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, tumorogenesis, 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://geopia2.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://geopia2.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 (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.
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 and IFITM10, 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 IFITM members in expression.

The differential levels of IFITM1, IFITM2, IFITM3 and IFITM5 expression in normal and tumor tissues have been searched in the GCB 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
higher than that of $IFITM5$ in tumor and normal tissues.

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.
tissues, including adrenocortical carcinoma (ACC), lymphoid neoplasm diffuse large b-cell lymphoma (DLBC), mesothelioma (Meso), acute myeloid leukemia (AML), 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.
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 IFITM3 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.

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