



Deciphering the Roles of IFITM1 in Tumors

Renba Liang¹ · Xinxiao Li² · Xiaodong Zhu^{1,3,4}

Published online: 11 May 2020
© Springer Nature Switzerland AG 2020

Abstract

Interferon (IFN)-induced transmembrane protein 1 (IFITM1), a member of the IFN-induced transmembrane protein family, is reported to be highly expressed in tumor tissues as well as cancer cell lines, and it is an independent prognostic biomarker for patients with certain tumor types, such as gallbladder carcinoma, esophageal adenocarcinoma, colorectal cancer, and gastric cancer. Moreover, overexpression of IFITM1 promotes tumor cell proliferation, invasion, metastasis, angiogenesis, and therapeutic resistance, including endocrine therapy, chemotherapy, and radiotherapy resistance. Due to these diverse functions of IFITM1 in tumors, targeting IFITM1 may provide a novel strategy for cancer treatment and be highly desirable to improve cancer patient outcomes. Herein, we decipher the role of IFITM1 in cancer in detail.

Key Points

The expression level of interferon-induced transmembrane protein 1 (IFITM1) is upregulated in a variety of tumor tissues and cancer cell lines.

IFITM1 stimulates cancer progression and is an independent prognostic factor for cancer patients.

IFITM1 may be a promising target for cancer treatment.

1 Introduction

The interferon-induced transmembrane (*IFITM*) gene family was first discovered in neuroblastoma cells treated with interferon (IFN) in 1984 [1]. The human IFN-induced

transmembrane protein 1 (IFITM1), also named 9–27 or Leu13, is a member of the IFITM protein family, which is comprised of three proteins, IFITM-1, IFITM-2, and IFITM-3. IFITM1 is a 17-kDa membrane protein with a conserved CD225 domain and two transmembrane domains [2, 3]. A schematic of the IFITM1 structure and location is depicted in detail in Fig. 1. It has been more than 20 years since IFITM1 was identified as a Leu-13 leukocyte membrane surface antigen responsible for signal transduction in lymphocytes, such as antiproliferative and homotypic adhesion signaling [4–6]. It is also important to note that IFITM1 is known as a modulator of immunity and antiviral activity [3]. Interestingly, during the last decade, increasing evidence has shown that IFITM1 is overexpressed in a large number of solid human tumors (Table 1). Using EnVision immunohistochemistry for 69 squamous cell/adenosquamous carcinomas (SC/ASC) and 146 ordinary adenocarcinomas (ACs) of gallbladder cancer tissues, Li et al. found that IFITM1 expression was significantly higher in SC/ASC patients with high Tumor Node Metastasis (TNM) stage, lymph node metastasis, and invasion compared to patients with low TNM stage, no lymph node metastasis, and no invasion. Positive IFITM1 expression was closely related to a decreased overall survival in SC/ASC and AC patients [7]. In addition, IFITM1 messenger RNA (mRNA) levels were elevated in colorectal and stomach carcinoma samples, as detected by cancer array profiling [8]. Likewise, a recent study indicated that IFITM1 expression is positive in 93% (87/94) estrogen receptor positive (ER+) breast cancer samples and negative in all six normal breast tissues, as determined with immunohistochemistry; and it was also overexpressed in aromatase inhibitor (AI)-resistant MCF-7:5C cells assayed by reverse transcriptase-polymerase chain reaction

Renba Liang and Xinxiao Li contributed equally to this work.

✉ Xiaodong Zhu
zhuxdongxmu@126.com

¹ Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, P.R. China

² Department of Research, Guangxi Medical University Cancer Hospital, Nanning, Guangxi, P.R. China

³ Key Laboratory of Early Prevention and Treatment for Regional High-Incidence-Tumor, Guangxi Medical University, Ministry of Education, Nanning, Guangxi, P.R. China

⁴ Wuming Hospital of Guangxi Medical University, Nanning, Guangxi, P.R. China

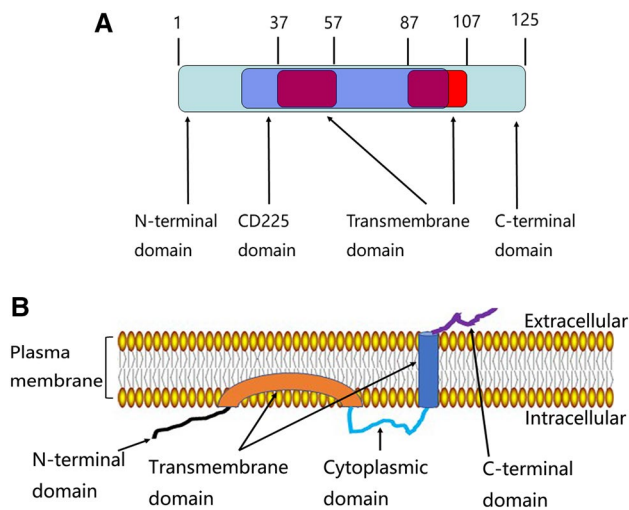


Fig. 1 Structure and topology of IFITM1. **a** IFITM1 contains a conserved CD225 domain and two transmembrane domains. IFITM1 is made up of 125 AAs. The two transmembrane domains consist of AA residues 37–57 and residues 87–107, respectively. The number and sequence of AAs that make up the CD225 domain are unclear. The positions of AAs are described above the scheme. **b** Localization of IFITM1 in the plasma membrane. AA amino acid, *IFITM1* interferon-induced transmembrane protein 1

(RT-PCR) and immunoblotting [9]. A high IFITM1 intensity score (an indicator of immunohistochemical score) was associated with increased clinical stage and increased risk of recurrence, suggesting that high IFITM1 expression in ER+ breast cancer significantly correlates with poor clinical outcome and poor response to endocrine therapy [9]. Aberrant expression of IFITM1 plays a vital role in cancer development. It promotes tumor cell proliferation, inhibits cell death, stimulates invasion and metastasis, and also results in the induction of resistance to endocrine therapy, chemotherapy, and radiotherapy, and has prognostic value for patient clinical outcomes [7–14] (Fig. 2). As a result, it is important to gain full insights into the functions of IFITM1 in cancer biology in order to design new, targeted approaches to treat solid tumors. This review concentrates on the roles of IFITM1 in cancer cells.

2 Role of IFITM1 in Tumorigenesis

2.1 Proliferation

Unlimited proliferation is one of the most striking characteristics of malignant tumors. Notably, IFITM1 not only plays an essential role in IFN- γ -induced inhibition of cell proliferation of B-lymphocytes [3], it has also been shown to be one of the key modulators of tumor cell proliferation [15]. Yu et al. found that blocking IFITM1 expression inhibited proliferation of glioma cells (U-87 MG and U-373

MG) and led to cell cycle arrest, accompanied by a reduction of cyclin A, cyclin B1, cyclin D1, cyclin E, CDK2, and CDK4, and upregulation of p27^{kip1} [16]. This finding is corroborated by the recent data in the inflammatory breast cancer SUM149 cell line [17]. Moreover, further support for this finding is provided by data suggesting that silencing IFITM1 significantly reduces tumor growth in a mouse model of breast, lung, and colorectal cancers [9, 18, 19]. For example, loss of IFITM1 markedly increases p21 transcription, expression, and nuclear localization, which was mediated by Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway activation (Fig. 3), eventually resulting in the suppression of tumor growth of the orthotopic (mammary fat pad) and mouse mammary intraductal (MIND) models of breast cancer [9].

2.2 Invasion and Metastasis

Because invasion and metastasis affect patients overall survival and represent a significant obstacle in tumor therapy [20], a series of studies has been conducted to probe the intrinsic mechanism involved in this process. Aside from its importance in tumor cell proliferation, IFITM1 also has a role contributing to invasion and metastasis of human malignancies, suggesting that it could become a promising biomarker for determining the likelihood of a malignancy having invasive properties [9, 17, 21–23] (Table 2). Employing a signal sequence trap, Yang et al. found that IFITM1 was overexpressed in gastric tumor tissues as well as cancer cell lines (SNU-216, SNU-620, and SNU-638) when compared with their normal counterpart. The IFITM1-overexpressed cells had a stronger capability for invasiveness [24]. This finding was supported by the work of Lee et al., who suggested that there was an upregulated level of IFITM1 in gastric cancer tissues and cancer cell lines (AGS and SNU-638), and silencing IFITM1 decreased migration and invasiveness of cancer cells [25]. Interestingly, several studies have demonstrated that IFITM1 is correlated with the expression of matrix metalloproteinases (MMPs) [11, 16, 19]. MMPs are involved in the extracellular matrix (ECM) degradation and regulation of adhesion and cytoskeletal proteins, as related to tumor invasion [26]. Overexpression of IFITM1 gives rise to the promotion of invasion of head and neck squamous cell carcinoma (HNSCC) cells; this together with upregulation of MMPs was detected by microarray [11]. Along with the modulation of MMPs, the underlying mechanism by which IFITM1 facilitates invasion is through targeting caveolin-1, as shown by the finding that knockdown of caveolin-1 abrogated small interfering IFITM1-induced decrease of invasion of colorectal cancer cells [10]. However, the mechanisms discussed above are not the only way

Table 1 The high expression level of IFITM1 in different tumors

Types	Models	Detection methods	Main findings	Refs
Colorectal cancer	Tissues from 144 subjects	Immunohistochemistry	IFITM1 is highly expressed in colonic cancer tissues but not in rectal cancer tissues	[39]
	Samples from 10 colon and 10 rectal carcinomas	Cancer profiling array	The results show a significant increase in IFITM mRNA levels in colon and rectal carcinomas	[8]
Gastroesophageal adenocarcinoma	Tissues from 174 patients	Immunohistochemistry	IFITM1 is overexpressed in gastroesophageal adenocarcinoma	[38]
Gastric cancer	27 gastric cancer tissues and 6 cell lines	RT-qPCR and Western blot analysis	IFITM1 is highly upregulated in cancer cell lines and tissues	[25]
	10 stomach carcinoma samples	Cancer profiling array	IFITM1 is elevated in tumor tissues	[8]
	Samples from 4 patients and 4 tumor cell lines	Samples: in situ analysis; cell lines: Northern blot analysis	IFITM1 is increased in all tumor tissues compared with their normal counterpart and detected in 3 cell lines	[24]
	Cisplatin-resistant YCC-3/R and YCC-3 cancer cell lines	ACP RT-PCR	The mRNA level of IFITM1 is markedly increased in YCC-3/R cells	[42]
Hepatocellular carcinoma	HepG2 and HuH7 cell lines	RT-PCR, Western blotting and immunofluorescence analysis	IFITM1 is highly expressed in cancer cell lines compared with normal liver cell line (LO2)	[15]
Lung cancer	Tissues from 30 patients and 2 cancer cell lines	RT-PCR and Western blot analysis	The study confirms high expression of IFITM1 in lung cancer tissues and cell lines	[18]
	10 lung carcinoma samples	Cancer profiling array	IFITM1 expression increases significantly in lung carcinomas	[8]
	3 non-small cell lung cancer cell lines	RT-qPCR and immunoblotting	IFITM1 is highly expressed in non-small cell lung cancer cell lines	[27]
Breast cancer	94 ER+ breast cancer patient samples and MCF-7:5C cell line	Samples: immunohistochemistry; cell line: RT-PCR and immunoblotting	IFITM1 expression is positive in 93% (87/94) tumor samples and negative in all 6 normal breast tissues and overexpressed in MCF-7:5C cells	[9]
	Triple-negative SUM149 cell line	Western blot and RT-PCR	The mRNA and protein level of IFITM1 is constitutively overexpressed in triple-negative SUM149 cells	[17]
	MDR MCF7 cell line	Western blot and RT-PCR	MDR MCF7 cells constitutively express IFITM1-3 at both the mRNA and protein levels	[47]
Head and neck cancer	20 frankly invasive HNSCC, 11 early invasive HNSCC, and 10 normal oral mucosal tissues; 6 HNSCC cell lines	Tissues: immunohistochemistry; cell lines: RT-PCR and Western blot analysis	IFITM1 is observed in early invasive HNSCC and is higher in invasive HNSCC tissues as well as positive in all HNSCC cell lines, but not in normal epithelial cells	[11]
	19 paired oral neoplasm cases and CAL27 and TSCC1 cell lines	Tissues: RT-qPCR and immunohistochemistry; cell lines: RT-qPCR	IFITM1 overexpression is verified in oral neoplasm tissues and cells, and IFITM1 is upregulated in CAL27 and TSCC1 cell lines with increases in dose and time of radiation	[12]
Gallbladder cancer	Tissues from 69 squamous cell/adenosquamous carcinomas and 146 adenocarcinomas	EnVision immunohistochemistry	IFITM1 expression is higher in squamous cell/adenosquamous carcinomas and adenocarcinomas patients with high TNM stage, lymph node metastasis, and invasion	[7]
Ovarian cancer	Metastatic implants from the xenograft mice	Microarray and RT-qPCR	The expression of IFITM1 is greatly increased in metastatic implants	[23]
Glioma	Five human glioma cell lines	RT-PCR and Western blotting	Four cell lines with higher IFITM1 expression have tumorigenic properties in nude mice, but not for U-138 MG, whose IFITM1 level is the lowest	[16]
Nasopharyngeal carcinoma	Radioreistant CNE-2R and CNE-2 cell lines	cDNA microarrays	The analysis identifies that IFITM1 is increased in CNE-2R	[44]

ACP RT-PCR annealing control primer-based RT-PCR, cDNA complementary DNA, ER+ estrogen receptor positive, HNSCC head and neck squamous cell carcinoma, IFITM1 interferon-induced transmembrane protein 1, MDR multidrug resistant, mRNA messenger RNA, RT-PCR reverse transcription-polymerase chain reaction, RT-qPCR Real-time quantitative polymerase chain reaction, TNM Tumor Node Metastasis

by which IFITM1 stimulates cancer invasion. For instance, the latest findings indicate that the epidermal growth factor receptor/sex-determining region Y-box 2 (EGFR/SOX2) signaling axis plays an essential role in IFITM1-induced migration and invasion of non-small cell lung cancer cells (NSCLCs) [27]. Furthermore, IFITM1 is also essential for the maintenance of the epithelial-to-mesenchymal transition (EMT) signature of NSCLC cells, as evidenced by the fact that IFITM1 depletion gives rise to upregulation of *E*-cadherin expression and downregulation of *N*-cadherin and SNAIL expression in NSCLC cells (H1650 and A549) [27]. However, another study challenges this concept; it showed that IFITM1 expression is not significantly associated with EMT markers, *E*-cadherin, and vimentin expression in lung AC tissues examined by immunohistochemistry [28]. Hence, the role of IFITM1 in EMT remains elusive, and it still warrants further investigation to address this concern.

2.3 Angiogenesis

In order to grow without limitations and to metastasize, tumors rely on newly formed vessels, which provide the nutrition needed. It is of importance to point out that the level of IFITM1 has a positive correlation with microvessel density in lung AC specimens and orthotopic models of breast cancer [9, 28], as measured by CD31 staining (a biomarker of microvessel density). To the best of our knowledge, angiogenesis is a complex multistep process that involves several pivotal components, such as endothelial cells (ECs), pro-angiogenic [vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF)] and angiostatic [thrombospondin-1 (TSP-1) and endostatin] [29–31] factors. A link between IFITM1 and ECs is suggested by a study that explored angiogenesis [32]. Specifically, IFITM1 expression in ECs increases when ECs sprout and form lumens. In accordance with this result, suppression of IFITM1 disorganizes lumen formation both *in vitro* and *in vivo*. The molecular study demonstrated that IFITM1 modulates tight junction assembly in ECs through binding to occludin, a tight junction protein [32]. In addition, Kim et al. found that zoledronate, which was usually used in osteoporosis treatment and prevention of bone metastases in several cancers, inhibited ECs proliferation, VEGF-induced tube formation, and IFITM1 expression in human umbilical vein ECs. Moreover, the mRNA and protein level of IFITM1 in ECs was elevated when treating ECs with VEGF [33]. This may suggest that IFITM1 has a role to play in angiogenesis).

3 Cancer Therapy Resistance

Endocrine therapy, chemotherapy, and radiotherapy are crucial and effective strategies in the treatment of many types of cancer. Unfortunately, cancer cells gradually become resistant to these approaches, resulting in disease relapse and ultimately metastasis. As a result, there is an urgent need to perform relevant studies to probe the intrinsic molecular mechanism of treatment resistance in order to exploit new therapeutic approaches. Given that IFITM1 functions in many kinds of cellular processes, it would be foolish not to question whether it might also play a significant role in treatment resistance. Intriguingly, some investigations show that IFITM1 is a potential candidate which participates in endocrine therapy, chemo- and radio-resistance (Table 3).

3.1 Endocrine Therapy Resistance

About 70–80% of breast cancers are ER+, and ER pathway signaling plays a key role in the progress of breast cancer [34]. Given the importance of ER signaling in breast cancer, therapies targeting this pathway, such as AIs, have been used in clinical therapy for ER+ breast cancer. However, approximately 30% of patients eventually have a poor response to AIs [35]. With regard to the underlying mechanism of poor response, researchers find that IFITM1 is overexpressed in AI-resistant breast cancer cells and tissues [9, 22, 36, 37]. As anticipated, silencing of IFITM1 expression with small interfering RNA (siRNA) in letrozole-resistant breast cancer cells results in therapy re-sensitization [37]. Moreover, reduction of IFITM1 leads to an increase in the expression of p21, Bax, and Noxa and induces cell death in resistant cells [22]. Aside from the breast cancer, there is, to date, no evidence that IFITM1 is involved in the resistance of other tumors to endocrine therapy.

3.2 Chemoresistance

IFITM1 is associated with poor clinical prognosis in some cancer patients [7, 10, 25, 38–40]. One of the main drivers of clinical outcomes is the development of chemoresistance, as chemotherapy is one of the standard treatments for many types of tumors. A study more than 10 years ago suggested firstly that IFITM1 was a potent marker for cisplatin sensitivity in human esophageal SC carcinoma cell lines KYSE-170 and KYSE-2270 *in vitro* [39]. The sensitivity to cisplatin was suppressed or enhanced by IFITM1 overexpression or knockdown, respectively [41]. Consistent with the findings in esophageal cancer cells, Lee et al. applied annealing control primer-based reverse transcriptase-polymerase

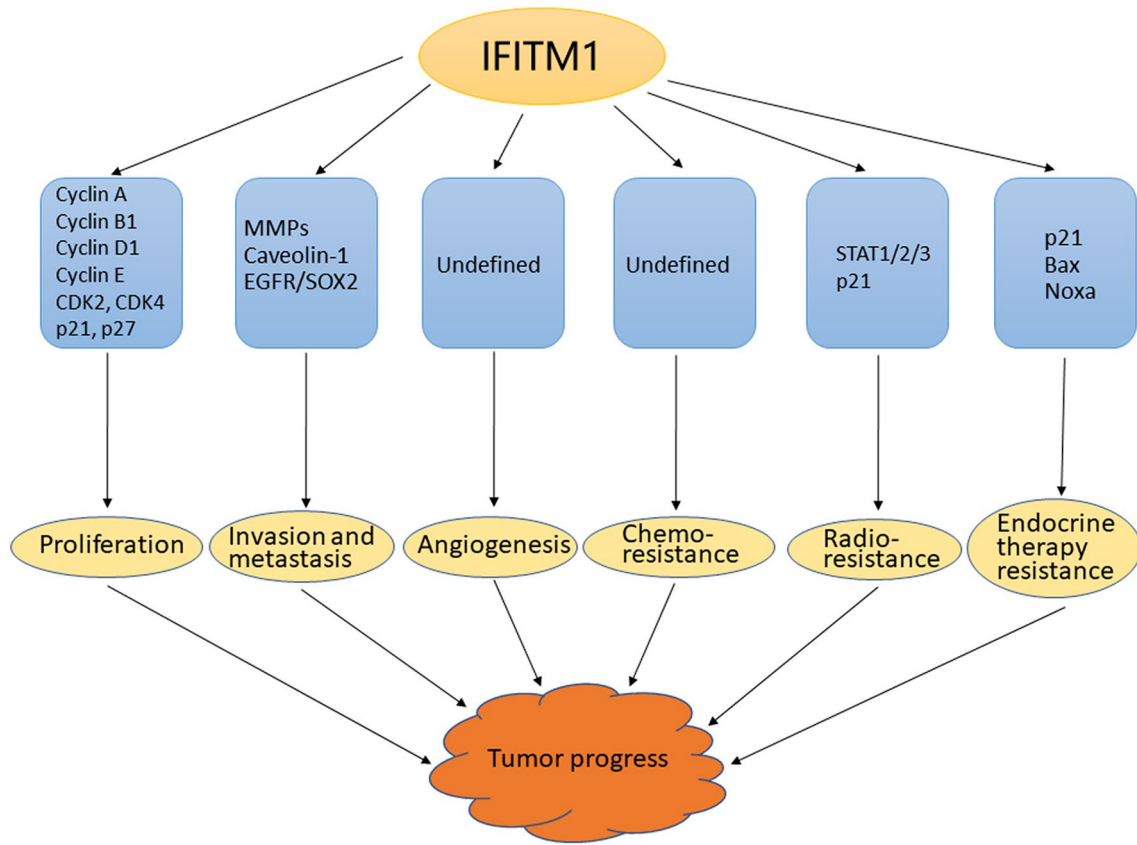


Fig. 2 Tumor-promoting functions of IFITM1. Overexpression of IFITM1 is involved in cancer development and therapy, such as promoting tumor cell proliferation, stimulating invasion and metastasis, increasing angiogenesis, and inducing resistance to endocrine therapy, chemotherapy, and radiotherapy. Smaller letters are impor-

tant target genes through which IFITM1 modulates these processes. *EGFR* epidermal growth factor receptor, *IFITM1* interferon-induced transmembrane protein 1, *MMPs* matrix metalloproteinases, *SOX2* sex-determining region Y-box 2, *STAT* signal transducer and activator of transcription

Fig. 3 The scheme of molecular signaling of IFITM1 in tumors. Knockdown of IFITM1 results in activation of the JAK/STAT pathway. After that, STAT translocates into the nucleus, in which it binds to promoter of p21, ultimately leading to p21 transcription. In addition, IFITM1 silencing inhibits the phosphorylation of p21 and increases p21 nuclear translocation. *IFITM1* interferon-induced transmembrane protein 1, *JAK* Janus kinase, *STAT* signal transducer and activator of transcription

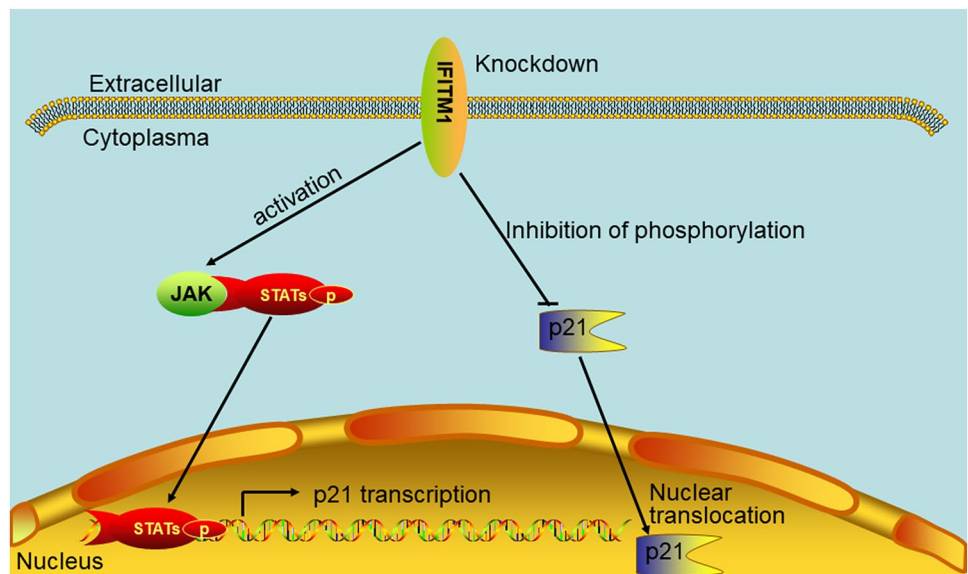


Table 2 The role of IFITM1 in tumor invasion and metastasis

Year	Tumor types	Evidence	References
2019	NSCLC	Silencing IFITM1 reduces the capacity of sphere formation, migration, and invasion of NSCLC cells in vitro, and IFITM1 is essential for the progression of NSCLC in vivo	[27]
2017	Breast cancer	IFITM1 depletion in AI-resistant MCF-7:5C cells decreases tumor growth and invasion, whereas these phenomena reverse with the ectopic expression of IFITM1	[9]
2016	Breast cancer	Inhibition of IFITM1 obviously diminishes the aggressive phenotype of triple-negative SUM149 cells	[17]
2015	Colorectal cancer	Increased IFITM1 level is remarkably associated with CRC lymph node and distance metastasis, and downregulation of IFITM1 suppresses cell migration/invasion and tumorigenicity in vitro	[10]
2015	Breast cancer	IFITM1 silence significantly inhibits migration and invasion of the AI-resistant cells	[22]
2014	Ovarian cancer	Overexpression of IFITM1 promotes migration and invasiveness in SK-OV-3 cells	[23]
2012	Gastric cancer	Knockdown of IFITM1 reduces the migration and invasiveness of cancer cells, whereas its overexpression results in the opposite	[25]
2012	Colorectal cancer	The SW480 cells transfected with IFITM1 have more aggressive properties than the parental ones	[19]
2011	Glioma	Suppression of IFITM1 significantly decreases migration and invasion of glioma cells, together with downregulation of MMP9	[16]
2008	HNSCC	The study shows that IFITM1 is positive at the invasive front of early invasive HNSCC and higher in invasive HNSCC, and IFITM1 overexpression increases invasion of HNSCC cells in vitro	[11]
2005	Gastric cancer	Cancer cells with IFITM1 overexpression exhibit greater migration and invasion compared with the control ones	[24]

AI aromatase inhibitor, CRC colorectal cancer, HNSCC head and neck squamous cell carcinoma, IFITM1 interferon-induced transmembrane protein 1, MMP9 matrix metalloproteinase 9, NSCLC non-small cell lung cancer

chain reaction (ACP RT-PCR) technology to confirmed that IFITM1 was highly expressed in a cisplatin-resistant human gastric cancer cell line compared with the parental one [42]. However, these studies mainly explored drug sensitivity in vitro and did not take into account the host in vivo environment, which is of prime importance to clinical response. Interestingly, gene expression profiles in a human ovarian carcinoma mouse xenograft model suggested that the expression of IFITM1 decreased 24 h after administrating drug-sensitive xenografts with paclitaxel, which also hinted that IFITM1 was involved with the responsiveness to chemotherapy drugs [43].

3.3 Radioresistance

There is also evidence that IFITM1 may be involved in radioresistance [44]. In human RSa cells, interferon α induces resistance of the cells to cytotoxicity of X rays, along with the up-regulation of IFITM1 levels detected by mRNA differential display and Northern blotting analysis. High IFITM1-expressing cells show increased resistance to X-rays. In good agreement with this phenomenon, silencing of IFITM1 by antisense oligonucleotides results in the loss of IFN- α -induced resistance of RSa cells to killing by X-rays [45]. In addition, this notion is further supported by recent findings in oral cancer [12]. Herein, IFITM1 has been shown to be overexpressed in oral neoplasm tissues and cells, and the expression level elevates with the increase in

the time and dose of radiation. Moreover, siRNA-mediated knockdown of IFITM1 gives rise to an increase in radiation-induced DNA damage and cell apoptosis in vitro, and it also significantly inhibits oral neoplasm tumorigenesis in a mouse xenograft model, which implies that the combination of radiotherapy with inhibition of IFITM1 maybe a promising strategy for oral cancer therapy. At the molecular level, IFITM1 silence results in an increase in pSTAT1/2/p21 as well as a decline of pSTAT3/p-p21, through which IFITM1 affects the radiation tolerance of oral cancer cells after radiotherapy [12].

4 Conclusions

Tumors are one of the major causes of death across the world [46]. Most patients are in the middle/advanced stage at the time of diagnosis. Unfortunately, some tumors undergo intrinsic molecular changes after therapy and become resistant to conventional treatments (endocrine, chemo-, and radiotherapy), eventually resulting in a poor prognosis. Consequently, it is imperative to search for new molecular targets in order to circumvent this dilemma. Accumulating evidence has indicated that IFITM1 may have great potential. As seen from this article, IFITM1 is overexpressed in a wide range of neoplasms and plays a promoting role in cell proliferation, invasion, metastasis, angiogenesis, and therapy resistance. However, it is still unclear how IFITM1 is activated by the upstream pathway.

Table 3 The role of IFITM1 in tumor therapy resistance

Therapy resistance	Year	Tumor types	Main findings	References
Endocrine therapy resistance	2018	Breast cancer	PITX2 increases IFN- α -induced AKT activation through the transcription of IFITM1, which results in resistance to letrozole in breast cancer cells	[37]
	2017	Breast cancer	IFITM1 is overexpressed in AI-resistant MCF-7:5C cells and negative in AI-sensitive MCF-7 cells, and inhibiting IFITM1 in AI-resistant MCF-7:5C cells decreases tumor growth and invasion and induces cell death	[9]
	2015	Breast cancer	IFITM1 overexpression is confirmed in AI-resistant MCF-7:5C breast cancer cells and tumors, and knockdown of IFITM1 obviously increases estradiol-induced cell death, along with upregulation of p21, Bax, and Noxa in AI-resistant MCF-7:5C cells	[22]
Chemoresistance	2013	Gastric cancer	The mRNA level of IFITM1 is markedly increased in cisplatin-resistant YCC-3/R cells compared with YCC-3 cells	[42]
	2008	Esophageal cancer	The sensitivity to cisplatin in esophageal cancer cells is suppressed or enhanced by IFITM1 overexpression or knockdown, respectively	[41]
	2004	Ovarian carcinoma	The level of IFITM1 decreases 24 h after administering responsive xenografts with paclitaxel	[43]
Radioresistance	2019	Hepatocellular carcinoma	The study suggests that a combination of radiotherapy and AT- <i>MSC</i> therapy improves the efficacy through downregulating IFITM1 expression in hepatocellular carcinoma cell lines	[15]
	2018	Oral cancer	IFITM1 is upregulated with increases in dose and time of radiation, and knockdown of IFITM1 increases cell apoptosis in oral neoplasm cells after radiation	[12]
	2012	Nasopharyngeal carcinoma	The results show that IFITM1 is increased in radioresistant CNE-2R cells compared with CNE-2 cells	[44]

AI aromatase inhibitor, AKT protein kinase B, AT-*MSC* adipose tissue-derived mesenchymal stem cell, IFN- α interferon- α , mRNA messenger RNA, PITX2 paired-like homeodomain transcription factor 2

Furthermore, studies about IFITM1 in tumor therapy resistance are relatively few and the underlying molecular mechanisms by which IFITM1 is involved in angiogenesis and therapy resistance are not fully understood. Whether targeting IFITM1 may become an additional, feasible, and effective tool for personalized therapy of patients requires further research, including investigations to (1) shed light on more biochemical features of IFITM1; (2) decipher the upstream and downstream signaling pathways of the IFITM1 network; and (3) exploit inhibitors of IFITM1 and confirm their effectiveness in tumors. In all, this short review provides an overview of our current understanding of the tumor-promoting role of IFITM1 and points out the direction for future research in tumors.

Compliance with Ethical Standards

Funding This work was supported by the National Natural Science Foundation of China (81760544), the Key Research and Development Program Project of Guangxi Zhuang Autonomous Region (Grant no. GuikeAB18221007), and the Independent Project of Key Laboratory of Early Prevention and Treatment for Regional High-Incidence Tumor (Grant no. GKE2019-17).

Conflict of Interest The authors (RL, XL, and XZ) declare that they have no conflicts of interest.

References

- Friedman RL, Manly SP, McMahon M, Kerr IM, Stark GR. Transcriptional and posttranscriptional regulation of interferon-induced gene expression in human cells. *Cell*. 1984;38(3):745–55.
- Lu J, Pan Q, Rong L, He W, Liu SL, Liang C. The IFITM proteins inhibit HIV-1 infection. *J Virol*. 2011;85(5):2126–37.
- Siegrist F, Ebeling M, Certa U. The small interferon-induced transmembrane genes and proteins. *J Interferon Cytokine Res*. 2011;31(1):183–97.
- Takahashi S, Doss C, Levy S, Levy R. TAPA-1, the target of an antiproliferative antibody, is associated on the cell surface with the Leu-13 antigen. *J Immunol*. 1990;145(7):2207–13.
- Bradbury LE, Kansas GS, Levy S, Evans RL, Tedder TF. The CD19/CD21 signal transducing complex of human B lymphocytes includes the target of antiproliferative antibody-1 and Leu-13 molecules. *J Immunol*. 1992;149(9):2841–50.
- Matsumoto AK, Martin DR, Carter RH, Klickstein LB, Ahearn JM, Fearon DT. Functional dissection of the CD21/CD19/TAPA-1/Leu-13 complex of B lymphocytes. *J Exp Med*. 1993;178(4):1407–17.

7. Li D, Yang Z, Liu Z, Zou Q, Yuan Y. DDR2 and IFITM1 are prognostic markers in gallbladder squamous cell/adenosquamous carcinomas and adenocarcinomas. *Pathol Oncol Res.* 2019;25(1):157–67.
8. Andreu P, Colnot S, Godard C, Laurent-Puig P, Lamarque D, Kahn A, et al. Identification of the IFITM family as a new molecular marker in human colorectal tumors. *Cancer Res.* 2006;66(4):1949–55.
9. Lui AJ, Geanes ES, Ogony J, Behbod F, Marquess J, Valdez K, et al. IFITM1 suppression blocks proliferation and invasion of aromatase inhibitor-resistant breast cancer in vivo by JAK/STAT-mediated induction of p21. *Cancer Lett.* 2017;399:29–43.
10. Yu F, Xie D, Ng SS, Lum CT, Cai MY, Cheung WK, et al. IFITM1 promotes the metastasis of human colorectal cancer via CAV-1. *Cancer Lett.* 2015;368(1):135–43.
11. Hatano H, Kudo Y, Ogawa I, Tsunematsu T, Kikuchi A, Abiko Y, et al. IFN-induced transmembrane protein 1 promotes invasion at early stage of head and neck cancer progression. *Clin Cancer Res.* 2008;14(19):6097–105.
12. Yang J, Li L, Xi Y, Sun R, Wang H, Ren Y, et al. Combination of IFITM1 knockdown and radiotherapy inhibits the growth of oral cancer. *Cancer Sci.* 2018;109(10):3115–28.
13. Tsai MH, Cook JA, Chandramouli GV, DeGraff W, Yan H, Zhao S, et al. Gene expression profiling of breast, prostate, and glioma cells following single versus fractionated doses of radiation. *Cancer Res.* 2007;67(8):3845–52.
14. Li J, Chen N, Gong X. Prognostic implications of aberrantly expressed methylation-driven genes in hepatocellular carcinoma: a study based on the Cancer Genome Atlas. *Mol Med Rep.* 2019;20(6):5304–14.
15. Wu L, Tang Q, Yin X, Yan D, Tang M, Xin J, et al. The therapeutic potential of adipose tissue-derived mesenchymal stem cells to enhance radiotherapy effects on hepatocellular carcinoma. *Front Cell Dev Biol.* 2019;7:267.
16. Yu F, Ng SS, Chow BK, Sze J, Lu G, Poon WS, et al. Knockdown of interferon-induced transmembrane protein 1 (IFITM1) inhibits proliferation, migration, and invasion of glioma cells. *J Neurooncol.* 2011;103(2):187–95.
17. Ogony J, Choi HJ, Lui A, Cristofanilli M, Lewis-Wambi J. Interferon-induced transmembrane protein 1 (IFITM1) overexpression enhances the aggressive phenotype of SUM149 inflammatory breast cancer cells in a signal transducer and activator of transcription 2 (STAT2)-dependent manner. *Breast Cancer Res.* 2016;18(1):25.
18. Yan J, Jiang Y, Lu J, Wu J, Zhang M. Inhibiting of proliferation, migration, and invasion in lung cancer induced by silencing interferon-induced transmembrane protein 1 (IFITM1). *Biomed Res Int.* 2019;2019:9085435.
19. He JD, Luo HL, Li J, Feng WT, Chen LB. Influences of the interferon induced transmembrane protein 1 on the proliferation, invasion, and metastasis of the colorectal cancer SW480 cell lines. *Chin Med J (Engl).* 2012;125(3):517–22.
20. Wang Y, Wu D, Wu G, Wu J, Lu S, Lo J, et al. Metastasis-on-a-chip mimicking the progression of kidney cancer in the liver for predicting treatment efficacy. *Theranostics.* 2020;10(1):300–11.
21. Ramanathan A, Ramanathan A. Interferon induced transmembrane protein-1 gene expression as a biomarker for early detection of invasive potential of oral squamous cell carcinomas. *Asian Pac J Cancer Prev.* 2016;17(4):2297–9.
22. Choi HJ, Lui A, Ogony J, Jan R, Sims PJ, Lewis-Wambi J. Targeting interferon response genes sensitizes aromatase inhibitor resistant breast cancer cells to estrogen-induced cell death. *Breast Cancer Res.* 2015;17:6.
23. Kim NH, Sung HY, Choi EN, Lyu D, Choi HJ, Ju W, et al. Aberrant DNA methylation in the IFITM1 promoter enhances the metastatic phenotype in an intraperitoneal xenograft model of human ovarian cancer. *Oncol Rep.* 2014;31(5):2139–46.
24. Yang Y, Lee JH, Kim KY, Song HK, Kim JK, Yoon SR, et al. The interferon-inducible 9–27 gene modulates the susceptibility to natural killer cells and the invasiveness of gastric cancer cells. *Cancer Lett.* 2005;221(2):191–200.
25. Lee J, Goh SH, Song N, Hwang JA, Nam S, Choi IJ, et al. Overexpression of IFITM1 has clinicopathologic effects on gastric cancer and is regulated by an epigenetic mechanism. *Am J Pathol.* 2012;181(1):43–52.
26. Gonzalez-Avila G, Sommer B, Mendoza-Posada DA, Ramos C, Garcia-Hernandez AA, Falfan-Valencia R. Matrix metalloproteinases participation in the metastatic process and their diagnostic and therapeutic applications in cancer. *Crit Rev Oncol Hematol.* 2019;137:57–83.
27. Yang YG, Koh YW, Sari IN, Jun N, Lee S, Phi L, et al. Interferon-induced transmembrane protein 1-mediated EGFR/SOX2 signaling axis is essential for progression of non-small cell lung cancer. *Int J Cancer.* 2019;144(8):2020–32.
28. Koh YW, Han JH, Jeong D, Kim CJ. Prognostic significance of IFITM1 expression and correlation with microvessel density and epithelial–mesenchymal transition signature in lung adenocarcinoma. *Pathol Res Pract.* 2019;215(7):152444.
29. Baeriswyl V, Christofori G. The angiogenic switch in carcinogenesis. *Semin Cancer Biol.* 2009;19(5):329–37.
30. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. *Nat Rev Cancer.* 2008;8(8):592–603.
31. Joo YY, Jang JW, Lee SW, Yoo SH, Kwon JH, Nam SW, et al. Circulating pro- and anti-angiogenic factors in multi-stage liver disease and hepatocellular carcinoma progression. *Sci Rep.* 2019;9(1):9137.
32. Popson SA, Ziegler ME, Chen X, Holderfield MT, Shaaban CI, Fong AH, et al. Interferon-induced transmembrane protein 1 regulates endothelial lumen formation during angiogenesis. *Arterioscler Thromb Vasc Biol.* 2014;34(5):1011–9.
33. Kim BS, Yang SS, Kim CS, Lee J. Zoledronate suppresses VEGF-induced capillary tube formation and inhibits expression of interferon-induced transmembrane protein1 in human umbilical vein endothelial cells. *Int J Mol Med.* 2018;41(5):2879–84.
34. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin.* 2016;66(4):271–89.
35. Miller WR, Larionov AA. Understanding the mechanisms of aromatase inhibitor resistance. *Breast Cancer Res.* 2012;14(1):201.
36. Escher TE, Lui AJ, Geanes ES, Walter KR, Tawfik O, Hagan CR, et al. Interaction between MUC1 and STAT1 drives IFITM1 overexpression in aromatase inhibitor-resistant breast cancer cells and mediates estrogen-induced apoptosis. *Mol Cancer Res.* 2019;17(5):1180–94.
37. Xu YY, Yu HR, Sun JY, Zhao Z, Li S, Zhang XF, et al. Upregulation of PITX2 promotes letrozole resistance via transcriptional activation of IFITM1 signaling in breast cancer cells. *Cancer Res Treat.* 2019;51(2):576–92.
38. Borg D, Hedner C, Gaber A, Nodin B, Fristedt R, Jirstrom K, et al. Expression of IFITM1 as a prognostic biomarker in resected gastric and esophageal adenocarcinoma. *Biomark Res.* 2016;4:10.
39. He J, Li J, Feng W, Chen L, Yang K. Prognostic significance of INF-induced transmembrane protein 1 in colorectal cancer. *Int J Clin Exp Pathol.* 2015;8(12):16007–13.
40. Balbous A, Cortes U, Guilloteau K, Villalba C, Flamant S, Gaillard A, et al. A mesenchymal glioma stem cell profile is related to clinical outcome. *Oncogenesis.* 2014;3:e91.
41. Fumoto S, Shimokuni T, Tanimoto K, Hiyama K, Otani K, Ohtaki M, et al. Selection of a novel drug-response predictor in esophageal cancer: a novel screening method using microarray

- and identification of IFITM1 as a potent marker gene of CDDP response. *Int J Oncol.* 2008;32(2):413–23.
42. Lee HR, No HK, Ryu CJ, Park HJ. Brahmarelated gene 1-associated expression of 9–27 and IFI-27 is involved in acquired cisplatin resistance of gastric cancer cells. *Mol Med Rep.* 2013;8(3):747–50.
 43. Bani MR, Nicoletti MI, Alkharouf NW, Ghilardi C, Petersen D, Erba E, et al. Gene expression correlating with response to paclitaxel in ovarian carcinoma xenografts. *Mol Cancer Ther.* 2004;3(2):111–21.
 44. Guo Y, Zhu XD, Qu S, Li L, Su F, Li Y, et al. Identification of genes involved in radioresistance of nasopharyngeal carcinoma by integrating gene ontology and protein–protein interaction networks. *Int J Oncol.* 2012;40(1):85–92.
 45. Kita K, Sugaya S, Zhai L, Wu YP, Wano C, Chigira S, et al. Involvement of LEU13 in interferon-induced refractoriness of human RSa cells to cell killing by X-rays. *Radiat Res.* 2003;160(3):302–8.
 46. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7–30.
 47. Alam U, Kennedy D. G3BP1 and G3BP2 regulate translation of interferon-stimulated genes: IFITM1, IFITM2 and IFITM3 in the cancer cell line MCF7. *Mol Cell Biochem.* 2019;459(1–2):189–204.