Original Article

DOI: 10.5582/irdr.2021.01041

Integrative overview of IFITMs family based on Bioinformatics analysis

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SUMMARY Human interferon-induced transmembrane proteins (IFITMs) family is a multi-functional biomacromolecule family playing a critical role in various physiological processes, such as, antiviral immunity, tumor suppression, and bone formation. Although there are many studies proving that a subset of tumors strongly links to the changes of IFITMs, the link between different IFITMs mutant types and diverse tumors has not been studied thoroughly. To investigate the law of expression among IFITMs internal members and the linking of IFITMs mutant types and cancers, online databases were used to pool together relevant data for bioinformatics analysis. Here, we summarize mutations, expression, and functions of human *IFITMs*, analyze diverse expression levels of *IFITMs* in physiological and pathological tissues, predict protein-protein interaction (PPI) networks, and target miRNAs and relevant signaling pathways of *IFITMs*. The results show that *IFITM1*, *IFITM2*, and *IFITM3* have similar motif pattern constructions and physiological functions, while *IFITM5* and *IFITM10* show far diversity from them. Particularly, *IFITM1-3*, in conjunction with interacting proteins, is strongly related to development and overall survival rates of a portion of cancers, including renal cancer and uveal melanoma (UVM). This trait may make *IFITM1-3* become a prognostic marker of cancers. Meanwhile, hsa_circ_0116375 has been found as the common circRNA for *IFITM2*, *IFITM3*, *IFITM5*, and *IFITM10*.

Keywords *IFITM*, *IFITM* mutations, *IFITM* expression, Tumor, In silico prediction

1. Introduction

Human interferon-induced transmembrane proteins (IFITMs), first reported in 1984, are proteins that can be induced by interferon (IFN) (*1*). There are five members of human IFITMs namely IFITM1, IFITM2, IFITM3, IFITM5 and IFITM10, respectively (*2*). IFITMs, clustering in a 26.5 kb region on human chromosome 11, play a critical role in physiological functions (*3*). IFITMs process the CD225 domain, which is also shared by more than 300 members of the CD225 and pfam04505 family (*4*). Significantly, the CD225 domain of IFITMs is highly conserved among family members, while the family's respective N-terminal domains (NTDs) display heterogeneity in both sequence and length, which is being considered as the functional structure of antiviral specificities (*5*).

There are studies showing that *IFITM* expression or genetic variation may result in diseases. Specifically, the extent of variation in *IFITMs* are considered strongly associated with illness severity, and there is proof that specific mutations can reverse the function of IFITMs, from inhibiting to promoting the infection of coronaviruses (*6,7*). Functionally, IFITMs mainly play a role in immune signal transduction, cell adhesion, tumorigenesis, and antiviral activity (*8*). Specifically, IFITM1, IFITM2 and IFITM3 have important roles in antiviral invasion and act as tumor markers, while mutations of *IFITM5* cause type V osteogenesis imperfecta. Additionally, *IFITM10* with Cathepsin D (*CTSD*) has been regarded as a molecular marker for breast cancer (*9-11*). Studies indicated that the homotypic interactions between IFITM proteins, are essential for their antiviral activity and signaling pathways associated with IFITMs (*5,12*). Our study summarizes the expression, mutation, interacting molecular function and signaling pathways related to human *IFITMs* based on comprehensive bioinformatics analysis. The study

provides a basis for further understanding of IFITMs and explores its potential functions and applications.

2. Materials and Methods

2.1. Phylogenetic analysis of IFITMs

The protein sequences of the IFITMs with Fasta format were downloaded from the NCBI database (*https://www.ncbi.nlm.nih.gov/*). Multiple sequences alignments were performed with CLUSTAL 2.0 software. A phylogenetic tree was constructed using molecular evolutionary genetic analysis (MEGA) software. Motif detection of IFITMs protein sequences was performed in MEME tools (*https://meme-suite.org/meme/index.html*), and visualized by TBtools software (*13*).

2.2. Analysis of human diseases related to IFITMs

IFITMs-related human diseases were pooled with the published data of the GCBI website (*https://www.gcbi.com.cn*). The mutation profiles and copy number changes of the *IFITMs* in different cancers were summarized by cBioPortal (*http://www.cbioportal.org*) (*14,15*). The mutation types and nucleotide changes of *IFITMs* were analyzed by the Catalogue of Somatic Mutations in Cancer (COSMIC) tools (https://cancer.sanger.ac.uk/cosmic).

2.3. IFITMs expression in tumors and survival analysis of IFITMs-related cancers

Standardized analysis of *IFITMs* expression data in different normal tissues, obtained from Human Protein Atlas database (*https://www.proteinatlas.org*), was based on transcriptome provided by GTEx database. We analyzed the co-expression of both human *IFITMs* genes with the GEPIA2 (*http://gepia2.cancer-pku.cn/#index*) website, and a heatmap was mapped by TBStools through the co-expression results. The GCBI database was used to distinguish the difference of *IFITMs* expression between normal tissues and tumor tissues. The cancers related to *IFITMs* were screened from the PrognoScan database (*http://dna00.bio.kyutech.ac.jp/PrognoScan/*), and the survival curves of the corresponding cancers were drawn by TCGA and GTEx databases on the GEPIA2 website (*http://gepia2.cancer-pku.cn/#index*).

2.4. Prediction of coexisting proteins, PPI networks, targeted miRNA and signaling pathway of IFITMs

The IFITMs-related protein-protein interactions networks were predicted with GeneMANIA database (*http://genemania.org*) and STRING (*https://string-db.org/cgi/input.pl*) online tools (*16,17*). The targeted miRNAs of IFITMs were predicted based on the data extracted from MiRWalk database (*http://mirwalk.umm.uni-heidelberg.de/search_genes*), and then the concurrent targeted miRNAs of different *IFITM* members were found from the predicted miRNAs. The corresponding circRNAs of the concurrent targeted miRNAs were predicted with circBank database (http://www.circbank.cn), and then the concurrent target circRNAs were selected from the predictions. The relationship among *IFITMs*, targeted miRNA and targeted circRNA were mapped by Cytoscape software. KEGG database (http://www.kegg.jp) was used to predict the pathways relevant to *IFITMs* (*18,19*).

3. Results

3.1. Phylogenetic analysis of IFITMs protein

Human *IFITMs* family, located on human chromosome 11, can be divided into five subtypes: *IFITM1*, *IFITM2*, *IFITM3*, *IFITM5*, and *IFITM10*. Phylogenetic analysis was performed with the amino acid sequences of IFITMs proteins based on the results of multiple sequence alignments. IFITM2 and IFITM3 are very close in the phylogenetic tree (Figure 1A) and share the same motif structure of motif1, motif2, and motif3. Compared to IFITM2 and IFITM3, motif 2 is absent in IFITM1 (Figure 1B). The results are consistent with the findings of existing studies that IFITM1, IFITM2, and IFITM3 have similar physiological functions.

3.2 Human diseases related to IFITMs mutations

As listed in GCBI database, all *IFITMs* family members are all related to human immunodeficiency virus (HIV) infections (Figure 2A). IFITM1, IFITM2, and IFITM3 are, particularly, related to influenza, neoplasms, amino acid metabolism, infection, and hepatitis C. Interestingly, there are studies that show *IFITM1* is one of the hub-genes of schizophrenia (*20*), and *IFITM3* is responsible for leukemia and acute liver injury (*21,22*), *IFITM1* and *IFITM3* are related to tumors, and *IFITM5* is the pathogenic gene for type V osteogenesis imperfecta (*2,23-25*).

Five mutation types of *IFITMs*, including mutations, fusions, amplifications, deep deletions, and multiple

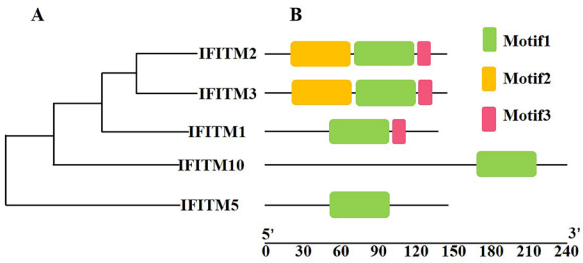

Figure 1. Phylogenetic analysis of IFITMs and motif prediction. **(A)** Phylogenetic Tree, **(B)** Motif prediction.

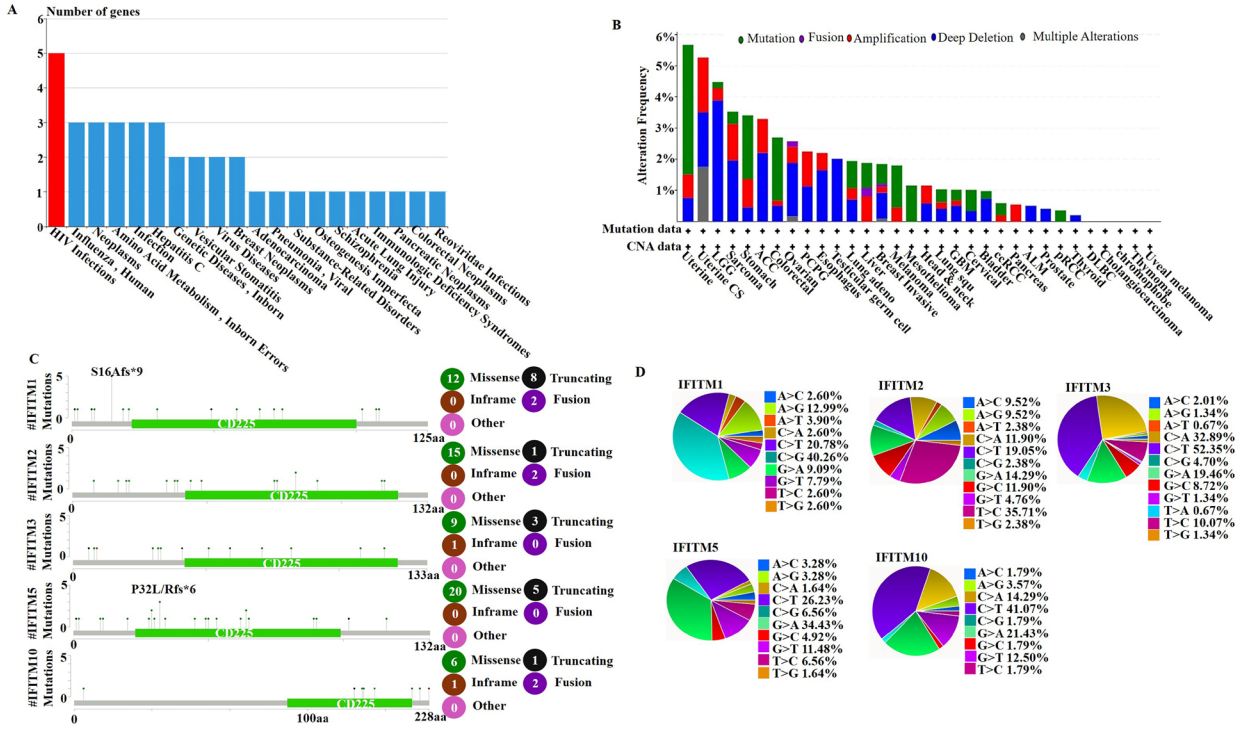

Figure 2. Human diseases related to *IFITMs* mutations. (A) Diseases related to *IFITMs*, **(B)** Mutation frequency of *IFITMs* in different tumors, **(C)** Mutation types of *IFITMs* in cBioPortal database, **(D)** The distribution of different mutation types recorded in COSMIC database.

alterations, were analyzed with 10,967 samples which we obtained from 10,953 patients in 32 types of cancer using cBioPortal tools (Figure 2B). Uterine corpus endometrial carcinoma and uterine carcinosarcoma have the highest mutation frequency, accounting for more than 5%. Most of the mutation types are missense mutations among all *IFITMs* mutations, and the C>T substitution mutations are the most common according to all the base mutation types (Figure 2C and 2D).

Different mutation types of *IFITMs* have been found in the amino acid sequences of these samples (Table S1 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=76*), Figure 2C). The S16Afs*9 change of IFITM1 is included in numerous tumors, including astrocytoma, colon adenocarcinoma, diffuse type stomach adenocarcinoma, intestinal type stomach adenocarcinoma and tubular stomach adenocarcinoma. Moreover, the other mutation types of *IFITM1* exist in tumors such as colon adenocarcinoma, stomach adenocarcinoma, uterine endometrioid carcinoma, *etc*. As for *IFITM5*, P32L change was related to tumors of rectal adenocarcinoma and breast invasive lobular carcinoma. *PTDSS2*, and *IGF2BP2* were identified fused with *IFITM1* and *IFITM2* to cause hepatocellular carcinoma, and uterine carcinoma, respectively. *DENND5A* and *CFLL1* were fused with *IFITM10* (Table S1 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=76*), Figure 2C). According to the mutation samples, we can see that *IFITMs* may cause different tumors, and the missense mutation was the most common mutation type among all tumor-related *IFITMs* mutations.

3.3. IFITMs expression in tumors and survival analysis of IFITMs-related cancers

The expressions of *IFITMs* in different tissues were obtained from the Human Protein Atlas database. There are 34 normal tissues that express *IFITM1*, *IFITM2*, *IFITM3*, and *IFITM10*, while only 13 normal tissues express *IFITM5*, according to the transcriptome data on the GTEx database (Figure 3A). Based on this database, the expression of *IFITM1*, *IFITM2*, *IFITM3*, compared with *IFITM5* and *IFITM10*, is higher in the uterus, ovary, fallopian tube, and adipose tissue. However, the tissues with highest level of *IFITM5* expression are the pancreas, lung, and thyroid gland. The highest level of *IFITM10* expression is in the adrenal gland and urinary bladder. The expression levels of *IFITM5* and *IFITM10* were significantly lower than those of other *IFITM* family members in normal tissues. Then, we analyzed the co-expression profiles of *IFITMs* family members in partial normal physiological tissues (Figure 3B). It can be found that the relevance among *IFITM1*, *IFITM2*, and *IFITM3* were closer than other *IFITMs* members in expression.

The differential levels of *IFITM1*, *IFITM2*, *IFITM3* and *IFITM5* expression in normal and tumor tissues have been searched in the GCBI database (Figure 3C). In totality, the expression levels of *IFITMs* in most tumor tissues were higher than that in normal tissues. The expression of *IFITM1*, *IFITM2* and *IFITM3* were

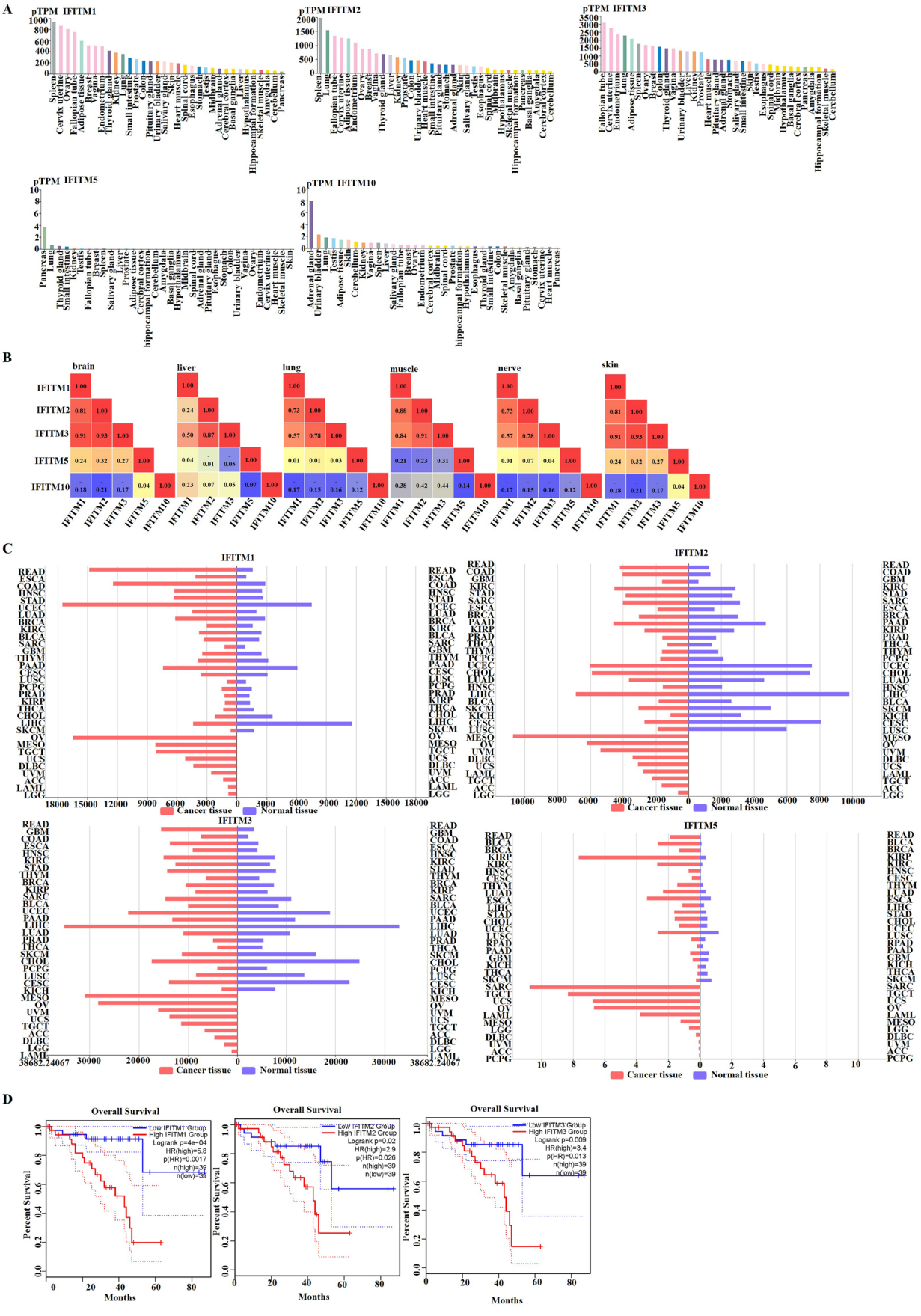

Figure 3. *IFITMs* expression and survival analysis of UVM cancer. (A) Expression of *IFITMs* in different normal tissues, **(B)** Co-expression HeatMap of *IFITMs* in normal tissues, **(C)** Expression of *IFITMs* in tumor tissues, **(D)** Overall survival curve for the *IFITM1-3* signature in UVM.

Table 1. Tumors related to *IFITMs* in PrognoScan database

Tumors	IFITM1	IFITM2	IFITM3	IFITM5	IFITM10
acute myeloid leukemia (LALM)	√	×	√	×	√
breast invasive carcinoma (BRCA)	√	√	√	×	√
bladder urothelial carci-noma (BLCA)	√	√	√	×	×
Colon adenocarcinoma (COAD)	√	×	×	×	√
glioma (GBMLGG)	√	√	√	×	√
lung adenocarcinoma (LUAD)	√	√	√	√	√
lung squamous cell carci-noma (LUSC)	√	×	×	×	×
ovarian serous cystadeno-carcinoma (OV)	√	×	×	×	×
uveal melanoma (UVM)	√	√	√	×	√

tissues, including adrenocortical carcinoma (ACC), lymphoid neoplasm diffuse large b-cell lymphoma (DLBC), mesothelioma (MESO), acute myeloid leukemia (LAML), brain lower grade glioma (LGG), ovarian serous cystadenocarcinoma (OV), testicular germ cell tumors (TGCT), uterine carcinosarcoma (UCS) and uveal melanoma (UVM), were not studied, so that there are no data showing the corresponding information.

Different types of tumors associated with *IFITMs* are summarized through the PrognoScan database. By setting the selection condition COX P-VALUE < 0.05, the cancers related to *IFITMs* are listed (Table 1). Accordingly IFITMs show significant expression differences in different tumors, and cancer survival curves were drawn with GEPIA2 tools based on TCGA and GTEx databases. The log rank $P < 0.05$ is the screening condition to show significantly different curves of the overall survival analysis (Figure 3D). The log rank values of *IFITM1*, *IFITM2*, *IFITM3* were < 0.05 in UVM, and the survival percentage of *IFITM1*, *IFITM2*, *IFITM3* low-expression group was significantly higher than that of the high-expression group. The log rank $p > 0.05$ of *IFITM5* and *IFITM10* showed no significant difference in overall survival (OS). Based on the above data, the high expression of *IFITM1*, *IFITM2*, *IFITM3* is an unfavorable factor in UVM.

The expressions of *IFITM1*, *IFITM2*, and *IFITM3* are very significant in renal cancer and can be used as a prognostic marker (unfavorable), while *IFITM5* and *IFITM10* products are not prognostic according to Human Protein Atlas database.

3.4. Prediction of PPI networks, targeted miRNA and signaling pathway of IFITMs

Twenty proteins related to the function of IFITMs were predicted with the GeneMANIA database (Figure 4A and 4B). GeneMANIA and String databases predict that IFITM1, 2, 3 are related to CD81, IFIT1, IFIT3, IFI35, IFI6, and IFITM5, and IFITM10 are not significantly related to IFITM1, IFITM2, IFITM3 (Figure 4A-4C). IFITM1-3 interacts with CD81 to inhibit the entry of hepatitis C; IFITMs interact with MX1, ISG15, ISG20, IRF9, IFIT1, IFIT2, IFIT3, IFI, BST2, GBP2 and RSAD2 to play an antiviral immunity role (*26-29*). There is evidence confirmed that IFITM1 combines with CD81 and makes a complex with CD19 and CD21 (*30*). Moreover, there are reports that showed the constitutive up-regulation of CD81 associated with tumor progression in mouse skin tumor models (*31,32*).

The target miRNAs and circRNAs of *IFITMs*, gathered from MiRWalk and circBank, are listed in Table S2 and Table S3 (*http://www.irdrjournal.com/action/getSupplementalData.php?ID=76*). The interactions among IFITMs, the concurrent target miRNA and the concurrent target circRNA has been drawn in the Cytoscape software (Figure 4D). Interestingly, there are 13 miRNAs jointly targeted by *IFITM5* and *IFITM10*, with *IFITM1* sharing no common miRNAs among the family members. Among all the 22 coexisting targeted miRNAs, there are 7 miRNAs, including miR-29b-2-5p, miR-4418, miR-4463, miR-4519, miR-5093, miR-6860, and miR-6895-5p, related to *IFITM2*, *IFITM3*, *IFITM5*, and *IFITM10*, targeting to the hsa_circ_0116375.

According to the prediction results based on KEGG database, the disease related to the IFITM family is osteogenesis imperfecta, and the signaling pathway related to IFITM1 is B cell receptor signaling pathway.

4. Discussion

IFITMs family is associated with various human diseases including anti-virus, immunity, osteogenesis imperfecta, and tumors. The induced type interferons activate many interferon-stimulating genes (ISG) that have direct antiviral effects and block viruses from entering the human body (*33*). The immune defense against a variety of viruses is mainly participated by IFITM1, 2, and 3 (*34*). However, the IFITMs family has also been involved in other processes, such as tumorigenesis, and bone mineralization (IFITM5) (*35*). Also, *IFITMs* mutations may cause different effects on diseases, for example, a single recurrent mutation in the 5'-UTR of *BRIL* (bone-restricted *IFITM*-like, or *IFITM5*) causes osteogenesis imperfecta type V in humans (*36*). Interestingly, most of the mutations in *IFITMs* family are mistranslation mutations, and the location of the mutations is not limited to NTDs.

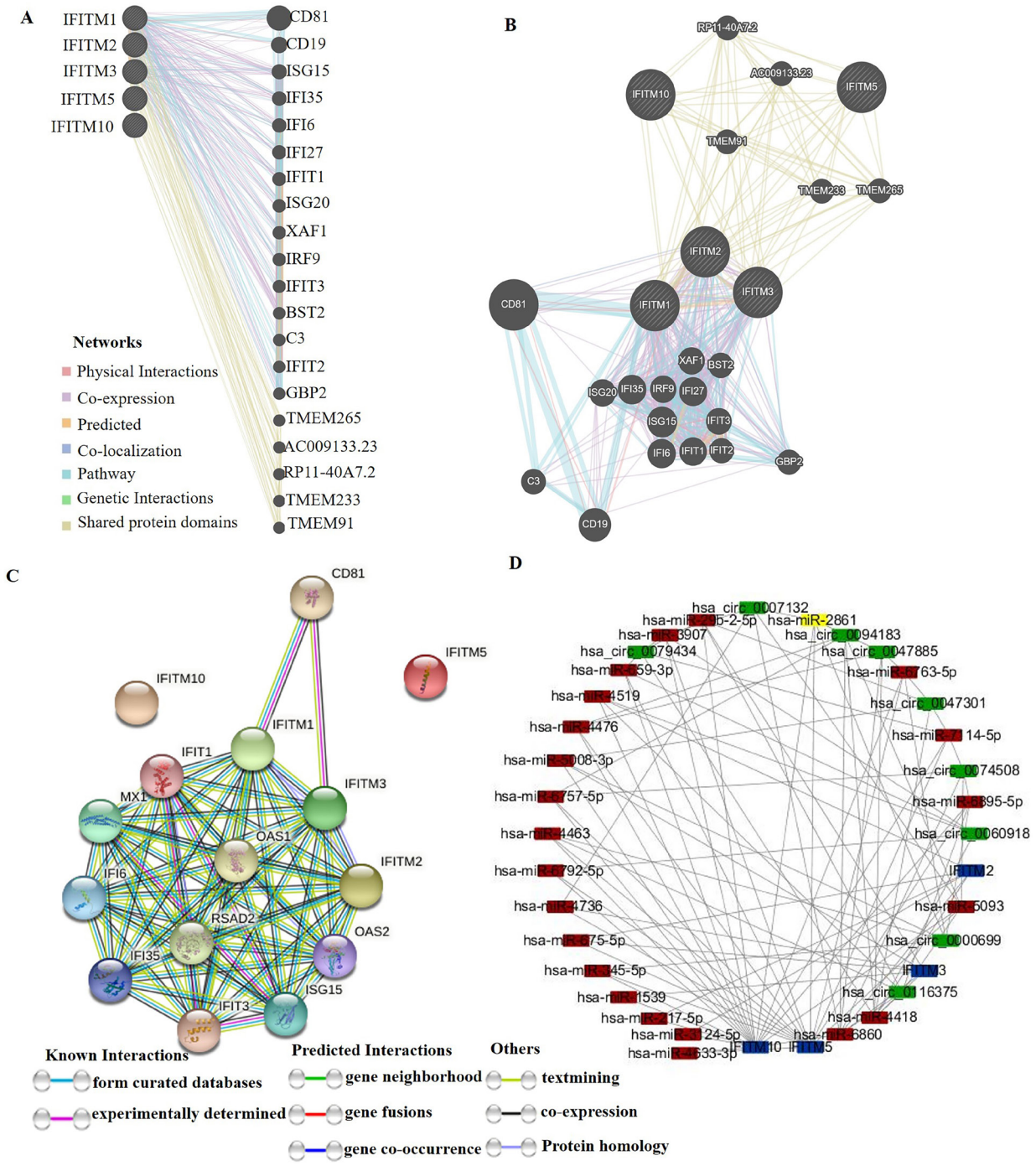

Figure 4. Predicted IFITMs- interacting proteins and targeting non-coding RNAs. (A-C) IFITMs -related proteins predicted by GeneMania and String, respectively, **(D)** MiRNAs and circRNAs targeting IFITMs predicted by MiRWalk and circBank, respectively.

The corresponding mutations in CD225 structure have been found in our study. Tissues of colorectal cancer in humans were confirmed with over-expressed *IFITM3*, while *IFITM3* knock-offs caused significant suppression of the proliferation, colony formation, and migration (*37,38*). Also, *IFITM1* knock-offs significantly suppressed the invasiveness of head and neck tumor cells (*31*). There is evidence, which showed that deletion of adenomatous polyposis coli (APC) alleles, which leads to the formation of colon adenomas, results in *IFITM3* expression dropping sharply in conditional APC mutant mice (*39*). Based on the mutation samples, different *IFITMs* are related to different tumors, and diverse mutants may appear in one type of tumor. Among all the mutation types of IFITMs in tumors, missense mutations were the most frequent mutation type, and the C > T substitution mutation was the most common mutation according to all the tumor-related *IFITMs* mutations.

IFITM1, IFITM2, IFITM3 have higher similarity

in motif structure, while IFITM5 and IFITM10 have lower similarity compared to them. Based on the online database, the similarity of *IFITM1*, *IFITM2* and *IFITM3* expression in normal tissues and tumor tissues has been found through our study. In normal tissues, the expression levels of *IFITM1-3* were significantly higher than those of *IFITM5*, *IFITM10*, and *IFITM1-3* was highly expressed in female reproductive organs, but lower in brain tissues. These findings support *IFITM1*, *IFITM2* and *IFITM3* are similar not only in structure but also in function.

More and more studies have shown that *IFITMs* can be used as markers for tumor prognosis. *IFITMs* are reported to be frequently overexpressed in colorectal tumors (*38*), and the IFITMs family can be used as marker molecules for human colorectal cancer (*39*), and *IFITM1* can be used as a rare type of squamous cell/adenosquamous carcinoma (SC/ASC) and common adenocarcinoma (AC) marker molecule (*40*).

The comprehensive bioinformatics analysis of our study indicated that *IFITM1*, *IFITM2*, and *IFITM3* can be used as prognostic markers of kidney cancer (unfavorable), while the products of *IFITM5* and *IFITM10* cannot be used as markers of tumor prognosis. It is consistent with this result that the expression levels of *IFITMs* in tumor tissues, including rectum adenocarcinoma (READ), COAD, kidney renal clear cell carcinoma (KIRC) and esophageal carcinoma (ESCA), were higher than that in normal tissues. In addition, for several kinds of tumors without normal tissue as control, we found that high expression of *IFITM1-3* is closely related to the decline in overall survival, which indicates that the expression level of *IFITM1-3* can be used as a diagnostic indicator for UVM.

Our study summarized the mutation, expression, and function of the human IFITMs family based on comprehensive bioinformatics analysis. The expression of IFITM and proteins interacting with it was involved in various cancers and is significantly related to survival in some cancers. The altered expression of *IFITMs* and proteins interacting with it may be a prognostic marker in some cancers.

Funding: This work was supported by a grant from the State Major Infectious Disease Research Program (China Central Government, 2017ZX10103004-007), Academic Promotion Programme of Shandong First Medical University (LJ001).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received February 22, 2021; Revised March 26, 2021; Accepted May 13, 2021.

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Released online in J-STAGE as advance publication May 27, 2021.