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ARTICLE

High *IFITM3* expression predicts adverse prognosis in acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is a malignancy caused by the uncontrolled and dysregulated clonal expansion of abnormal myeloid primordial cells. In general, the prognosis of AML remains poor despite new discoveries in its pathogenesis and treatment. It is crucial to find early and sensitive biomarkers and continue to explore active targeted treatments. Interferon-induced transmembrane protein (*IFITM*) family is an important part of the interferon signaling pathway and participate in the regulation of immune cell signaling, adhesion, cancer, and liver cell migration. However, the clinical and prognostic value of the *IFITM* family in AML has rarely been studied. We screened The Cancer Genome Atlas database and found 155 AML patients with *IFITM* family (*IFITM1–5*) expression data. In patients who only received chemotherapy, those with high *IFITM3* expression had significantly shorter event-free survival (EFS) and overall survival (OS) than patients with low expression (all $P < 0.05$). Multivariate analysis demonstrated that high *IFITM3* expression was an independent risk factor for EFS and OS in patients only received chemotherapy (all $P < 0.05$). In patients who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT), however, all *IFITM* members had no impact on either EFS or OS. In conclusion, our study elucidated that high *IFITM3* expression could be an adverse prognostic factor for AML, whose effect might be overcome by allo-HSCT.

Introduction

Acute myeloid leukemia (AML) is a complex and dynamic disease. The malignant myeloid cells are composed of coexisting competing clones and the disease evolves over time [1]. People have discovered and used

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some molecular biomarkers, including genetic mutations, to help decipher this heterogenic and often deadly disease, to predict clinical outcome and guide treatment [2]. For example, *DNMT3A* and *FLT3-ITD* mutations are independent poor prognostic factors [3, 4], whereas the biallelic *CEBPA* mutation is associated with good prognosis [5, 6]. With the improvement molecular diagnostic technology, not only the mutations but also the aberrant expression levels of some genes could be integrated into the refined risk stratification of AML. The overexpressions of *MN1*, *ERG*, *BAALC*, *EVI1*, *DOK4/5, PDK2/3, FHL2*, and *iASPP* have been associated with poor prognosis, whereas high *DOK7* expression is associated with good prognosis in AML [7–10].

The genes encoding the interferon (IFN)-induced transmembrane proteins (*IFITMs*) belong to the IFN-stimulated genes. These proteins are powerful suppressor of viral infections. Human *IFITM* genes are located on chromosome 11 and translates into four highly homologous membrane surface proteins IFITM1, IFITM2, IFITM3, and IFITM5, whereas *IFITM4P* is a fake gene [11]. At present, the functions and related mechanisms of *IFITM1* and *IFITM3* as tumor-promoting genes, if not oncogenes per se, have been reported in various solid tumors. For example, high expression of *IFITM1* promotes the proliferation, invasion, and distant metastasis of squamous cell carcinoma of the head and neck [12], and also predicts adverse outcome of esophageal cancer [13]. In breast cancer tissue, the expression of *IFITM3* is significantly higher than adjacent tissues and is closely related to the estrogen and progesterone receptors. Knocking down *IFITM3* suppresses breast cancer cell growth and colony formation, and affects the cell cycle [14]. *IFITM3* is also abnormally overexpressed in colon cancer, especially in patients with positive lymph node metastasis. It is an independent risk factor for disease-free survival (DFS) in colon cancer [15]. *IFITM5* is only expressed in osteoblasts [16]. Overexpression of *IFITM5* promotes osteosarcoma cell apoptosis, inhibits invasion, and promotes osteogenic differentiation [17]. Study on *IFITM2* is lacking but there has been one study showing that it is significantly upregulated in intestinal cancer and has a p53-independent role in promoting apoptosis [18].

The prognostic significance of the *IFITM* family in AML has not been reported. In this study, we aimed to investigate the effects of *IFITM* on AML survival. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment for AML, which can reduce recurrence and prolong the survival by significantly reducing the leukemia residual disease [19]. Herein, we also analyzed whether allo-HSCT could overcome the prognostic effects of the *IFITM* family.

Materials and methods

Patients

From The Cancer Genome Atlas database (https://cancergenome.nih.gov/), a total of 155 AML patients with *IFITM* family (*IFITM1–5*) expression data were included in this study [20]. Eighty-four patients received chemotherapy only and 71 also underwent allo-HSCT. Clinical characteristics at diagnosis, including peripheral white blood cell (WBC) counts, blast percentages in peripheral blood (PB) and bone marrow (BM), French–American–British (FAB) subtypes, cytogenetic risk group, and frequencies of common recurrent genetic mutations, were downloaded from the database. Event-free survival (EFS) and overall survival (OS) were the primary endpoints of the study. EFS was defined as the time from diagnosis to removal from the study due to relapse, death, or failure to achieve complete remission, or was censored at the last follow-up. OS was defined as the time from diagnosis to death from any cause or was censored at the last follow-up. Informed consents were obtained from all patients and the study protocol was approved by the Human Research Council of the University of Washington.

Statistical analysis

The clinical and molecular characteristics of patients were summarized using descriptive statistics. Data sets were described with median and/or range. Survival was estimated using the Kaplan–Meier method and the log-rank test. Numerical data were compared using the Mann–Whitney *U*-test and categorical data were compared using the χ^2-test. Multivariate Cox proportional hazard models were constructed for EFS and OS using a limited backward elimination procedure. The confidence interval was 95%. All statistical analyses were performed by SPSS software 20.0 and GraphPad Prism software 7.0.

Results

Clinical and molecular characteristics of the patients

The clinical and molecular characteristics of all patients were shown in Table 2. Median age was 63 years (range 22–88), with 58 cases over 60 years old. Forty-five patients were men. The median WBC, BM blast, and PB blast count were 38.3×10^9/L, 67.5, and 36.3%, respectively. The major FAB subtypes were M1, M2, and M4 (72.6%). Forty-four patients had abnormal karyotypes. The proportion of good, intermediate, and poor-risk AML were 14.3%, 54.8%, and 28.6%, respectively. *NPM1* had the highest mutation frequency ($n = 27$, 32.1%), followed by *DNMT3A*

Table 1 Comparison of EFS and OS between different expression levels of *IFITM1–5*

Variables	EFS		OS	
	χ^2	*P*-value	χ^2	*P*-value
Chemotherapy-only group				
IFITM1 (high vs. low)	0.234	0.629	0.473	0.492
IFITM2 (high vs. low)	0.685	0.408	1.154	0.283
IFITM3 (high vs. low)	5.593	0.018	6.694	0.010
IFITM5 (high vs. low)	1.534	0.215	2.513	0.113
Allo-HSCT group				
IFITM1 (high vs. low)	0.244	0.622	0.857	0.355
IFITM2 (high vs. low)	2.248	0.134	1.306	0.253
IFITM3 (high vs. low)	1.613	0.204	1.825	0.177
IFITM5 (high vs. low)	1.156	0.282	0.533	0.465

Allo-HSCT allogeneic hematopoietic stem cell transplantation, *EFS* event-free survival, *OS* overall survival

($n = 23$, 27.4%), *FLT3* ($n = 22$, 26.2%), *IDH1/2* ($n = 15$, 17.9%), *NRAS/KRAS* ($n = 12$, 14.3%), *TP53* ($n = 12$, 14.3%), *TET2* ($n = 11$, 13.1%), and *RUNX1* ($n = 8$, 9.5%).

Prognostic significance of *IFITM* family in AML

To evaluate the prognostic significance of the *IFITM* family in AML, all patients were divided into high- and low-expression subgroups by the median expression levels of each *IFITM* member (*IFITM1/2/3/5*). EFS and OS of the expression subgroups of each gene were analyzed with the Kaplan–Meier method and the log-rank test (Table 1). In the chemotherapy-only group, high *IFITM3* expression had adverse effects on EFS and OS ($P = 0.018$ and $P = 0.010$, Fig. 1a, b). None of the *IFITM* members had impact on survival in the allo-HSCT group.

Association of *IFITM3* expression with other clinical and molecular characteristics in the chemotherapy-only group

The clinical and molecular characteristics of high and low *IFITM3* expression subgroups were compared (Table 2). *IFITM3*^{high} had more age ≥ 60 patients ($P = 0.018$), more FAB-M0 ($P = 0.006$), and fewer FAB-M5 ($P = 0.002$) patients, fewer normal karyotype patients, and more complex karyotype (all $P < 0.001$). No significant differences were found in gender distribution, peripheral WBC count, BM blasts, PB blasts, risk-group distribution, and frequency of common genetic mutations (*FLT3*, *NPM1*, *DNMT3A*, *RUNX1*, *TET2*, *TP53*, *IDH1/IDH2*, *and NRAS/KRAS*) between the two groups.

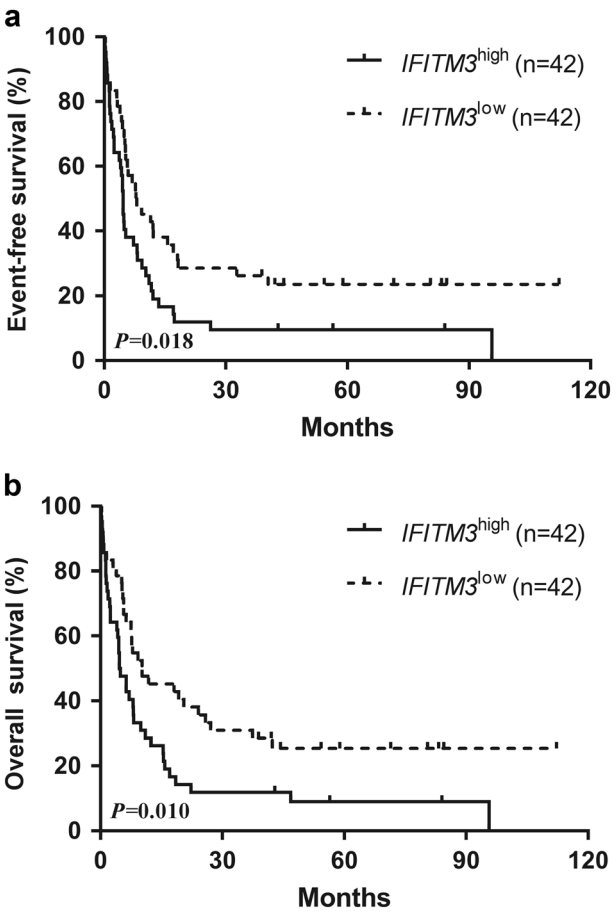

Fig. 1 Kaplan–Meier curves of event-free survival (EFS) and overall survival (OS) in patients who received chemotherapy only. **a**, **b** High *IFITM3* expressers had shorter EFS and OS than the low expressers

Multivariate analysis of EFS and OS in the chemotherapy-only group

To further evaluate prognostic value of *IFITM3*, multivariate Cox proportional hazard models were constructed, selecting the expression levels of *IFITM3* (high vs. low), age (≥ 60 vs. < 60 years), peripheral WBC count (≥ 15×10^9/L vs. < 15×10^9/L), BM blasts (≥ 70% vs. < 70%), PB blasts (≥ 70 vs. < 70%), *FLT3-ITD* (positive vs. negative), and common AML mutations (*NPM1*, *DNMT3A*, *CEBPA*, *RUNX1*, *IDH1/IDH2*, and *NRAS/KRAS*, mutated vs. wild type). Results were shown in Table 3.

Multivariate analysis showed that high *IFITM3* expression and age ≥ 60 years were independent risk factors for both EFS and OS (all $P < 0.05$). Besides, BM blasts ≥ 70%, PB blasts ≥ 70%, and *DNMT3A* mutation were independent risk factors for EFS (all $P < 0.05$) and *RUNX1* mutation was an independent risk factor for OS ($P < 0.05$)

Table 2 Comparison of clinical and molecular characteristics in different groups

Characteristics	Total	*IFITM3*		*P*
		High ($n = 42$)	Low ($n = 42$)	
Age/years, median (range)	63 (22–88)	67 (34–88)	59 (22–82)	0.803[a]
Age group/*n* (%)				0.018[b]
≥60 years	58 (69.0)	34 (81.0)	24 (57.1)	
<60 years	26 (31.0)	8 (19.0)	18 (42.9)	
Gender/*n* (%)				0.126[b]
Male	45 (53.6)	26 (61.9)	19 (45.2)	
Female	39 (46.4)	16 (38.1)	23 (54.8)	
WBC/$\times 10^9$/L, median (range)	38.3 (0.7–297.4)	28.3 (0.7–171.9)	48.3 (1.4–297.4)	0.122[a]
BM blasts/%, median (range)	67.5 (30–99)	64.0 (32–98)	71.0 (30–99)	0.298[a]
PB blasts/%, median (range)	36.3 (0–98)	34.5 (0–97)	37.6 (0–98)	0.397[a]
FAB subtypes/*n* (%)				
M0	7 (8.3)	7 (16.7)	0 (0.0)	0.006[b]
M1	20 (23.8)	10 (23.8)	10 (23.8)	1.000[b]
M2	21 (25.0)	12 (28.6)	9 (21.4)	0.450[b]
M4	20 (23.8)	8 (19.0)	12 (28.6)	0.306[b]
M5	12 (14.3)	1 (2.4)	11 (26.2)	0.002[b]
M6	1 (1.2)	1 (2.4)	0 (0.0)	0.314[b]
M7	3 (3.6)	3 (7.1)	0 (0.0)	0.078[b]
Cytogenetics/*n* (%)				
Normal	40 (47.6)	12 (28.6)	28 (66.7)	0.000[b]
Complex	11 (13.1)	11 (26.2)	0 (0.0)	0.000[b]
inv(16)/CBFβ-MYH11	6 (7.1)	1 (2.4)	5 (11.9)	0.090[b]
t(8;21)/RUNX1-RUNX1T1	6 (7.1)	4 (9.5)	2 (4.8)	0.397[b]
11q23/MLL	3 (3.6)	0 (0.0)	3 (7.1)	0.078[b]
−7/7q-	3 (3.6)	3 (7.1)	0 (0.0)	0.078[b]
t(9;22)/BCR-ABL1	1 (1.2)	1 (2.4)	0 (0.0)	0.314[b]
Others	14 (16.7)	10 (23.8)	4 (9.5)	0.079[b]
Risk/*n* (%)				
Good	12 (14.3)	5 (11.9)	7 (16.7)	0.823[b]
Intermediate	46 (54.8)	19 (45.2)	27 (64.3)	0.205[b]
Poor	24 (28.6)	17 (40.5)	7 (16.7)	0.053[b]
FLT3/*n* (%)				0.390[b]
FLT3-ITD	15 (17.9)	9 (21.4)	6 (14.3)	
FLT3-TKD	7 (8.3)	2 (4.8)	5 (11.9)	
Wild type	62 (73.8)	31 (73.8)	31 (73.8)	
NPM1/*n* (%)				0.815[b]
Mutation	27 (32.1)	14 (33.3)	13 (31.0)	
Wild type	57 (67.9)	28 (66.7)	29 (69.0)	
DNMT3A/*n* (%)				0.463[b]
Mutation	23 (27.4)	13 (31.0)	10 (23.8)	
Wild type	61 (72.6)	29 (69.0)	32 (76.2)	
IDH1/*IDH2*/*n* (%)				0.393[b]
Mutation	15 (17.9)	9 (21.4)	6 (14.3)	
Wild type	69 (82.1)	33 (78.6)	36 (85.7)	
RUNX1/*n* (%)				0.137[b]
Mutation	8 (9.5)	6 (14.3)	2 (4.8)	

Table 2 (continued)

Characteristics	Total	*IFITM3*		*P*
		High ($n = 42$)	Low ($n = 42$)	
Wild type	76 (90.5)	36 (857)	40 (95.2)	
NRAS/KRAS/n (%)				0.533[b]
Mutation	12 (14.3)	5 (11.9)	7 (16.7)	
Wild type	72 (85.1)	37 (88.1)	35 (83.3)	
TET2/n (%)				0.332[b]
Mutation	11 (13.1)	4 (9.5)	7 (16.7)	
Wild type	73 (86.9)	38 (90.5)	35 (83.3)	
TP53/n (%)				0.533[b]
Mutation	12 (14.3)	7 (16.7)	5 (11.9)	
Wild type	72 (85.1)	35 (83.3)	37 (88.1)	

BM bone marrow, *FAB* French–British–American, *PB* peripheral blood, *WBC* white blood cell

[a]Mann–Whitney *U*-test

[b]χ^2-test

Table 3 Multivariate analysis of EFS and OS

Variables	EFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
IFITM3 (high vs. low)	1.919 (1.108–3.323)	0.020	2.037 (1.177–3.525)	0.011
Age (≥60 vs. <60 years)	3.994 (2.003–7.966)	0.000	3.105 (1.596–6.038)	0.001
WBC (≥15 vs. $<15 \times 10^9$/L)	1.206 (0.644–2.258)	0.559	1.241 (0.661–2.329)	0.502
BM blasts (≥70 vs. <70%)	1.857 (1.052–3.277)	0.033	1.713 (0.962–3.050)	0.068
PB blasts (≥70 vs. <70%)	2.157 (1.046–4.446)	0.037	1.487 (0.707–3.126)	0.295
FLT3-ITD (positive vs. negative)	0.701 (0.340–1.443)	0.335	0.870 (0.419–1.807)	0.708
NPM1 (mutated vs. wild)	0.567 (1.269–1.196)	0.136	0.571 (0.269–1.210)	0.144
DNMT3A (mutated vs. wild)	1.893 (1.008–3.553)	0.047	1.603 (0.853–3.013)	0.142
CEBPA (mutated vs. wild)	0.591 (0.120–2.922)	0.519	0.683 (0.141–3.320)	0.637
RUNX1 (mutated vs. wild)	2.327 (0.963–5.623)	0.061	2.432 (1.017–5.815)	0.046
NRAS/KRAS (mutated vs. wild)	1.052 (0.442–2.503)	0.909	0.775 (0.321–1.869)	0.571
IDH1/IDH2 (mutated vs. wild)	0.761 (0.388–1.492)	0.427	0.878 (0.450–1.712)	0.703

BM bone marrow, *CI* confidence interval, *EFS* event-free survival, *HR* hazard ratio, *OS* overall survival, *PB* peripheral blood, *WBC* white blood cell

Discussion

In this retrospective study, we found that high *IFITM3* expression was an adverse prognostic factor for AML, but not in those who underwent allo-HSCT, implying that allo-HSCT might be able to overcome its prognostic impact.

Increasing number of studies have shown that *IFITM3* participates in the development and progression of various tumors and is involved in myriads of cell biology processes, including cancer cell proliferation, invasion and metastasis, apoptosis, and the epithelial-to-mesenchymal transition (EMT). A study indicated that downregulating *IFITM3* in U251 cells could inhibit cell proliferation and cloning, arrest the cell cycle in the G0/G1 phase, especially in the pre-G1 phase that could lead to apoptosis. In addition, the cell migration was also significantly suppressed after downregulation of *IFITM3* [21]. In gastric cancer, high *IFITM3* expression was found to promote tumor cell migration, invasion, and proliferation by activating Wnt/β-catenin signaling pathway. Another study revealed that *IFITM3* silencing would effectively reverse the EMT phenotype and reduce *MMP-2* and *MMP-9* expression [22]. Overexpression of *IFITM3* may also predict poor prognosis in stage IIA esophageal squamous cell carcinoma patients after Ivor Lewis esophagectomy [23]. Consistent with these findings, our study pointed out that *IFITM3* might also be a tumor-promoting gene or oncogene in AML. Its overexpression coincided with other established poor prognostic factors, such as older age and complex karyotype, although its effect was independent.

Out results concurred with previous studies that age ≥ 60 years had unfavorable effects on AML survival, probably due to the higher mutation burden, poorer baseline performance status, and more co-morbidities in this age group [24]. We identified that BM blasts ≥ 70% and PB blasts ≥ 70% also were independent risk factors for EFS, consistent with a former finding that abnormal proliferation of BM blasts and PB blasts had significant negative effects on survival in AML [25]. In our study, *DNMT3A* mutation was an independent risk factor for EFS and *RUNX1* mutation was an independent risk factor for OS, which was in line with other reports that *DNMT3A* mutation was associated with inferior DFS and a trend toward shorter OS in cytogenetically normal AML [26], and *RUNX1* mutation being a strong independent predictor for inferior OS in complex karyotype AML [27].

In conclusion, high *IFITM3* expression was associated with poor prognosis in AML, but its effects on survival could be overcome by allo-HSCT. Due to the small sample size, larger prospective researches are needed to further validate the role of *IFITM3* as an independent poor prognostic factor for AML. In addition, precise experiments need to be designed to explain the mechanisms of *IFITMs* in tumorigenesis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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