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FAM83D and Malignant Tumors: A Brief Literature Review

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Abstract

FAM83D is a spindle related protein and plays critical roles in mid-plate formation during mitosis. Aberrant FAM83D expression was reported in multiple cancers. Here, we summarized the latest researches of FAM83D in recent five years, and discussed the relationship of FAM83D and cancer diagnosis, development and prognosis, aiming to provide new perspectives for the research of FAM83D in tumors.

Keywords: FAM83D; Malignant tumors; Tumor biomarkers

Introduction

The FAM83D gene (Family with sequence similarity 83 member D), also named as CHICA or C20Orf129, is located on chromosome 20 [1]. FAM83D is relative highly expressed during cell division, playing critical roles in mid-plate formation, regulating the location of human Chromokines in Kid to spindle during metaphase and sister chromatid separation [2,3]. Loss of FAM83D leads to dysfunctional spindle, failure of chromatid separation and consequential generation of aneuploidy. Furthermore, researchers have found that FAM83D was co-expressed with many known mitosis-related factors, including Aurora-A, Aurora-B, Plk-1, Plk-4, Cdc20, Cdk1, Nek2, Geminin and CENP protein family, in types of cancers [4]. FAM83D belongs to FAM83 protein family (FAM83A-H), whose functions had long been elusive. The proteins in FAM83 family share a common Domain of Unknown Function 1669 (DUF1669), which has weak homology to Phospholipase D [5]. Phospholipase D has been widely investigated in cell proliferation and differentiation. Besides, database analysis showed that the expression level of FAM83D is negatively correlated with overall survival time in various types of cancers. Therefore, FAM83D is tightly related to cell division and may be correlated to cancer development. Here, we summarized the updated cancer-related studies of FAM83D and discuss the possibility of FAM83D as biomarker or target in cancer diagnosis or therapy.

FAM83D and Lung Cancer

Up to date, three independent researchers investigated the relationship of FAM83D expression and lung cancer development. First, through analysis of TCGA LUAD (Lung Adenocarcinoma) datasets, Shi R found that compared to adjacent normal tissues, LUAD tissues showed significant upregulation of FAM83D expression and higher FAM83D expression related to higher DNA ploidy, corresponding well to previous *in vitro* study that loss of FAM83D leads to aneuploidy. Besides, higher FAM83D expression was associated with shorter survival time. Finally, they performed *in vitro* assay and showed that FAM83D deficiency inhibited lung cancer cell lines A549 and H1299 proliferation and mobility [6]. Similarly, Yin C found elevated FAM83D expression levels in high invasive Non-Small Cell Lung Cancer (NSCLC) cell lines and in the distant metastasis of clinical samples. Interestingly, they illustrated that FAM83D promoted Epithelial-Mesenchymal Transition (EMT) in BEAS2B NSCLC cells but not in A549 and H1299 NSCLC cells, implying the discrepancy of FAM83D functions in different NSCLC cells. Additionally, they showed that FAM83D knockdown increases A549 and H1299 sensitivity to cisplatin *in vitro and in vivo* [7]. The latest article concerning FAM83D and lung cancer found that circFOXM1 promote NSCLS development by sponging miR-614, and FAM83D was one of the targets of miR-614. Consequently, they conclude that circFOXM1/miR-614/FAM83D axis may regulate lung cancer diagnosis and prognosis in clinic and cell proliferation and progression *in vitro* and *in vivo* [8].

FAM83D and Digestive System Cancer

In total, four independent researches concerned the relationship of FAM83D and liver cancer.

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Table 1: Summary of the role of FAM83D in cancers.

Cancer type	No. of literature reported	*In vitro*	*In vivo*	Pathway regulated
Lung	3	OE: promote growth, mobility KD: increase sensitivity to cisplatin	Higher expression in cancer tissues and related to shorter OS.	influencing CCND1, CCNE1 expression
Liver	4	OE: promotes growth, colony formation. KD: inhibits growth, colony formation; inhibits stem cancer cells growth and self-renewal.	Higher expression in cancer tissues; positive correlation with AFP, TNM stages, PVTT presence, recurrence rate; Negative with OS, PFS. KD inhibits metastasis in mice.	AKT/mTor; TGF-β, MAPK; CRAF, CD44, Hippo.
Pancreas	1	KD: inhibits the growth and increases the gemcitabine sensitivity	higher expression in cancer tissues; relates to poor prognosis	Wnt/β-catenin
Esophagus	1	KD: inhibits the growth and EMT and increases the radiosensitivity	higher expression in cancer tissues; correlates to poorer clinical outcome; increases their radiosensitivity in mice	Akt/GSK-3β/Snail
Stomach	2	positively relates to cells growth, invasion and migration	positively relates to tumor growth, invasion and migration	Wnt/β-catenin
Colorecta	2	OE: promotes growth, invasion KD: inhibits the growth, colony formation, migration and invasion	higher expression in cancer tissues	PTEN/PI3K/AKT/mTor; FBXW7/Notch-1
Ovary	2	promotes growth, migration and invasion	higher expression in cancer tissues, relates to shorter OS and DFS times and more advanced stages	PI3K/AKT/mTOR
Endometria	2	-----	higher expression in cancer tissues, relates to more advanced stages	-----
Breast	4	OE: promotes migration, invasion transformation, KD: inhibits growth and invasion	higher expression and negatively associated with the recurrence-free survival in TNBC, poor relapse-free survival and OS in Luminal A type, poor DFS.	suppresses ERK phosphorylation; downregulates FBXW7 expression

In clinical research, Liao W found the positive correlation between FAM83D levels and Alpha-Fetoprotein Levels (AFP), the clinical TNM stage and the presence of a Portal Vein Tumor Thrombus (PVTT), while negative correlation with Disease Free Survival (DFS) and Overall Survival (OS) times no matter in the collected unadjusted group or in adjusted groups according to diagnostic indicators. Soon afterwards, Lin B got the similar results by analyzing 150 clinic samples collected between 2006 and 2013 [9]. Additionally, they found better outcomes of patients with lower FAM83D after liver transplantation. More recently, another research confirmed the role of FAM83D through analysis of TCGA and GEO (33006, 45436, 84402) datasets, demonstrating that compared to adjacent normal tissues, liver tumors exhibited higher FAM83D expression, and the higher FAM83D levels implied worse DFS and OS, higher recurrence rate and mortality and more advanced AJCC stages [10]. Their results indicated that FAM83D may serve as one independent marker for liver cancer progression diagnosis and survival times [11]. *In vitro*, Wang D. et al compared 30 liver cancer samples and corresponding adjacent normal tissues and found no differences in expression levels of FAM83A, FAM83B and FAM83C except for FAM83D. Besides, FAM83D levels were elevated in most liver cancer cell lines compared to normal liver cells. Moreover, FAM83D over expression promoted proliferation and colony formation of Hep3B and Focus cell, while FAM83D knockdown inhibited that of SK-hep-1 and YY-8103 cells [12]. Lin B reported FAM83D deficiency inhibited liver cancer stem cell growth and self-renewal *in vitro*, as well as tumor growth and tumor metastasis in mice [9]. As to pancreatic cancer, only one literature stated that FAM83D levels were up-regulated in Pancreatic Adenocarcinoma (PDAC) no matter in TCGA datasets or in collected clinical samples, and related to poor prognosis. Meanwhile, *in vitro* assay showed that FAM83D knockdown inhibited the growth and increased the gemcitabine sensitivity of PDAC cells BxPC3 and SW1990 [13]. Apart from digestive glands, FAM83D were also related to digestive tracts cancer development. Firstly, one group described FAM83D and esophageal cancer, revealing higher FAM83D expression in Esophageal Squamous Cell Carcinoma (ESCC) tissues compared to adjacent normal tissues and tightly correlated to poorer clinical outcomes. Furthermore, FAM83D deficiency inhibited ESCC cells ECA109 and KYSE30 growth and increased their radiosensitivity *in vitro* and *in vivo* [14]. Secondly, two articles reported FAM83D expression is positively related to Gastric Cancer (GC) cells HS-746T, AGS and SGC-7901 growth, invasion and migration *in vitro* and *in vivo*. Besides, clinical samples and database analysis showed that FAM83D upregulation was observed in GC tissues and cell lines, and implicated poor prognosis of GC patients [15,16]. Thirdly, two groups studied the role of FAM83D in Colorectal Cancer (CRC). One reported that FAM83D over expression may promote HCT-15 and HT-29 cells proliferation and invasion *in vitro* [17]. The other study found that FAM83D levels are upregulated in clinical CRC samples and in CRC cells lines. Besides, FAM83D knockdown inhibited proliferation, colony formation, migration and invasion of HCT116 and SW480 CRC cells [18].

FAM83D and Female Reproductive System Cancer

In the year of 2019, two groups conducted the research about FAM83D and ovarian cancer. Both groups reported higher FAM83D levels in cancer tissues than normal tissues. Besides, patients with higher FAM83D levels exhibited shorter OS and DFS times and more advanced stages. One of the researches proposed that FAM83D may serve as an effective marker to distinguish low malignant potential tumor from invasive epithelial ovarian cancer. Like in other cancer types, FAM83D over expression promoted growth, migration and invasion of ovarian cells *in vitro* [19,20]. Similar to ovarian cancer, two groups' researches indicated that FAM83D is one of the genes that up-regulated in Endometrial Cancer (EC), and higher expression was related to more advanced stages. It is worth to note that they showed that FAM83D levels in patients' blood would be a efficacious marker to predict the EC prognosis [21,22]. Through database mining, four studies dig out the correlation between the expression of FAM83D and breast cancer. Zhai X reported that FAM83D expression was negatively associated with the recurrence-free survival in Triplet-

Negative Breast Cancer (TNBC) samples by analyzing GSE45827, GSE38959, GSE65194 datasets from GEO, while another research found FAM83D was associated with poor relapse-free survival and OS of Luminal A type of breast cancers by analyzing dataset GDS2250 [23,24]. Furthermore, RNA-seq data from GEO showed that FAM83D was one of the most highly regulated genes in TNBC [25]. Additional two studies reported that FAM83D was upregulated in breast cancer tissues and related to poor DFS regardless of breast cancer classification [26,27]. Besides, *in vitro* assays showed that FAM83D over expression promoted human mammary epithelial cell (HMEC and MCF10A) transformation, migration, invasion and Anchorage-Independent Growth (AIG) (Table 1). One the other hand, knockdown of FAM83D in breast cancer MDA468 and BT549 cells dramatically inhibited cell growth and invasion [26,28,29].

Conclusion

Above, we summarized the role of FAM83D in multiple types of cancers with clinical data and laboratory *in vivo* and *in vitro* research data. To get one step further, we compressed all the key information in one table (Table 1). In the table, we involved the reported cellular pathways that FAM83D may regulate in cancer cells. Collectively, up to date, FAM83D has been reported critical roles to cell proliferation, migration and invasion in nine types of cancers. Through high throughput screenings and validations, the downstream regulating factors/pathways of FAM83D have been identified. Meanwhile, several studies indicated upstream factors that may regulate human FAM83D expression, including circFOXM1/miR-614 axis, miRNA-495 and promoter methylations. However, we found no relationship between promoter methylation status and FAM83D expression levels in mice tissues during development, implying different regulating mechanisms in different physiological or pathological conditions. As one protein that tightly related to mitosis and had highly correlational expressions with CYCLINB1, FAM83D was intensively investigated these years for its mechanisms in regulating cellular behavior. Prospectively, FAM83D may serve as one effective biomarker for cancer diagnosis or prognosis. Furthermore, given that FAM83D deficiency inhibited proliferations and migrations of in many types of cancer cells *in vitro* and *in vivo*, it has the potential to be one promising target for cancer therapy. Further studies of FAM83D may focus on three aspects: 1) how it regulates cell division or chromatin separation; 2) how it regulates downstream factors or cellular pathways and what is its biochemical features. 3) More retrospective and prospective clinical study to validate its role as biomarkers for cancer diagnosis and prognosis and its mutations landscape in cancer cases.

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