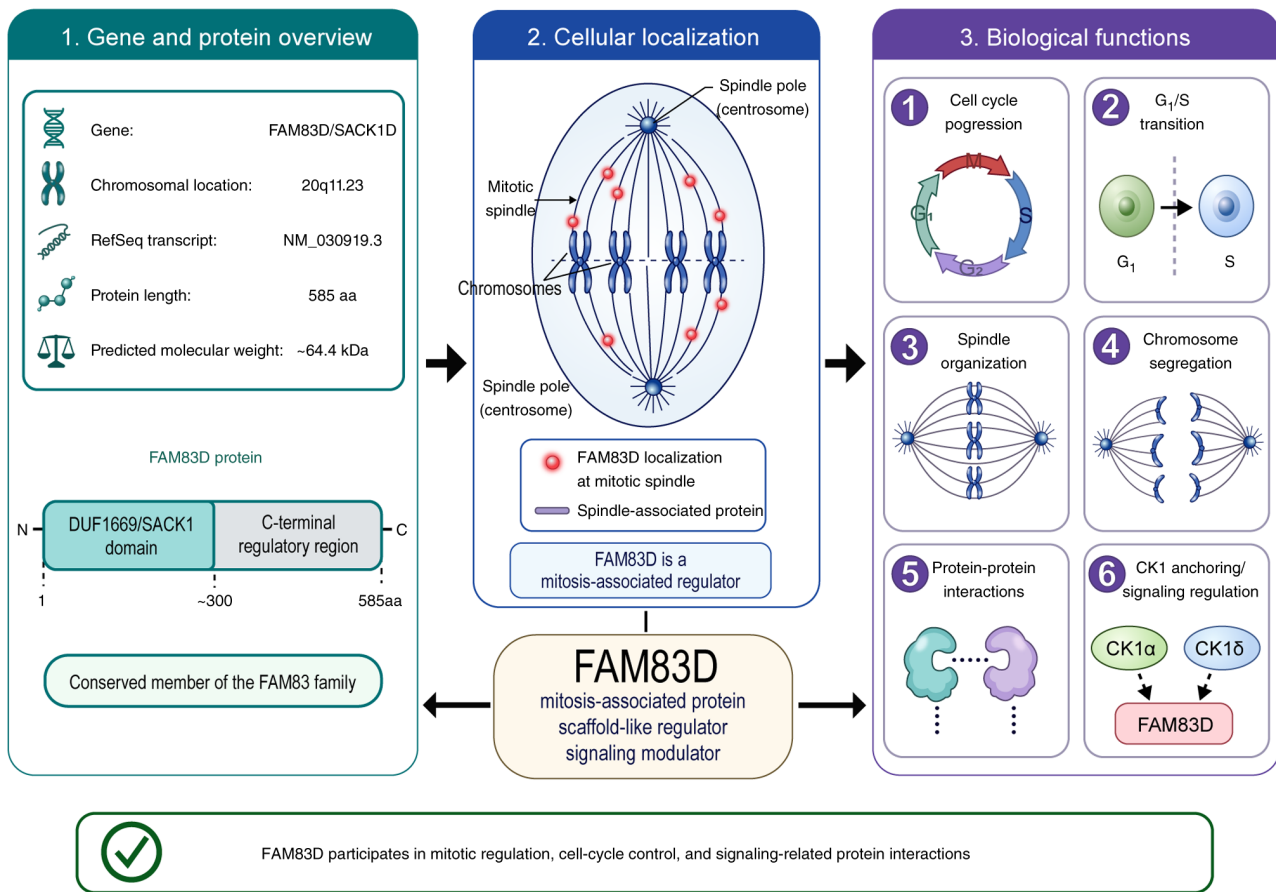


Figure 1. Structural features, cellular localization and biological functions of FAM83D. FAM83D, also referred to as FAM83D/SACK1D in some annotations, is a conserved member of the FAM83 protein family and contains an N-terminal DUF1669/SACK1 domain, which is associated with CK1 isoform anchoring and protein-protein interactions. The protein information summarized in this figure indicates a protein length of 585 aa and a predicted molecular weight of ~64.4 kDa. FAM83D has been reported to localize to the mitotic spindle and participate in mitotic regulation, spindle organization, chromosome segregation, cell cycle progression G₁/S transition and signaling-related protein interactions. FAM83D, family with sequence similarity 83 member D; CK1, casein kinase 1; DUF1669, domain of unknown function 1669; SACK1, scaffolding CK1 anchoring protein D; RefSeq, reference sequence; aa, amino acids.

likely a result of the combined effects of abnormal transcriptional regulation, epigenetic alterations and disrupted RNA homeostasis.

3. Roles of FAM83D in different malignant tumors

Taken together, existing studies indicate that FAM83D is highly expressed in multiple malignancies and is, to some extent, associated with malignant phenotypes. The relatively consistent functions of FAM83D include promoting tumor cell proliferation and accelerating cell cycle progression, enhancing migration and invasion while participating in epithelial-mesenchymal transition (EMT), affecting apoptosis and therapeutic tolerance, and is associated with unfavorable clinical outcomes (8,9,14). It should be noted that the depth of research and strength of evidence regarding FAM83D vary among types of cancer, and some conclusions require further validation using independent cohorts and mechanistic experiments.

Lung cancer. Lung cancer is one of the most common malignancies worldwide and a leading cause of cancer-related mortality (2). NSCLC accounts for 80-85% of all types of lung cancer diagnosed (33). FAM83D is notably upregulated in lung cancer tissues and cell lines, and high FAM83D expression is

associated with tumor differentiation, clinical stage, lymph node metastasis and unfavorable prognosis (19). Functional studies further demonstrate that FAM83D-silencing may suppress lung cancer cell proliferation, induce G₁-phase arrest and reduce invasion, migration and EMT, whereas FAM83D overexpression enhances malignant phenotypes in lung cancer cells (10,19).

Mechanistically, current evidence suggests that FAM83D promotes lung cancer progression via the AKT/mTOR pathway. Additionally, YTHDF2 has been reported to inhibit cell migration by negatively regulating the FAM83D-TGFβ1-SMAD2/3 axis, implying that FAM83D promotes this pathway (10,32). In addition, high FAM83D expression has been linked to reduced cisplatin sensitivity, suggesting that FAM83D contributes to chemotherapeutic resistance in lung cancer cells (10). Evidence for these findings has been derived from both *in vitro* functional experiments and clinical tissue analyses, although functional differences among histological subtypes require further clarification.

HCC. FAM83D has been proposed as a potential oncogenic molecule in HCC. FAM83D expression is higher in HCC tissues than in adjacent non-tumor tissues, and its abundance is associated with clinical features including sex, lesion size,

clinical stage, metastatic tendency and overall survival (34). Functional experiments have demonstrated that FAM83D silencing reduces the proliferation, migration and invasion of HCC cells and increases apoptosis (35). Mechanistically, FAM83D promotes HCC cell proliferation by activating the MEK/ERK pathway and upregulating cyclin D1 and c-Myc. FAM83D may also interact with F-box/WD repeat-containing protein 7 (FBXW7) and inhibit FBXW7-mediated degradation of oncoproteins, such as cyclin E1, thereby promoting tumor progression (36).

A recent study has also suggested that FAM83D may be related to changes in the immune microenvironment of HCC, for example, by influencing CD8⁺ T-cell and natural killer (NK)-cell infiltration and M2 macrophage polarization (37). However, evidence in this area is still mainly derived from bioinformatics analyses and preliminary experimental work (37), and the specific regulatory mechanisms remain to be validated. Therefore, at the current stage, there is a certain basis for the pro-tumorigenic role of FAM83D in HCC (35), and conclusions regarding immune regulation should be interpreted with caution.

Ovarian cancer (OC). OC is a common malignancy of the female reproductive system. Since early symptoms are atypical, the majority of patients are diagnosed at an advanced stage and have an unfavorable prognosis (38). FAM83D expression is increased in OC tissues and is associated with the clinical stage, metastatic status and patient prognosis (39). A study found that FAM83D expression was higher in patients with advanced OC and that patients with high FAM83D expression had relatively poor survival outcomes (40,41). Functional experiments indicate that FAM83D silencing suppressed OC cell proliferation, migration and invasion, induced cell cycle arrest and promoted apoptosis, whereas FAM83D overexpression produced the opposite effects (42).

Mechanistically, FAM83D may promote cell cycle progression by affecting the expression of cell cycle-related proteins, such as cyclin D1 and cyclin E1 (19), and participates in OC progression through the PI3K/AKT/mTOR pathway (42). Notably, miR-142-3p has been identified as a negative upstream regulator of FAM83D in OC (25). However, clinical application of FAM83D in OC remains limited, and evidence regarding its value in hematological detection and auxiliary diagnosis is still scarce, requiring further validation in larger cohorts (39).

Breast cancer. Breast cancer is the most common malignancy in women, and different molecular subtypes display marked differences in biological behavior and prognosis (43). Triple-negative breast cancer (TNBC) lacks effective targeted therapies, is highly aggressive, and has relatively unfavorable outcomes (43). FAM83D is generally highly expressed in breast cancer, particularly in the TNBC and HER2⁺ subtypes (44). High FAM83D expression is associated with tumor diameter, lymph node metastasis, clinical stage and unfavorable survival outcomes (45).

In vitro studies have indicated that FAM83D silencing notably suppresses breast cancer cell proliferation, migration and invasion, promotes apoptosis and inhibits EMT, whereas FAM83D overexpression enhances malignant progression and

metastatic potential (12,45). At the mechanistic level, FAM83D may activate the Wnt/ β -catenin pathway, promote β -catenin nuclear translocation and upregulate downstream target genes, thereby promoting the proliferation and invasion (26). METTL3-mediated m⁶A modification has been suggested to enhance FAM83D expression in TNBC (26). FAM83D interacts with FBXW7, suppressing its tumor-suppressive function and leading to the accumulation of oncogenic proteins and tumor progression (45). Overall, FAM83D has attracted attention in breast cancer, especially in aggressive subtypes; however, its functional differences and clinical notability across molecular subtypes warrant further investigation.

Digestive-system and other malignant tumors. In addition to the aforementioned types of tumors, aberrant FAM83D expression has been reported in digestive system tumors such as gastric cancer, colorectal cancer, esophageal cancer and pancreatic cancer and is associated with proliferation, invasion, metastasis and a poor prognosis (8,9).

High FAM83D expression levels are associated with the malignant progression of esophageal squamous cell carcinoma (ESCC) (46). FAM83D knockdown suppresses cell proliferation and invasion and induces apoptosis, potentially through regulation of the Akt/glycogen synthase kinase-3 β /Snail pathway and EMT (47). A recent study identified hyaluronan-mediated motility receptor (HMMR) as an upstream regulator of FAM83D in ESCC, where it promotes ESCC progression by upregulating FAM83D expression and promoting EMT (46). Moreover, Li *et al* (48) reported that FAM83D promotes ESCC progression by inhibiting FBXW7 and that FAM83D expression is associated with tumor size, TNM stage and reduced survival.

In colorectal cancer, high FAM83D expression is associated with advanced clinical stage, lymph node metastasis and poor prognosis, and may promote tumor cell proliferation and metastasis by affecting FBXW7/Notch-1 signaling (49). In addition, miR-495 has been shown to directly target FAM83D and suppresses colorectal cancer cell proliferation and migration, suggesting a miRNA-FAM83D regulatory axis in colorectal cancer (27).

In gastric cancer, FAM83D upregulation promotes proliferation, invasion and EMT through activation of the Wnt/ β -catenin signaling pathway and is associated with a poor prognosis and aggressive clinicopathological features, including lymph-node metastasis and TNM stage (20,22).

In pancreatic cancer, high FAM83D expression has been reported to enhance malignant phenotypes and participate in gemcitabine resistance through the Wnt/ β -catenin pathway, suggesting that it may be a potential marker of unfavorable prognosis (21,50). FAM83D expression is also associated with lymph node metastasis and worse overall and progression-free survival (34), and pan-cancer analyses have suggested potential associations with immune cell infiltration (22).

However, the role of FAM83D in glioblastoma has not been extensively investigated. Wang *et al* (51) reported that FAM83D inhibition exerted antitumor effects in glioblastoma cells by downregulating the Akt/Wnt/ β -catenin pathway. However, this evidence is currently limited to a single *in vitro* study and no *in vivo* or clinical data are available to support the functional relevance of FAM83D in this malignancy.

Therefore, the findings in glioblastoma should be interpreted with caution and further validation in animal models and clinical cohorts is warranted.

These studies further support the possibility that FAM83D is a multi-cancer oncogenic molecule. However, compared with lung cancer, HCC and breast cancer, where research is relatively concentrated, studies on other tumors remain scattered and differences in sample size, methodology and consistency of conclusions remain. Overall, FAM83D demonstrates certain common pro-tumorigenic features across different malignancies, including the promotion of cell cycle progression, enhancement of malignant biological behaviors and association with patient prognosis (9,44). Nevertheless, specific downstream pathways and key interacting proteins demonstrate clear cancer-type heterogeneity. Therefore, cross-cancer integrative analyses are key for a more comprehensive understanding of the common oncogenic mechanisms and cancer-specific roles of FAM83D. The expression patterns, biological functions and clinical importance of FAM83D in different malignancies is summarized in Table I. These include lung cancer (10,19,32), hepatocellular carcinoma (24,34-37), ovarian cancer (39-42), breast cancer (44,45), gastric cancer (20,22), colorectal cancer (27,49), esophageal cancer (46-48) and pancreatic cancer (21,50).

4. Molecular mechanisms by which FAM83D regulates the occurrence and progression of malignant tumors

DUF1669-mediated CK1 anchoring: A central mechanism of FAM83D function. The DUF1669 domain, a conserved feature of FAM83 family proteins, mediates the anchoring of CK1 isoforms to specific subcellular compartments (6,15). In normal mitosis, FAM83D directs CK1 α to the mitotic spindle, where it participates in proper spindle positioning and chromosome segregation (7). This scaffolding function is disrupted in cancer, where FAM83D upregulation may cause CK1 mis-localization and the aberrant phosphorylation of downstream substrates. Whether cancer-associated mutations or upregulation of FAM83D alters CK1 substrate specificity remains unclear and warrants further investigation. Of note, much of the oncogenic signaling of FAM83D, including its effects on Wnt/ β -catenin, MAPK/ERK and PI3K/AKT pathways, is likely downstream of CK1 mis-localization, positioning this scaffolding function as a central mechanistic node (6,15). Studies have further identified HMMR as a key regulator that recruits the FAM83D-CK1 α complex to the mitotic spindle, providing additional insight into the upstream control of this scaffolding function (15,52).

Participation in cell cycle regulation. Cell cycle dysregulation is a hallmark of malignant tumors, and FAM83D may participate in cell cycle regulation and promote tumor cell proliferation through multiple mechanisms. Studies have demonstrated that FAM83D can affect the expression of cell cycle-related proteins, such as cyclin D1 and cyclin E1, promote G₁/S transition and cell cycle progression, and thereby enhance the proliferative capacity of tumor cells (19,36). In addition, FAM83D localizes to the mitotic spindle, interacts with spindle-associated proteins such as KIF22, participates in chromosome alignment, segregation and spindle assembly and

maintains cell division stability (5). When FAM83D expression is suppressed, the expression of cell cycle-related proteins decreases, cells typically undergo G₁-phase arrest and tumor cell proliferation is inhibited. The loss of FAM83D may also affect spindle function and chromosome alignment stability, thereby interfering with normal cell division. These findings suggest that the roles of FAM83D in cell cycle and mitotic regulation may constitute a basis for its pro-tumorigenic effects. The evidence for this regulation is derived from both basic mechanistic studies (5,7) and functional experiments in cancer cells (19).

Regulation of tumor-associated signaling pathways. FAM83D may participate in tumor initiation and progression by influencing multiple tumor-associated signaling pathways, among which the MAPK/ERK, PI3K/AKT/mTOR, Wnt/ β -catenin and TGF- β pathways have attracted considerable attention.

In the MAPK/ERK pathway, a study demonstrated that FAM83D can promote ERK1/2 phosphorylation and subsequently upregulate downstream molecules such as cyclin D1 and c-Myc, thereby promoting tumor-cell proliferation and invasion (36). These findings suggest that FAM83D acts upstream of the MAPK/ERK cascade, likely at the level of ERK1/2 activation, which is supported by experimental studies in HCC models (36).

In the PI3K/AKT/mTOR pathway, FAM83D enhanced the activation of AKT and mTOR, promoted cell proliferation, inhibited apoptosis and participated in the regulation of chemotherapy resistance in lung cancer and ovarian cancer (10). This indicates that FAM83D functions upstream of the PI3K/AKT/mTOR pathway, promoting phosphorylation of AKT and mTOR. This pathway has been validated through functional experiments in lung cancer and OC cells, including assessments of cell proliferation, migration, invasion and drug sensitivity (10,42).

In the Wnt/ β -catenin pathway, FAM83D may affect β -catenin activity and downstream target-gene expression through interactions with CK1 isoforms, thereby driving tumor progression (22). Evidence for this pathway was derived from multiple types of cancer, including gastric cancer, breast cancer, pancreatic cancer and glioblastoma, with functional validation through *in vitro* and *in vivo* experiments (21,22,26,51).

In addition, in a study of lung adenocarcinoma, FAM83D has been reported to promote EMT, invasion and metastasis through the TGF β 1-SMAD2/3 axis (32). This conclusion was derived primarily from mechanistic experiments in lung adenocarcinoma cells, in which YTHDF2 was demonstrated to negatively regulate this axis.

It should be emphasized that current studies on the involvement of FAM83D in these signaling pathways have mostly concentrated on specific types of cancer and preclinical models, and the key nodes and effect strengths reported in different studies are not entirely consistent. Therefore, FAM83D is more appropriately regarded as a potential regulator of multiple pro-oncogenic signaling pathways, whereas the core signaling dependencies of FAM83D in different tumors require further clarification.

Interactions with other proteins. Protein-protein interactions represent a mechanism by which FAM83D exerts its biological

Table I. Expression patterns, biological functions and clinical importance of FAM83D in different malignancies.

Type of cancer	Main materials/ evidence sources	FAM83D expression pattern	Major biological functions	Related molecular mechanisms/signaling pathways	Clinical relevance	Evidence level	(Refs.)
Lung cancer (NSCLC/LUAD)	Tumor tissues, cell lines and <i>in vitro</i> functional assays	Upregulated/highly expressed	Promotes proliferation, migration, invasion, EMT and cisplatin resistance	Cell cycle regulation, the AKT/mTOR pathway and FAM83D-TGFβ1- SMAD2/3 axis	Associated with differ- entiation status, clinical stage, lymph node metastasis and worse prognosis	<i>In vitro</i> , <i>in vivo</i> and clinical tissue	(10,19, 32)
Hepatocellular carcinoma	Tumor tissues, database analyses and cell-based experiments	Upregulated/highly expressed	Promotes proliferation, migration and invasion; and inhibits apoptosis	MEK/ERK pathway, and the FBXW7/MCL1 axis. May be associated with changes in the tumor immune microenvironment	Associated with sex, AJCC stage, overall survival and disease-free survival	<i>In vitro</i> , database and clinical tissue	(24,34, 37)
Ovarian cancer	Tumor tissues, cell lines and <i>in vitro</i> functional assays	Upregulated/highly expressed	Promotes proliferation, migration, invasion and cell-cycle progression; inhibits autophagy	PI3K/AKT/mTOR pathway and the miR-142-3p/FAM83D axis	Associated with clinical stage, metastatic status and worse prognosis; may have auxiliary diagnostic value	<i>In vitro</i> and clinical tissue	(25,39, 42)
Breast cancer	Tumor tissues, database analyses and cell-based experiments	Upregulated/highly expressed, especially in TNBC and HER2 ⁺ subtypes	Promotes proliferation, migration, invasion, EMT and malignant progression	Wnt/β-catenin pathway, FBXW7-related regulation and METTL3-mediated m ⁶ A modification	Associated with tumor size, lymph node metastasis, clinical stage and unfavorable survival outcomes	<i>In vitro</i> , database, clinical tissue	(12,26, 44,45)
Gastric cancer	Tumor tissues and cell-based experiments	Upregulated/highly expressed	Promotes tumor growth, cell proliferation, invasion, migration and EMT	Wnt/β-catenin pathway	Associated with worse prognosis	<i>In vitro</i> , and clinical tissue	(20,22)
Colorectal cancer	Tumor tissues and cell-based experiments	Upregulated/highly expressed	Promotes cell proliferation, migration and invasion	FBXW7/Notch-1 signaling and the miR-495/FAM83D axis	Associated with clinical stage, lymph node metastasis and worse prognosis	<i>In vitro</i> clinical tissue	(27,49)
Esophageal cancer	Cell-based experiments and radiotherapy-related functional studies	Upregulated/highly expressed	Promotes proliferation, invasion and EMT; affects radiosensitivity	Akt/GSK-3β/Snail signaling pathway	Associated with malignant progression; knockdown enhances radiosensitivity	<i>In vitro</i>	(47)
Pancreatic cancer	Cell-based experiments and database analyses	Upregulated/highly expressed	Promotes tumorigenesis, proliferation, malignant phenotypes and gemcitabine resistance	Wnt/β-catenin pathway	May serve as a potential marker of worse prognosis and a therapeutic target	<i>In vitro</i> studies and databases	(21,50)

Table I. Continued.

Type of cancer	Main materials/ evidence sources	FAM83D expression pattern	Major biological functions	Related molecular mechanisms/signaling pathways	Clinical relevance	Evidence level	(Refs.)
Glioblastoma	Cell-based experiments	Functionally upregulated/ oncogenic	Suppression of FAM83D exerts antitumor effects	AKT/Wnt/ β -catenin pathway	Suggests potential therapeutic target value	<i>In vitro</i> only (preliminary)	(51)

Table I summarizes the expression patterns, biological functions, molecular mechanisms, clinical relevance and evidence levels of FAM83D across major cancer types. FAM83D is generally upregulated in multiple solid tumors and exhibits relatively consistent pro-tumorigenic roles, including promotion of tumor cell proliferation, migration, invasion, EMT and treatment resistance. However, the dominant downstream mechanisms and the strength of evidence vary considerably among types of cancer. The 'Level of evidence' column indicates the experimental and clinical evidence supporting the role of FAM83D in each type of cancer, categorized as bioinformatic analysis (database mining or *in silico* prediction), *in vitro* experiments (cell-based functional assays), *in vivo* studies (animal models) and clinical tissue validation (patient samples and cohort analyses). Of note, for several types of cancer, particularly glioblastoma and esophageal cancer, the evidence remains preliminary and requires further validation. The table is based on the studies cited in the main text and is not intended to be exhaustive. EMT, epithelial-mesenchymal transition; FAM83D, family with sequence similarity 83 member D; FBXW7, F-box/WVD repeat-containing protein 7; TNBC, triple negative breast cancer; METTL3, methyltransferase 3; GSK-3 β , glycogen synthase kinase-3; MCL1, myeloid cell leukemia 1; LUAD, lung adenocarcinoma; NSCLC, non-small cell lung cancer; AJCC, American Joint Committee on Cancer.

functions. Proteins currently reported to interact with FAM83D include the CK1 isoforms, KIF22 and FBXW7. CK1 is a serine/threonine protein kinase. FAM83D can bind CK1 α , CK1 δ and other isoforms and may regulate Wnt/ β -catenin signaling through these interactions (15). CK1 can also phosphorylate FAM83D, thereby affecting its localization and function (5,7). KIF22 is a spindle protein closely related to mitosis. Although the FAM83D-KIF22 interaction was first identified in 2008, its functional relevance in cancer remains largely unexplored and warrants further investigation (5).

FBXW7 is a classical tumor suppressor that promotes the degradation of oncoproteins such as cyclin E1 and c-Myc through the ubiquitination pathway. The interaction between FAM83D and FBXW7 was first reported by Wang *et al* (45) in breast cancer, in which FAM83D down-regulated FBXW7 expression through physical interactions, leading to mTOR hyperactivation and malignant progression. Recent studies have substantially advanced understanding of its mechanism of action. Jiang *et al* (12) systematically mapped the FBXW7-binding sites on FAM83D through comprehensive mutational analysis and demonstrated that FAM83D promoted the ubiquitination and proteasomal degradation of FBXW7 via these binding sites. In HCC, the FAM83D-FBXW7-myeloid cell leukemia 1 axis has been implicated in promoting cell proliferation and migration, further supporting the broad relevance of this regulatory mechanism in cancer (35).

In addition to its downstream effects on FBXW7, FAM83D is also subject to upstream regulation. Recent studies have identified HMMR as an upstream regulator of FAM83D expression. In nasopharyngeal carcinoma, HMMR interacts with FAM83D and stabilizes its expression by inhibiting ubiquitination, thereby activating β -catenin signaling and promoting tumor progression (23). Similarly, in ESCC, HMMR promotes malignant progression by upregulating FAM83D expression (46). These findings suggest a complex regulatory network in which FAM83D is not only a downstream effector, but also a target of upstream oncogenic signals.

Overall, FAM83D does not appear to act through a single fixed signaling pathway. Instead, it may function as a node in multiple protein interaction networks, integrating cell cycle regulation, spindle function, signal transduction and protein stability control to collectively participate in tumor progression. However, the key interaction landscape of FAM83D and its dynamic changes in different biological contexts have not yet been systematically studied.

Effects on the tumor immune microenvironment. The tumor immune microenvironment is a key factor that influences tumor initiation, progression and therapeutic response. In recent years, studies have focused on the relationship between FAM83D and the tumor immune microenvironment. For example, in HCC, high FAM83D expression has been suggested to be associated with reduced infiltration of effector immune cells, such as CD8⁺ T cells and NK cells, as well as increased numbers of M2 macrophages and regulatory T cells (37). In addition, some studies suggest that FAM83D may be associated with tumor immune escape and immune checkpoint regulatory networks (14,37,53).

However, research on the role of FAM83D in regulating the tumor immune microenvironment is still in the early stages of development. The majority of evidence has been derived from database analyses, bioinformatics inferences or limited preliminary experimental validation. For example, the association between FAM83D expression and altered immune cell infiltration in HCC has been primarily derived from bioinformatic analyses (37), whereas direct experimental evidence demonstrating the causal role of FAM83D in modulating immune cell function remains scarce. Similarly, the proposed link between FAM83D and immune checkpoint regulatory networks (53) is based on computational predictions rather than experimental validation. Whether FAM83D directly regulates programmed death-ligand 1 expression or serves as a predictor of immunotherapy response requires further investigation. Therefore, although this field has considerable research potential, current statements should remain cautious. The upstream regulatory networks and downstream molecular mechanisms of FAM83D in cancer are summarized in Table II. Potential upstream regulatory networks, protein interactions, downstream signaling pathways and malignant phenotypes associated with FAM83D are summarized in Fig. 2.

5. Potential clinical applications of FAM83D in malignant tumors

Potential as a tumor diagnostic biomarker. Biomarkers serve a role in early tumor detection, auxiliary diagnosis and subtype assessment. Recent studies have suggested that FAM83D is highly expressed in the tumor tissues of numerous malignancies, including lung cancer, HCC, ovarian cancer, breast cancer and gastric cancer, and is closely related to tumor occurrence and progression (9,39). Based on its differential expression between tumors and normal tissues, FAM83D is considered a potential diagnostic biomarker.

However, evidence for the diagnostic value of FAM83D is mainly derived from tissue-level expression analyses, public-database mining, retrospective sample studies and preclinical experiments (8,9,54). Its sensitivity and specificity for early tumor screening, as well as its diagnostic performance across different types of cancer and molecular subtypes, lack sufficient and consistent clinical evidence. Therefore, at present, FAM83D is more appropriately regarded as a candidate molecule with research value than a mature diagnostic indicator with a clear basis for clinical application.

Detection of FAM83D in bodily fluid samples has also begun to receive attention. A study has suggested that serum FAM83D expression may be abnormally elevated in patients with OC and may have auxiliary diagnostic importance (39). However, the overall number of relevant studies is limited, sample sizes are small and detection platforms and analytical methods have not been standardized. Therefore, the reproducibility and clinical generalizability of these findings require further validation. Future studies should systematically evaluate the feasibility of FAM83D as a non-invasive diagnostic biomarker in combination with liquid biopsy and related technologies. In addition, differential expression of FAM83D among molecular subtypes suggests that it may have potential value in tumor classification and biological characterization (12,55), but whether this potential can be

translated into a clinically meaningful stratification indicator still requires a larger sample and prospective studies. Overall, current evidence for the diagnostic value of FAM83D is largely derived from retrospective tissue studies and preclinical experiments, and large-scale prospective multicenter validation is still lacking.

Potential value as a prognostic indicator. Prognostic evaluation is key for individualized cancer treatment and follow-up management. Existing studies demonstrate that high FAM83D expression in multiple malignancies is frequently associated with advanced stage, lymph-node metastasis, enhanced invasiveness and unfavorable survival outcomes (8,9). In types of cancer with relatively extensive research, such as lung cancer, HCC, breast cancer and OC, high FAM83D expression showed a consistent association with shortened overall survival and reduced disease-free survival (20,34,39,55).

From a biological perspective, FAM83D is closely related to malignant processes such as cell cycle progression, invasion and metastasis, EMT, and therapeutic tolerance, providing a theoretical basis for its role as a prognostic molecule (10,12,45). Some studies have suggested that after adjustment for clinicopathological factors such as age, stage, tumor size and metastatic status, FAM83D may remain an independent factor associated with worse prognosis (8,9,55). However, the strength of evidence for this conclusion varies among different types of cancer, and most studies are single-center retrospective analyses. Therefore, its independent prognostic value requires further validation in high-quality multicenter studies.

Overall, FAM83D may be more suitable as a candidate variable in multi-indicator models than as a sole marker for prognostic judgment. In the future, integrating FAM83D expression with tumor stage, pathological grade, molecular subtype and treatment response to construct multidimensional risk-stratification models may help improve the accuracy and clinical utility of prognostic assessment. However, most prognostic studies are single-center retrospective analyses, and the independent prognostic value of FAM83D requires further validation in high-quality multicenter prospective cohorts.

Research prospects as a potential therapeutic target. With the development of precision medicine and molecular targeted therapies, the discovery of new therapeutic targets has become a key direction in cancer research. FAM83D is persistently upregulated in multiple malignancies and participates in key processes such as cell proliferation, migration, invasion, EMT, chemotherapy resistance and the tumor immune microenvironment. Therefore, it has a theoretical basis as a potential therapeutic target (10,51). Studies have indicated that silencing or inhibiting FAM83D expression can weaken malignant phenotypes in different tumor models, reduce cell proliferation and migration, and increase tumor cell sensitivity to chemotherapeutic drugs (18,49,52), suggesting its potential therapeutic value.

Nevertheless, current interventional studies targeting FAM83D remain mainly in the preclinical stage and include small interfering RNA, short hairpin RNA and other gene silencing strategies, as well as mechanistic studies of upstream and downstream regulatory networks (12,52,54). Although

Table II. Upstream regulatory network and downstream molecular mechanisms of FAM83D in cancer.

Type of cancer involved	Regulatory level	Key molecule/ event	Effect on FAM83D	Downstream effects/ biological consequences	Type of evidence	(Refs.)
Ovarian cancer	miRNA regulation	miR-142-3p	Directly suppresses FAM83D expression	Inhibits ovarian cancer cell proliferation and malignant progression	Mechanistic experiments (IHC, RT-qPCR and luciferase reporter assay)	(25)
Colorectal cancer	miRNA regulation	miR-495	Directly suppresses FAM83D expression	Inhibits colorectal cancer cell proliferation and migration	Mechanistic experiments (RT-qPCR, western blot, CCK-8, colony formation, transwell, IHC, luciferase reporter and flow cytometry assays)	(27)
Non-small cell lung cancer	ceRNA regulation	circFOXMI/ miR-614/ FAM83D	Upregulates FAM83D by sponging miR-614	Promotes tumor cell proliferation	Mechanistic experiments (RT-qPCR, RNA pull-down, RIP, luciferase assay, FISH, flow cytometry, xenograft and IHC)	(28)
Lung adenocarcinoma	ceRNA regulation	AC099850.3/ miR-101-3p/ FAM83D	May upregulate FAM83D through a ceRNA mechanism involving miR-101-3p	Associated with tumor progression and worse prognosis	Mechanistic experiments (RT-qPCR, CCK-8 and BrdU incorporation assay)	(29)
Hepatocellular carcinoma	Epigenetic regulation	Promoter hypomethylation	Enhances FAM83D transcription	Increases proliferative and invasive capacity	Mechanistic experiments (RT-PCR, RT-qPCR, IHC, CCK-8, scratch test, transwell invasion and bisulfite DNA sequencing)	(24)
Lung adenocarcinoma and related contexts	Transcriptional regulation	MYBL2	Promotes FAM83D transcription	Facilitates tumor progression	Mechanistic experiments (ChIP-seq, RNA-seq, RT-qPCR and western blot)	(30)
Multiple cancer contexts	Transcriptional regulation	FOXM1	May regulate FAM83D transcription	Enhances malignant biological behaviors	Literature-based summary/mechanistic inference (no original experiments)	(28,30)
Triple-negative breast cancer	RNA modification	METTL3-mediated m ⁶ A modification	Increases FAM83D expression	Activates Wnt/ β -catenin signaling and promotes tumorigenesis	Mechanistic experiments (m ⁶ A modification analysis, Wnt/ β -catenin pathway validation and <i>in vivo</i> tumor growth assay)	(26)
Lung adenocarcinoma	RNA-binding protein regulation	YTHDF2	Negatively regulates FAM83D	Suppresses migration and invasion	Database analysis and mechanistic experiments (MTT, colony formation, wound healing, transwell, flow cytometry, RT-qPCR, western blot, RIP and LC-MS/MS)	(32)
Lung cancer and multiple cancer-related contexts	Cell cycle regulation	Cyclin D1 and cyclin E1	Increased after FAM83D upregulation	Promotes G ₁ /S transition and cell proliferation	Bioinformatic analysis and mechanistic experiments (RT-qPCR, western blot, CCK-8, colony formation, transwell, flow cytometry, xenograft and IHC)	(19)

Table II. Continued.

Type of cancer involved	Regulatory level	Key molecule/ event	Effect on FAM83D	Downstream effects/ biological consequences	Type of evidence	(Refs.)
Multiple cancer-related basic contexts	Mitotic/spindle regulation	Spindle localization, chromosome segregation	FAM83D participates in spindle regulation and chromosome segregation	Maintains mitotic stability and supports sustained tumor cell proliferation	Mechanistic experiments (Indirect immunofluorescence, western blot, siRNA knockdown, live-cell imaging and co-immunoprecipitation)	(5,7)
Multiple cancer-related basic contexts	Protein interaction	CK1 α /CK1 δ	FAM83D acts as an anchoring protein for CK1 isoforms	Modulates signaling and mitosis-related processes	Mechanistic experiments (CRISPR/ Cas9 knock in/knock out, immuno- precipitation, mass spectrometry, western blot, immunofluorescence, <i>in vitro</i> kinase and binding assays)	(15)
Multiple cancer-related basic contexts	Protein interaction	KIF22	Interacts with spindle- associated proteins	Participates in chromosome alignment and mitosis	Mechanistic experiments (Indirect immunofluorescence, western blot, siRNA knockdown, live-cell imaging and co-immunoprecipitation)	(5)
Hepatocellular carcinoma, breast cancer and colorectal cancer	Protein interaction	FBXW7	FAM83D may antagonize the tumor-suppressive function of FBXW7	Promotes oncoprotein accumulation and tumor progression	Mechanistic experiments (RT-PCR, western blot, MTT, colony formation, transwell, flow cytometry and IHC)	(35,45, 49)
Hepatocellular carcinoma	MAPK/ERK signaling	ERK1/2 activation	FAM83D enhances ERK signaling	Upregulates cyclin D1 and c-Myc, promoting proliferation	Mechanistic experiments (RT-PCR, RT-qPCR, CCK-8, colony formation, flow cytometry, BrdU incorporation and western blot)	(36)
Lung cancer and ovarian cancer	PI3K/AKT/mTOR signaling	AKT/mTOR activation	FAM83D promotes pathway activation	Enhances proliferation, invasion and drug resistance while inhibiting apoptosis	Mechanistic experiments (RT-PCR, western blot, MTT, colony formation, transwell, flow cytometry and IHC)	(10,42)
Gastric cancer breast cancer, pancreatic cancer and glioblastoma	Wnt/ β -catenin signaling	β -catenin activation/ nuclear translocation	FAM83D activates the pathway	Promotes proliferation, migration and invasion	Mechanistic experiments (RT-PCR, IHC, western blot, CCK-8, colony formation, transwell, flow cytometry, xenograft and TCGA data analysis)	(21,22, 26,51)
Lung adenocarcinoma	TGF β /SMAD signaling	TGF β 1- SMAD2/3 axis	FAM83D participates in pathway activation	Promotes EMT, invasion and metastasis	Database analysis; Mechanistic experiments (MTT, colony formation, wound healing, transwell, flow cytometry, RT-qPCR, western blot, RIP and LC-MS/MS)	(32)

Table II. Continued.

Type of cancer involved	Regulatory level	Key molecule/ event	Effect on FAM83D	Downstream effects/ biological consequences	Type of evidence	(Refs.)
Hepatocellular carcinoma	Tumor immune microenvironment	CD8 ⁺ T cells, NK cells, M2 macrophages and Tregs	High FAM83D expression may be associated with altered immune infiltration	May contribute to immune evasion and tumor progression	Database analysis; Mechanistic experiments (MTT, colony formation, wound healing, transwell, flow cytometry, RT-qPCR, western blot, RIP and LC-MS/MS)	(37,53)

Available evidence suggests that aberrant FAM83D expression is unlikely to result from a single regulatory event. Instead, it may arise from the combined effects of non-coding RNA regulation, epigenetic alterations, transcriptional activation, RNA modification and protein interaction networks. Its downstream consequences mainly involve cell-cycle progression, activation of oncogenic signaling pathways and enhancement of malignant phenotypes. FAM83D, family with sequence similarity 83 member D; ceRNA, competing endogenous RNA; miRNA/miR, microRNA; EMT, epithelial-mesenchymal transition; NK, natural killer; Tregs, regulatory T cells; FBXW7, F-box/WD repeat-containing protein 7; METTL3, methyltransferase 3; MYBL2, MYB proto-oncogene like-2; THDF2, YTH N6-methyladenosine RNA binding protein F2; KIF22, kinesin family member 22; CK1, casein kinase 1; RT-qPCR, reverse transcription-quantitative PCR; siRNA, small interfering RNA; CCK-8, cell counting kit-8; ChIP, chromatin immunoprecipitation; LC-MS, liquid chromatography mass spectrometry; IHC, immunohistochemistry; seq, sequencing; TCGA, the cancer genome atlas; RIP, RNA immunoprecipitation.

these studies have provided preliminary support for the drug-gability or intervention of FAM83D, considerable distance remains from its clinical translation. On the one hand, FAM83D is not a classical enzymatic target, and its druggability, accessibility and specific inhibition strategies remain unclear (56). However, achieving efficient, safe and tumor-specific delivery remains a key barrier to translational applications.

In addition, considering the association of FAM83D with multiple oncogenic signaling pathways and resistance mechanisms, a more realistic application model may not be direct single-agent inhibition but rather its use as a key regulatory node in combination therapy (56). For example, FAM83D-targeted interventions could be explored in combination with chemotherapy, molecular targeted therapy or immunotherapy to improve treatment sensitivity and delay resistance. However, this direction currently lacks systematic animal experiments and clinical studies, and the therapeutic-target value of FAM83D requires further validation. At present, evidence for the therapeutic targeting of FAM83D remains confined to preclinical models, and substantial challenges, including druggability, delivery efficiency and tumor-specific targeting, must be addressed before clinical translation can be considered.

6. Current challenges and future perspectives

Major limitations of current research. Although studies on FAM83D in malignant tumors have increased in recent years and its role in tumor initiation and progression has attracted growing attention, the field remains at an early stage of transition from basic exploration to clinical translation. The present review considers several prominent limitations remaining in current research (12).

First, the core molecular mechanisms of FAM83D have not yet been fully elucidated. Although existing studies suggest that FAM83D is associated with cell cycle regulation, spindle function, CK1 isoform binding and the abnormal activation of multiple oncogenic signaling pathways, the specific functions of its conserved DUF1669 domain in different biological contexts, its key interacting proteins, and its upstream and downstream regulatory networks remain poorly characterized. This limits the understanding of oncogenic mechanisms and cancer type-specific roles (6,7,15,18).

Second, the overall evidence remains limited. The majority of findings are derived from public-database analyses, tissue-sample expression assays, *in vitro* functional experiments and selected animal experiments (8,9). Although these studies suggest that FAM83D may have relatively consistent pro-tumorigenic roles across multiple types of cancer, high-quality, multicenter and large-sample clinical validations remain insufficient. Prospective cohort studies and standardized evaluation systems are lacking in terms of diagnostic value, prognostic assessment and therapeutic translational potential. Therefore, the consistency and generalizability of the conclusions across different studies remains limited.

Third, although FAM83D appears to have some common functions across types of tumors, its cancer type-specific mechanisms remain unclear (9). As tumors of different tissue origins vary markedly in their molecular background, signaling pathway dependence and immune microenvironment

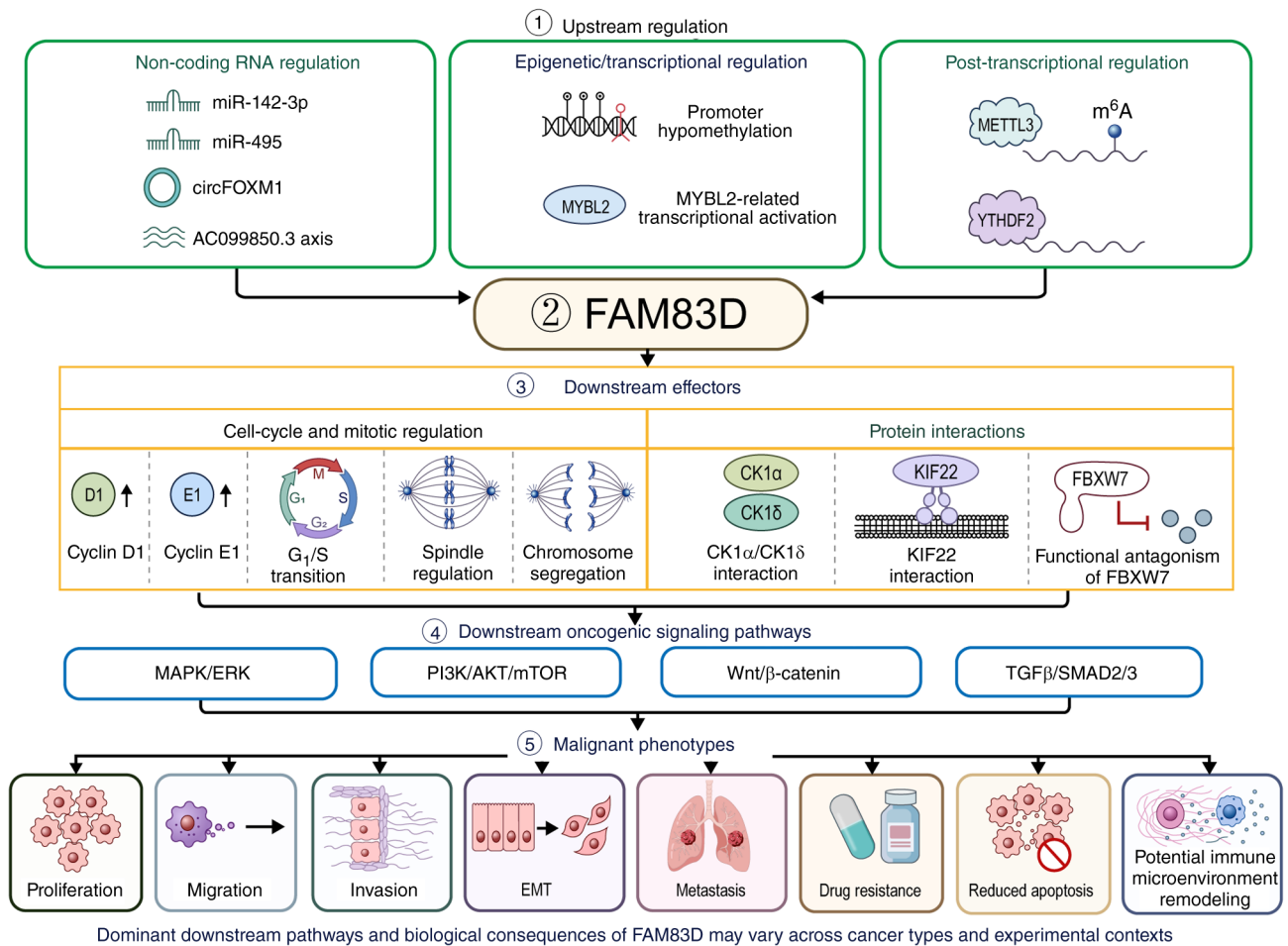


Figure 2. Schematic overview of the FAM83D molecular regulatory network in cancer. The figure is organized into five hierarchical layers to improve clarity. (1) Upstream regulation: Non-coding RNAs (miR-142-3p, miR-495, circFOXM1 and AC099850.3), epigenetic/transcriptional regulation (promoter hypomethylation: MYBL2 and FOXM1) and post-transcriptional regulation (METTL3-mediated m⁶A modification and YTHDF2). (2) FAM83D as the central hub: FAM83D serves as a scaffold-like, mitosis-associated and signaling modulator. (3) Downstream effectors: Cell-cycle and mitotic regulation (cyclin D1/E1, G₁/S transition, spindle regulation and chromosome segregation) and protein interactions (CK1α/δ anchoring, KIF22 interaction and FBXW7 functional antagonism). (4) Downstream signaling pathways: MAPK/ERK, PI3K/AKT/mTOR, Wnt/β-catenin and TGFβ-SMAD2/3. (5) Malignant phenotypes: Proliferation, migration, invasion, EMT, metastasis, drug resistance, reduced apoptosis and potential immune microenvironment remodeling. Arrows indicate the direction of regulation. The dominant pathways and phenotypes may vary across types of cancer and experimental contexts. EMT, epithelial-mesenchymal transition; FAM83D, family with sequence similarity 83 member D; CK1, casein kinase 1; MYBL2, MYB proto-oncogene like-2; METTL3, methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit; YTHDF2, YTH N6-methyladenosine RNA binding protein F2; KIF22, kinesin family member 22; FBXW7, F-box/WD repeat-containing protein 7; miR/miRNA, microRNA.

composition, the functional strength, downstream effects and clinical relevance of FAM83D may not be identical across tumors (14). Current studies often focus on a single type of cancer, and systematic cross-cancer integrative analyses and horizontal comparisons remain insufficient. Therefore, it is difficult to determine whether FAM83D is a broad-spectrum oncogenic molecule or a regulator with pronounced tissue specificity.

Additionally, clinical translational research on FAM83D is lagging. Although existing studies suggest that FAM83D has potential as a biomarker and therapeutic target, multiple practical barriers must be addressed prior to its clinical application. For example, standardized detection criteria for FAM83D as a diagnostic or prognostic molecule have not yet been established and evidence regarding its stability and reproducibility in bodily fluid samples remains insufficient. In therapeutic research, specific intervention strategies targeting FAM83D remain immature; small-molecule drug development is limited

and issues such as delivery efficiency, off-target effects and safety remain unresolved (54).

Finally, studies on the synergistic interactions between FAM83D and other tumor-associated molecules remain insufficient. Existing research involves multiple levels, including miRNAs, long non-coding RNAs, ceRNA networks, abnormal methylation and m⁶A modification (24-26,28,32). However, an integrated systematic framework for these mechanisms is still lacking, and the hierarchical position of FAM83D in complex tumor molecular networks has not been fully defined. Without further clarification of its coordinated regulation with key oncogenes, tumor suppressor genes and tumor microenvironment factors, a comprehensive evaluation of its true biological function and clinical value remains difficult.

Future research directions and prospects. In response to these limitations, future research on FAM83D should be conducted at multiple levels, including its basic mechanisms, clinical

validation and translational applications. First, basic research should focus on the core functional domains and molecular interaction mechanisms of FAM83D (7). Systematic studies are required to determine the functional characteristics of the DUF1669 domain, key binding proteins and dynamic changes under different cellular states. The integration of proteomics, transcriptomics, spatial omics and other technologies may help construct a more complete FAM83D regulatory network (15). This will facilitate the identification of key mechanistic nodes through which FAM83D promotes tumor progression and provide a theoretical basis for subsequent targeted interventions.

Second, in tumor biology research, cross-cancer integrative analyses and cancer-type-specific mechanistic studies should be performed in parallel (9). On the one hand, pan-cancer analyses can summarize common functional patterns of FAM83D across different tumors. However, the molecular background of specific types of tumors should be considered to explore the differences in FAM83D function, signaling pathway dependence and clinical relevance among tumors of different tissue origins. In particular, the mechanisms of FAM83D in the tumor immune microenvironment, therapeutic resistance and metastasis warrant further investigation (14,54).

Third, at the clinical research level, multicenter, large-sample, prospective study designs should be strengthened to systematically validate the value of FAM83D in tumor diagnosis, classification, prognostic evaluation and therapeutic response prediction (9). Future studies should not stop at describing expression differences, but should further evaluate whether FAM83D adds value to existing clinical models, for example, by improving early screening accuracy, optimizing risk stratification or helping predict treatment response. At the same time, standardization of detection methods should be promoted, including clarification of sample sources, detection platforms, threshold settings and interpretation standards to improve comparability and reproducibility across studies.

In terms of translational applications, future studies should focus on the development of feasible strategies for FAM83D-targeted interventions. In addition to traditional RNA, research should explore the blockade of protein-protein interactions, intervention with upstream regulatory molecules and combination treatment strategies (12). FAM83D may not be suitable as an independent single-agent target. Instead, it may be more valuable for enhancing chemotherapy sensitivity, reversing resistance and improving the efficacy of combination therapy (10). Therefore, more high-quality animal experiments and systematic preclinical studies are needed to evaluate its potential role in combination treatment systems and gradually promote its clinical translation. This may help clarify the cancer-type-specific regulatory mechanisms of FAM83D and provide new insights into its role in virus-associated tumorigenesis.

In addition to traditional approaches, emerging technologies, such as single-cell sequencing, spatial transcriptomics, proteomics, CRISPR-based functional screening and artificial intelligence-assisted biomarker discovery, may offer new opportunities to advance FAM83D research. With the advancements in single-cell sequencing and spatial transcriptomics, FAM83D-related research is expected to progress further. Studies have begun to elucidate the core molecular mechanisms of FAM83D, including the identification of HMMR

as a key interactor that recruits the FAM83D-CK1 α complex to the mitotic spindle for proper spindle alignment (7,52). Furthermore, emerging evidence suggests that targeting FAM83D can induce tumor cell senescence by activating the cyclic GMP-AMP synthase-stimulator of interferon genes signaling pathway and reprogramming tumor-associated macrophages in glioma (24). These findings, together with advances in multiomics technologies, may help move FAM83D research beyond expression-correlation analyses toward mechanistic dissection and precision translation.

In conclusion, FAM83D is increasingly recognized as a tumor-associated molecule that demonstrates relatively consistent pro-tumorigenic roles in multiple malignancies and has potential value in diagnosis, prognostic assessment and therapeutic interventions (9). However, the current research foundation remains insufficient, and clinical translational evidence remains limited. Only through deeper mechanistic research, stronger clinical evidence and more mature interventional strategies can FAM83D gradually develop from an experimental research target into a tumor-associated biomarker or potential therapeutic target with genuine clinical application prospects.

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Authors' contributions

JL, YY and LM drafted the manuscript. DD and HS collected and organized the literature and participated in revising the manuscript. HL designed and revised the manuscript. 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

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Competing interests

The authors declare that they have no competing interests.

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