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ARTICLE

Prognostic role of *SCAMP* family in acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is a malignant disease of myeloid hematopoietic stem or progenitor cells characterized by abnormal proliferation of primary and immature myeloid cells in bone marrow and peripheral blood. Gene mutation and expression profiles can be used as prognosis predictors for different prognostic subgroups. Secretory carrier-associated membrane proteins (SCAMPs) are a multigenic family with five members and act as cell surface vectors in the post-Golgi recycling pathways in mammals. Nevertheless, the prognostic and clinical influence of *SCAMP* family has hardly ever been illustrated in AML. In our study, expression patterns of *SCAMP* family (*SCAMP1–5*) were analyzed in 155 AML patients which were extracted from the Cancer Genome Atlas database. In chemotherapy, only subgroup, higher *SCAMP1* level was significantly associated with longer EFS and OS (all $P = 0.002$), and *SCAMP1* was confirmed to be an independent favorable factor in un-transplanted patients by Multivariate analysis (all $P < 0.05$). Nevertheless, in the allogeneic hematopoietic stem cell transplantation (allo-HSCT) treatment subgroup, none of the *SCAMP* genes had any effect on the clinical survival. Our study found that high expression level of *SCAMP1* is a favorable prognostic factor in AML, but allo-HSCT may neutralize its prognostic effect.

Introduction

Acute myeloid leukemia (AML) is a morphologically and genetically heterogeneous malignant disease characterized by clonal expansion of one or all myeloid lineages, bringing about hematopoiesis impairment and bone marrow failure [1]. According to the National Comprehensive Cancer Network (NCCN) guideline, the risk status is block into three subtypes based on validated cytogenetics and molecular abnormalities [2]. For example, cytogenetically normal AML patients with *NPM1* mutation (in the absence of *FLT3-ITD* or low frequency of *FLT3-ITD*) or double *CEBPA* mutations have a favorable prognosis [3–5], while those with *RUNX1*, *ASXL1*, *FLT3-ITD*, or *TP53* mutations have a poor prognosis [6–10]. Additionally, many other mutations occur in AML, and some also have prognostic significance, for instance, *DNMT3A* and *TET2* mutations can increase the risk of death in leukemia patients [11, 12]. In addition, the abnormal expression of some genes also contributes to the refinement of risk stratification of AML, such as *FHL2, iASPP*, *PDK2/3*, and *DOK4/5* overexpression are all related to poor prognosis, while high expression of *DOK7* is correlated with favorable prognosis in AML [13–15]. Therefore, more prognostic stratification indicators for AML should be investigated.

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Secretory carrier-associated membrane proteins (SCAMPs) are conserved membrane proteins that function as carriers in post-Golgi recycling pathways, and they are widely discovered in the post-Golgi membranes, synaptic vesicles, secretion granules, and transporter vesicles [16–21]. Five members (*SCAMP1–5*) of the SCAMP family have been characterized in mammalian cells. *SCAMP1/2/3* may primarily function at the same sites during vesicular transport [20], while *SCAMP4* is proved to be repressed by progesterone in brain regions associated with female sexual behavior [21], and another study shows that *hSCAMP5*, which is widely expressed by various of neuronal and nonneuronal tissues and cells, can promote the calcium-regulated signal peptide-containing cytokine [16]. Moreover, *SCAMP1* has been reported to be associated with kinds of solid tumors, such as ovarian cancer, pancreatic and gallbladder cancer, breast cancer and colorectal cancer [22–25].

Although the *SCAMP* family has been widely studied, its prognostic significance in AML is still unclear. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can reduce the incidence of minimal residual disease, reduce recurrence, and stretch the life of survival of AML patients [26]. This biomarker study was to elucidate the impact of the *SCAMP* family on the clinical outcomes of AML patients.

Patients and methods

Patients

SCAMP family (*SCAMP1–5*) expression data of one hundred and fifty-five de novo AML patients from The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/) were recruited in our study [27]. All the clinical data at diagnosis and the survival information were obtained from the enrolled patients. Among them, eighty-four patients had received chemotherapy only, and the other seventy-one patients were additionally treated with allo-HSCT. Clinical information at diagnosis was described, including age, gender, peripheral blood (PB) white blood cell (WBC) counts, blast percentages in PB and bone marrow (BM), French-American-British (FAB) subtypes, cytogenetics, risks, and genetic mutation frequencies. Endpoints were event-free survival (EFS) and overall survival (OS). Informed consent forms were provided by all the patients, and the study protocol was approved by the Washington University Human Studies Committee.

Statistical analysis

Descriptive statistics were applied to summarize the clinical and molecular characteristics of AML patients with median and/or range. Mann–Whitney *U* test was constructed to compare Numerical variables, and χ^2 test was used to compare categorical variables. Kaplan–Meier methods and log-rank test were applied to estimate survival data. In addition, EFS and OS were also estimated using Multivariate Cox proportional hazard models with a limited backward elimination procedure. Statistical significance was defined as a two-tailed $P < 0.05$ for all analyses. SPSS software 25.0 and GraphPad Prism software 5.0 were used to analysis the data.

Results

Prognostic significance of *SCAMPs* in AML

Based on the median expression levels of each *SCAMP* members (*SCAMP1–5*), the involved AML patients were separated into high and low expression groups, and EFS and OS were compared respectively (Table 1). As shown in Table 1, patients with high *SCAMP1*expression had longer EFS and OS in chemotherapy-only patients, (all $P = 0.002$, Fig. 1). However, in allo-HSCT group, *SCAMP* members have no significant impact on EFS and OS.

Characteristics of patients underwent chemotherapy

Clinical and molecular characteristics of the eighty-four patients were showed in Table 2. The age of the patients was between 22 and 88 (median age was 66.5), and fifty-eight of them were older than 60. Forty-five enrolled patients were male. The median WBC count was

Table 1 Comparison of EFS and OS between different expression levels of *SCAMP1–5*.

Variables	EFS		OS	
	χ^2	*P*-value	χ^2	*P*-value
Chemotherapy-only group				
SCAMP1 (high *vs.* low)	9.894	0.002	9.658	0.002
SCAMP2 (high *vs.*low)	0.137	0.711	0.461	0.497
SCAMP3 (high *vs.* low)	0.180	0.671	0.521	0.470
SCAMP4 (high *vs.* low)	0.268	0.605	0.314	0.575
SCAMP5 (high *vs.* low)	0.152	0.697	0.569	0.451
Allo-HSCT group				
SCAMP1 (high *vs.* low)	0.018	0.892	0.050	0.823
SCAMP2 (high *vs.* low)	0.586	0.444	0.192	0.661
SCAMP3 (high *vs.* low)	0.578	0.447	1.423	0.233
SCAMP4 (high *vs.* low)	0.821	0.365	0.045	0.831
SCAMP5 (high *vs.* low)	0.364	0.546	0.380	0.538

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

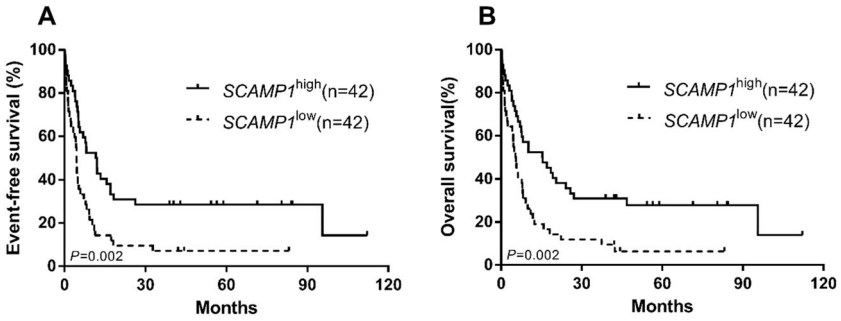

Fig. 1 Kaplan–Meier curves of event-free survival (EFS) and overall survival (OS) in patients who received chemotherapy-only. a, **b** High *SCAMP1* expressers had longer EFS and OS than the low expressers.

14.7×10^9/L, with the blast percentages in BM and PB were 72% and 23.5%, separately. The mainly FAB sub-types were M2 (25%), M1 (23.8%), and M4 (23.8%). Forty patients had normal cytogenetics. The intermediate-risk patients occupied the highest proportion with a percentage of 56.1%. Among the mutated genes in patients, *NPM1* is the most common one ($n = 27$, 32.1%), in addition *DNMT3A*, *FLT3*, *IDH1/IDH2*, *RUNX1*, *NRAS/KRAS*, and *TP53* also have relatively high mutation frequency (Table 2). Relapse happened in 31 patients.

The clinical and molecular characteristics were compared between *SCAMP1*^{high} and *SCAMP1*^{low} (Table 2). The *SCAMP1*^{high} group had fewer old patients (age ≥ 60, $P = 0.009$), higher PB blasts ($P < 0.001$), fewer FAB-M5 patients ($P = 0.003$), fewer patients with complex karyotype ($P = 0.048$), and fewer *TP53* mutations ($P = 0.048$) compared to the *SCAMP1*^{low} group. No significant differences were observed between two groups in gender, WBC, BM blasts, risk stratification, frequency of other recurrent genetic mutations and relapse rates.

Multivariate analysis in patients underwent chemotherapy

To better understand the prognostic value of *SCAMP1*, the expression level of *SCAMP1* (high vs. low), age (≥60 vs. <60 years), BM blasts (≥70 vs. <70%), PB blasts (≥20 vs. <20%), *FLT3-ITD* (positive vs. negative), and other common genetic mutations (*NPM1*, *DNMT3A*, *RUNX1*, and *TP53*; mutated vs. wild) were enrolled to implement Multivariate analysis (Table 3). High expression of *SCAMP1* was proved to be an independent positive prognosis factor for the survival of AML patients, whereas age ≥60, BM blasts ≥70%, and mutations in *DNMT3A* and *TP53* (all $P < 0.05$) were found to be independent risk factors.

Discussion

High expression of *SCAMP1* was found to be a positive prognostic predictor in AML in our study, nevertheless, its prognostic effect on survival had not been found in the allo-HSCT patients, suggesting that allo-HSCT can neutralize the prognostic impact.

In human pancreatic cancer and gallbladder cancer cells, *SCAMP1* is expressed in a relatively high level. And in a previous study, down-regulation of *SCAMP1* can effectively inhibit the activation of *VEGF* and other target genes, while the high *VEGF* activation is notably associated with LN metastasis and higher tumor stage. Hence, for patients with pancreatic cancer and gallbladder cancer, *SCAMP1* can be a potential therapeutic target [23]. However, a clinical research in HER2 breast cancer tissue has shown that *SCAMP1* and *MTSS1* can cooperate to prevent the aggressive of patients with HER2+/ER−/PR− breast cancer and the loss of *SCAMP1* is responsible for reducing their survival [24]. Besides, *SCAMP1* expresses differently in patients of cervical cancer with and without lymph node metastasis [28]. Taken together, the *SCAMP1* indeed has a function in the proliferation and migration of cancer tissues in solid tumor, but the effect varies in different cancer types. In our study, high expression of *SCAMP1* was proved to be a favorable prognosis factor in AML survival (Fig. 1), and it was more frequently to occur in young patients and doses not coexist with AML-M5 and *TP53* mutation. *TP53* mutation has been proved to be a poor prognosis factor in AML patients for many times [29–31], and high *SCAMP1* expression is incompatible with *TP53* mutation in our study, so the favorable prognosis in patients with high *SCAMP1* expression may also be related to carrying less *TP53* mutation. In multiple analysis, high *SCAMP1* expression was proved to be an independent favorable factor in AML. This suggests that high *SCAMP1* expression may play a positive role in the development of AML. Overall, *SCAMP1* might be used as a biomarker for risk stratification in AML patients.

In Multivariate analysis, both age ≥60 years and BM blasts ≥70% were proved to be unfavorable impact on patients survival, which in line with a previous report that overall survival declines with age in AML patients [32], and abnormal increase of BM has significantly poor influences on overall survival [33]. In addition, *DNMT3A* and *TP53*

Table 2 Comparison of clinical and molecular characteristics in different *SCAMP1* expression groups among chemotherapy group.

Characteristics	Total	*SCAMP1*		*P*
		High ($n = 42$)	Low ($n = 42$)	
Age/years, median (range)	66.5 (22–88)	62.5 (22–77)	70.5 (35–88)	0.000[a]
Age group/*n* (%)				0.009[b]
<60 years	26 (31.0)	19 (45.2)	7 (16.7)	
≥60 years	58 (69.0)	23 (54.8)	35 (83.3)	
Gender/*n* (%)				0.662[b]
Male	45 (53.6)	21 (50.0)	24 (57.1)	
Female	39 (46.4)	21 (50.0)	18 (42.9)	
WBC/$\times 10^9$/L, median (range)	14.7 (0.7–297.4)	16.1 (1–297.4)	13.4 (0.7–116.4)	0.314[a]
BM blasts/%, median (range)	72 (30–99)	73.5 (35–99)	61 (30–98)	0.056[a]
PB blasts/%, median (range)	23.5 (0–98)	51.5 (0–98)	9.5 (0–91)	0.000[a]
FAB subtypes/*n* (%)				
M0	7 (8.3)	4 (9.5)	3 (7.1)	1.000[b]
M1	20 (23.8)	10 (23.4)	10 (23.4)	1.000[b]
M2	21 (25.0)	14 (33.3)	7 (16.7)	0.129[b]
M4	20 (23.8)	13 (31.0)	7 (16.7)	0.200[b]
M5	12 (14.3)	1 (2.4)	11 (26.2)	0.003[b]
M6	1 (1.2)	0 (0.0)	1 (2.4)	1.000[b]
M7	3 (3.6)	0 (0.0)	3 (7.1)	0.241[b]
Cytogenetics/*n* (%)				
Normal	40 (47.6)	21 (50.0)	19 (45.2)	0.827[b]
Complex	11 (13.1)	2 (4.8)	9 (21.4)	0.048[b]
inv(16)/CBFβ-MYH11	6 (7.1)	4 (9.5)	2 (4.8)	0.676[b]
t(8;21)/RUNX1-RUNX1T1	6 (7.1)	5 (11.9)	1 (2.4)	0.202[b]
11q23/MLL	3 (3.6)	2 (4.8)	1 (2.4)	1.000[b]
−7/7q-	3 (3.6)	2 (4.8)	1 (2.4)	1.000[b]
t(9;22)/BCR-ABL1	1 (1.2)	0 (0.0)	1 (2.4)	1.000[b]
Others	14 (16.7)	6 (14.3)	8 (19.0)	0.771[b]
Risk/n (%)				
Good	12 (14.6)	9 (22.0)	3 (7.3)	0.116[b]
Intermediate	46 (56.1)	23 (56.1)	23 (56.1)	1.000[b]
Poor	24 (29.3)	9 (22.0)	15 (36.6)	0.225[b]
FLT3/*n* (%)				0.109[b]
FLT3-ITD	15 (17.9)	11 (26.2)	4 (9.5)	
FLT3-TKD	7 (8.3)	4 (9.5)	3 (7.1)	
Wild type	62 (73.8)	27 (64.3)	35 (83.3)	
NPM1/*n* (%)				0.641[b]
Mutation	27 (32.1)	15 (35.7)	12 (28.6)	
Wild type	57 (67.9)	27 (64.3)	30 (71.4)	
DNMT3A/*n* (%)				0.328[b]
Mutation	23 (27.4)	14 (33.3)	9 (21.4)	
Wild type	61 (72.6)	28 (66.7)	33 (78.6)	
IDH1/*IDH2*/*n* (%)				0.254[b]
Mutation	15 (17.9)	10 (23.8)	5 (11.9)	
Wild type	69 (82.1)	32 (76.2)	37 (88.1)	
RUNX1/*n* (%)				0.713[b]
Mutation	8 (9.5)	3 (7.1)	5 (11.9)	
Wild type	76 (90.5)	39 (92.9)	37 (88.1)	
NRAS/KRAS/*n* (%)				0.350[b]
Mutation	12 (14.3)	4 (9.5)	8 (19.0)	
Wild type	72 (85.7)	38 (90.5)	34 (81.0)	
TET2/n (%)				1.000[b]
Mutation	11 (13.1)	6 (14.3)	5 (11.9)	
Wild type	73 (86.9)	36 (85.7)	37 (88.1)	
TP53/n (%)				0.048[b]
Mutation	11 (13.1)	2 (4.8)	9 (21.4)	
Wild type	73 (86.9)	40 (95.2)	33 (78.6)	
Relapse/*n* (%)				1.000[b]
Yes	31 (36.9)	26 (61.9)	27 (64.4)	
No	53 (63.1)	16 (38.1)	15 (35.7)	

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

[a]Mann–Whitney *U*.[b]Chi-square test.

Table 3 Multivariate analysis of EFS and OS in chemotherapy group.

Variables	EFS		OS	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
SCAMP1 (high *vs.* low)	0.516 (0.298–0.892)	0.018	0.563 (0.331–0.955)	0.033
Age (≥60 *vs.* <60 years)	2.379 (1.262–4.485)	0.007	2.286 (1.194–4.377)	0.013
BM blasts (≥70 *vs.* <70%)	2.260 (1.258–0.795)	0.006	2.117 (1.187–3.775)	0.011
PB blasts (≥20 *vs.* <20%)	1.108 (0.631–1.585)	0.721	1.090 (0.614–1.937)	0.768
FLT3-ITD (positive *vs.* negative)	1.438 (0.716–2.890)	0.307	1.140 (0.571–2.273)	0.711
NPM1 (mutated *vs.* wild)	1.024 (0.543–1.931)	0.941	0.906 (0.473–1.735)	0.765
DNMT3A (mutated *vs.* wild)	1.776 (1.022–3.087)	0.042	1.838 (1.064–3.174)	0.029
RUNX1 (mutated *vs.* wild)	1.869 (0.811–4.304)	0.142	2.054 (0.887–4.754)	0.093
TP53 (mutated *vs.* wild)	3.431 (1.551–7.590)	0.002	3.002 (1.369–6.580)	0.006

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

mutations were independent negative factors for the survival of AML patients in our study, and this was in line with previous reports: *DNMT3A* mutation is recurrent and independently associated with unfavorable prognosis in de novo AML patients [11, 34], and *TP53* mutation is the mainly significant dismal prognostic factor in complex karyotype AML [35].

In summary, our research revealed that high level of *SCAMP1* is a detached positive prognostic predictor in AML, but its prognostic effect can be neutralized by allo-HSCT. The understanding of the molecular mechanisms involved in *SCAMP* family in AML is still warranted. Moreover, future study with larger sample size is needed.

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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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