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Prognostic value of *HMGN* family expression in acute myeloid leukemia

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Aim: The objective of this work was to investigate the prognostic role of the *HMGN* family in acute myeloid leukemia (AML). **Methods:** A total of 155 AML patients with *HMGN1–5* expression data from the Cancer Genome Atlas database were enrolled in this study. **Results:** In the chemotherapy-only group, patients with high *HMGN2* expression had significantly longer event-free survival (EFS) and overall survival (OS) than those with low expression (all $p < 0.05$), whereas high *HMGN5* expressers had shorter EFS and OS than the low expressers (all $p < 0.05$). Multivariate analysis identified that high *HMGN2* expression was an independent favorable prognostic factor for patients who only received chemotherapy (all $p < 0.05$). *HMGN* family expression had no impact on EFS and OS in AML patients receiving allogeneic hematopoietic stem cell transplantation. **Conclusion:** High *HMGN2/5* expression is a potential prognostic indicator for AML.

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Keywords: acute myeloid leukemia • heterogeneity • *HMGN2* • *HMGN5* • prognosis

Acute myeloid leukemia (AML) is a highly heterogeneous malignant tumor characterized by abnormal clonal proliferation of myeloid hematopoietic stem/progenitor cells in blood, bone marrow and other tissues [1]. Genetic abnormalities can predict the clinical outcome and reveal the pathogenesis of AML [2]. Previous researches have shown a few biomarkers to be associated with favorable or adverse outcomes: highly expressed *MN1*, *ERG*, *BAALC*, *EVII*, *DOK4/5* and *PDK2/3* and mutations in *FLT3-ITD* and *DNMT3A* are in the latter group [3–6], while the former group consists of high *DOK7* expression and mutations in *NPM1* [4,7]. Furthermore, gene–gene interactions should be considered. For example, *NPM1* mutations confer a good prognosis only in the absence of *FLT3-ITD* [8], whereas interaction between *FHL2* and *iASPP* leads to a poor prognosis in AML [9]. Due to the complexity of pathogenesis and clinical manifestations of AML, more comprehensive studies are required to stratify risks and determine treatment directions.

HMGN5 is a member of the *HMGN* family of proteins (*HMGN1–5*), which are highly conserved and widely found in the nucleus of almost all mammals and most vertebrates [10]. Abnormal expression of *HMGN* proteins is associated with the occurrence and development of varied cancers. For example, *HMGN1* is associated with tumor-infiltrating lymphocytes in HER2-positive breast cancers [11]. *HMGN2* can inhibit the proliferation and promote apoptosis of oral squamous cell carcinoma cells by arresting cells in the S phase of the cell cycle [12]. In addition,

HMGN2 can induce proliferation of CD4⁺ T cells in leukocytes from patients with B-cell chronic lymphocytic leukemia (CLL) [13]. Overexpression of *HMGN4* in the thyroid of transgenic mice increases tumorigenicity through colony formation, and promotes tumorigenesis and the formation of thyroid precancerous lesions in nude mice [14]. *HMGN5* is highly expressed in prostate cancer cells, and its downregulation can induce apoptosis by regulating the caspase-associated mitochondrial pathway and expression of BCL2 family proteins [15].

However, the prognostic value of HMGNs in AML has not been clear. In this study, we focus on investigating the effects of HMGNs on the survival of AML patients. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a curative treatment to reduce relapse of AML and prolong survival time via significant reduction of leukemia residual disease [16]. Here we also analyzed whether allo-HSCT can overcome the prognostic effects of *HMGN* family expression.

Patients & methods

Patients

A cohort of 155 AML patients with *HMGN1–5* expression data were enrolled into our study from the Cancer Genome Atlas database (<https://cancergenome.nih.gov/>) [17]. 81 patients received chemotherapy only, while 71 also underwent allo-HSCT. Clinical characteristics at diagnosis were enrolled, consisting of peripheral white blood cell (WBC) counts, blast percentages in peripheral blood (PB) and bone marrow (BM), French–American–British (FAB) classification subtypes, cytogenetic risk group and frequencies of common recurrent genetic mutations. Event-free survival (EFS) and overall survival (OS) were the primary end points of the study. EFS represented the time from diagnosis to removal from the study due to relapse, death or failure to achieve complete remission. OS was defined as the time from diagnosis to death from any cause or was censored at the last follow-up. Informed consent was obtained from all patients, and the study protocol was approved by the Human Research Council of the University of Washington.

Statistical analysis

Descriptive statistics were performed to summarize the clinical and molecular characteristics of patients. Datasets were described with median and/or range. The Mann–Whitney *U* test was performed to compare numerical data, while categorical data were compared using the chi-square test. Survival was analyzed using the Kaplan–Meier method and the log-rank test. Multivariate Cox proportional hazard models for EFS and OS were constructed via a limited backward elimination procedure. All statistical tests were two sided, and *p* < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp., NY, USA) and GraphPad Prism software version 7.0 (GraphPad, CA, USA).

Results

The prognostic value of HMGNs in AML

To evaluate the prognostic value of *HMGN* family members in AML, all patients were divided into high and low expression groups based on the median expression levels of each *HMGN* member (*HMGN1–5*). The cutoff values of *HMGN1/2/3/4/5* in the chemotherapy-only group were 52.18, 33.12, 39.07, 35.55 and 3.85, respectively. EFS and OS of the high and low expression groups are compared in Table 1. In the chemotherapy-only group, high *HMGN2* expression had a favorable effect on EFS and OS (all *p* < 0.05; Figure 1A & B), whereas high *HMGN5* expression had an adverse effect on EFS and OS (all *p* < 0.05; Figure 1C & D). In the allo-HSCT group, the expression levels of all *HMGNs* were independent of survival.

Comparison of clinical & molecular characteristics in different expression levels of *HMGN2/5* in the chemotherapy-only group

The clinical and molecular characteristics of the high and low *HMGN2* and *HMGN5* expression groups were compared (Table 2). The *HMGN2*^{high} group had lower peripheral WBC count (*p* = 0.019) and fewer patients with complex karyotype (*p* = 0.024). No significant differences were found in age, gender distribution, BM blasts, PB blasts, FAB subtypes, risk group distribution or frequency of common genetic mutations (*FLT3*, *NPM1*, *DNMT3A*, *RUNX1*, *TET2*, *TP53*, *IDH1/IDH2*, *NRAS/KRAS*) between the two groups.

Compared with the *HMGN5*^{low} group, *HMGN5*^{high} group had higher percentage of PB blasts (*p* = 0.005), more FAB-M1 patients (*p* = 0.010), fewer FAB-M5 patients (*p* = 0.002), fewer patients with *CBFβ-MYH11* and *RUNX1-RUNX1T1* rearrangements (all *p* = 0.011), fewer good-risk patients (*p* < 0.001) and more frequent *IDH1/IDH2*

Table 1. Comparison of event-free survival and overall survival between different expression levels of *HMGN1–5*.

Variables	Event-free survival		Overall survival	
	χ^2	p-value	χ^2	p-value
Chemotherapy-only group				
– <i>HMGN1</i> (high vs low)	0.395	0.530	0.685	0.408
– <i>HMGN2</i> (high vs low)	5.337	0.021 [†]	5.182	0.023 [†]
– <i>HMGN3</i> (high vs low)	0.739	0.390	1.108	0.293
– <i>HMGN4</i> (high vs low)	1.119	0.290	1.789	0.181
– <i>HMGN5</i> (high vs low)	6.600	0.010 [†]	5.199	0.023 [†]
Allo-HSCT group				
– <i>HMGN1</i> (high vs low)	1.069	0.301	0.437	0.509
– <i>HMGN2</i> (high vs low)	0.022	0.883	0.715	0.398
– <i>HMGN3</i> (high vs low)	2.043	0.153	1.414	0.234
– <i>HMGN4</i> (high vs low)	0.256	0.613	1.203	0.273
– <i>HMGN5</i> (high vs low)	0.698	0.403	0.030	0.862

† p < 0.05.

Allo-HSCT: Allogeneic hematopoietic stem cell transplantation.

Figure 1. Kaplan–Meier curves of event-free survival and overall survival in patients who received chemotherapy. (A & B) High *HMGN2* expressers had longer event-free survival and overall survival than low expressers. (C & D) High *HMGN5* expressers had shorter event-free survival and overall survival than low expressers.

Table 2. Comparison of clinical and molecular characteristics in different *HMGN2/5* expression groups among patients who received chemotherapy only.

Characteristics	<i>HMGN2</i>		p-value	<i>HMGN5</i>		p-value
	High (n = 42)	Low (n = 42)		High (n = 42)	Low (n = 42)	
Age (years), median (range)	63 (22–88)	63 (25–81)	0.830 [†]	64 (33–88)	62 (22–81)	0.328 [†]
Age group, n (%)			0.637 [‡]			0.345 [‡]
– ≥60 years	30 (71.4)	28 (66.7)		31 (73.8)	27 (64.3)	
– <60 years	12 (28.6)	14 (33.3)		11 (26.2)	15 (35.7)	
Gender, n (%)			0.512 [‡]			0.512 [‡]
– Male	21 (50.0)	24 (57.1)		21 (50.0)	24 (57.1)	
– Female	21 (50.0)	18 (42.9)				
WBC ($\times 10^9$ /l), median (range)	30.8 (1–131.5)	45.8 (0.7–297.4)	0.019 [†]	40.0 (0.7–297.4)	36.5 (1–116.2)	0.101 [†]
BM blasts (%), median (range)	65.7 (30–95)	69.3 (32–99)	0.074 [†]	68.0 (30–99)	67.0 (32–98)	0.951 [†]
PB blasts (%), median (range)	35.4 (0–97)	37.1 (0–98)	0.844 [†]	43.5 (0–98)	29.0 (0–86)	0.005 [†]
FAB subtypes, n (%)						
– M0	2 (4.8)	5 (11.9)	0.236 [‡]	2 (4.8)	5 (11.9)	0.236 [‡]
– M1	10 (23.8)	10 (23.8)	1.000 [‡]	15 (35.7)	5 (11.9)	0.010 [‡]
– M2	12 (28.6)	9 (21.4)	0.450 [‡]	14 (33.3)	7 (16.7)	0.078 [‡]
– M4	13 (31.0)	7 (16.7)	0.124 [‡]	7 (16.7)	13 (31.0)	0.124 [‡]
– M5	5 (11.9)	7 (16.7)	0.367 [‡]	1 (2.4)	11 (26.2)	0.002 [‡]
– M6	0 (0.0)	1 (2.4)	0.314 [‡]	0 (0.0)	1 (2.4)	0.314 [‡]
– M7	0 (0.0)	3 (7.1)	0.078 [‡]	3 (7.1)	0 (0.0)	0.078 [‡]
Cytogenetics, n (%)						
– Normal	21 (50.0)	19 (45.2)	0.662 [‡]	22 (52.4)	18 (42.9)	0.382 [‡]
– Complex	2 (4.8)	9 (21.4)	0.024 [‡]	8 (19.0)	3 (7.1)	0.106 [‡]
– inv(16), <i>CBFβ-MYH11</i>	3 (7.1)	3 (7.1)	1.000 [‡]	0 (0.0)	6 (14.3)	0.011 [‡]
– t(8;21), <i>RUNX1-RUNX1T1</i>	4 (9.5)	2 (4.8)	0.397 [‡]	0 (0.0)	6 (14.3)	0.011 [‡]
– 11q23, <i>MLL</i>	3 (7.1)	0 (0.0)	0.078 [‡]	2 (4.8)	1 (2.4)	0.557 [‡]
– -7/7q-	1 (2.4)	2 (4.8)	0.557 [‡]	3 (7.1)	0 (0.0)	0.078 [‡]
– t(9;22), <i>BCR-ABL1</i>	0 (0.0)	1 (2.4)	0.314 [‡]	1 (2.4)	0 (0.0)	0.314 [‡]
– Others	8 (19.0)	6 (14.3)	0.558 [‡]	6 (14.3)	8 (19.0)	0.558 [‡]
Risk, n (%)						
– Good	7 (17.1)	5 (12.2)	0.532 [‡]	0 (0.0)	12 (28.6)	0.000 [‡]
– Intermediate	24 (58.5)	22 (53.7)	0.656 [‡]	25 (59.5)	21 (50.0)	0.254 [‡]
– Poor	10 (24.4)	14 (34.1)	0.332 [‡]	15 (35.7)	9 (21.4)	0.110 [‡]
<i>FLT3</i> , n (%)			0.447 [‡]			0.136 [‡]
– <i>FLT3</i> -ITD	7 (16.7)	13 (31.0)		5 (11.9)	10 (23.8)	
– <i>FLT3</i> -TKD	1 (2.4)	3 (7.1)		2 (4.8)	5 (11.9)	
– Wildtype	34 (81.0)	26 (61.9)		35 (83.3)	27 (64.3)	
<i>NPM1</i> , n (%)			0.243 [‡]			0.102 [‡]
– Mutation	11 (26.2)	16 (38.1)		10 (23.8)	17 (40.5)	
– Wildtype	31 (73.8)	26 (61.9)		32 (76.2)	25 (59.5)	
<i>DNMT3A</i> , n (%)			0.221 [‡]			0.807 [‡]
– Mutation	9 (21.4)	14 (33.3)		11 (26.2)	12 (28.6)	
– Wildtype	33 (78.6)	28 (66.7)		31 (73.8)	30 (71.4)	
<i>IDH1/IDH2</i> , n (%)			0.393 [‡]			0.046 [‡]
– Mutation	6 (14.3)	9 (21.4)		11 (26.2)	4 (9.5)	
– Wildtype	36 (85.7)	33 (78.6)		31 (73.8)	38 (90.5)	
<i>RUNX1</i> , n (%)			0.457 [‡]			0.457 [‡]
– Mutation	3 (7.1)	5 (11.9)		5 (11.9)	3 (7.1)	

† Denotes Mann-Whitney *U* test.

‡ Denotes chi-square test.

BM: Bone marrow; FAB: French–American–British; PB: Peripheral blood; WBC: White blood cell.

Table 2. Comparison of clinical and molecular characteristics in different *HMGN2/5* expression groups among patients who received chemotherapy only (cont.).

Characteristics	<i>HMGN2</i>		p-value	<i>HMGN5</i>		p-value
	High (n = 42)	Low (n = 42)		High (n = 42)	Low (n = 42)	
– Wildtype	39 (92.9)	37 (88.1)		37 (88.1)	39 (92.9)	
<i>NRAS/KRAS</i> , n (%)			0.212 [‡]			0.533 [‡]
– Mutation	4 (9.5)	8 (19.0)		7 (16.7)	5 (11.9)	
– Wildtype	38 (90.5)	34 (81.0)		35 (83.3)	37 (88.1)	
<i>TET2</i> , n (%)			0.746 [‡]			0.106 [‡]
– Mutation	5 (11.9)	6 (14.3)		8 (19.0)	3 (7.1)	
– Wildtype	37 (88.1)	36 (85.7)		34 (81.0)	39 (92.9)	
<i>TP53</i> , n (%)			0.212 [‡]			0.533 [‡]
– Mutation	8 (19.0)	4 (9.5)		7 (16.7)	5 (11.9)	
– Wildtype	34 (81.0)	38 (90.5)		35 (83.3)	37 (88.1)	

[†] Denotes Mann-Whitney *U* test.

[‡] Denotes chi-square test.

BM: Bone marrow; FAB: French–American–British; PB: Peripheral blood; WBC: White blood cell.

Table 3. Multivariate analysis of event-free survival and overall survival in patients who received chemotherapy only.

Variables	Event-free survival		Overall survival	
	HR (95% CI)	p-value	HR (95% CI)	p-value
<i>HMGN2</i> (high vs low)	0.398 (0.225–0.703)	0.001	0.437 (0.249–0.767)	0.004
<i>HMGN5</i> (high vs low)	1.409 (0.740–2.685)	0.297	1.480 (0.779–2.812)	0.231
Age (≥ 60 vs < 60 years)	5.313 (2.558–11.04)	0.000	3.722 (1.864–7.433)	0.000
WBC (≥ 15 vs $< 15 \times 10^9$ /l)	1.300 (0.659–2.564)	0.449	1.350 (0.687–2.653)	0.384
BM blasts (≥ 70 vs $< 70\%$)	1.230 (0.678–2.232)	0.496	1.167 (0.638–2.135)	0.617
PB blasts (≥ 70 vs $< 70\%$)	2.288 (0.939–5.576)	0.069	1.389 (0.567–3.404)	0.472
<i>FLT3-ITD</i> (positive vs negative)	0.766 (0.366–1.604)	0.479	0.995 (0.473–2.091)	0.989
<i>NPM1</i> (mutated vs wildtype)	0.505 (0.241–1.055)	0.069	0.514 (0.246–1.076)	0.077
<i>DNMT3A</i> (mutated vs wildtype)	1.927 (1.027–3.616)	0.041	1.610 (0.857–3.037)	0.139
<i>CEBPA</i> (mutated vs wildtype)	0.501 (0.102–2.467)	0.396	0.629 (0.130–3.037)	0.564
<i>RUNX1</i> (mutated vs wildtype)	2.147 (0.877–5.254)	0.094	2.369 (0.980–5.733)	0.055
<i>NRAS/KRAS</i> (mutated vs wildtype)	0.686 (0.278–1.693)	0.414	0.468 (0.182–1.206)	0.116
<i>IDH1/IDH2</i> (mutated vs wildtype)	0.679 (0.343–1.345)	0.267	0.775 (0.391–1.538)	0.466

BM: Bone marrow; HR: Hazard ratio; PB: Peripheral blood; WBC: White blood cell.

mutations ($p = 0.046$). No significant differences were found in age, gender distribution, race, peripheral WBC count, BM blasts or frequency of other common genetic mutations (*FLT3*, *NPM1*, *DNMT3A*, *RUNX1*, *TET2*, *TP53*, *NRAS/KRAS*) between the two groups.

Multivariate analysis of potential prognostic factors in the chemotherapy-only group

To further evaluate prognostic value of *HMGN2* and *HMGN5*, multivariate Cox proportional hazard models were constructed, including expression levels of *HMGN2* and *HMGN5* (high vs low), age (≥ 60 vs < 60 years), peripheral WBC count (≥ 15 vs $< 15 \times 10^9$ /l), BM blasts (≥ 70 vs $< 70\%$), PB blasts (≥ 70 vs $< 70\%$), *FLT3-ITD* (positive vs negative) and common genetic mutations (*NPM1*, *DNMT3A*, *CEBPA*, *RUNX1*, *IDH1/IDH2* and *NRAS/KRAS*, mutated vs wildtype). The results are shown in Table 3.

Multivariate analysis showed that high *HMGN2* expression was an independent favorable factor for EFS and OS ($p = 0.001$ and $p = 0.004$, respectively), whereas age ≥ 60 years was an independent risk factor for EFS and OS (all $p < 0.001$). In addition, *RUNX1* mutations predicted shorter EFS ($p = 0.041$).

Discussion

In this study we report that overexpression of *HMGN2* is a favorable prognostic indicator in AML, while high *HMGN5* expression has an adverse effect on AML prognosis. Their effects on survival are not different in patients who have undergone allo-HSCT, which suggests that allo-HSCT may offset their prognostic impact.

The mechanisms of *HMGN2* and *HMGN5* in many types of cancers have been investigated. *In vitro* and *in vivo* experiments showed that recombinant human *HMGN2* can significantly inhibit the proliferation and migration, and increase the apoptosis, of breast cancer cells, acting as a tumor suppressor gene [18]. In addition, *HMGN2* can inhibit the growth of infected T24 bladder cancer cells *in vitro*, suggesting that the antitumor effect of *HMGN2* operates by inducing apoptosis [19]. Consistent with the above findings, we found that high expression of *HMGN2* was more likely to coexist with lower WBC counts and had a favorable impact on EFS and OS, indicating that *HMGN2* may also act as a tumor suppressor factor in AML. However, *HMGN5* plays an oncogenic role in solid tumors. Weng *et al.* found that *HMGN5* was highly expressed in breast cancer and promoted the proliferation and invasion of breast cancer cells [20]. Furthermore, the decrease of *HMGN5* expression in human glioma U251 and U87 cells resulted in cell cycle arrest in G1 phase and delayed cell proliferation, and led to more apoptosis and inhibition of clonal growth in U251 cells. These results suggest that *HMGN5* is necessary for tumorigenesis *in vitro* [21]. Consistent with the above results, we found that high expression of *HMGN5* was more likely to occur in patients with *CBFβ-MYH11* and *RUNX1-RUNX1T1* deficiency, and to coexist with *IDH1/IDH2* mutations. High *HMGN5* expression had an adverse effect on EFS and OS, indicating that it may be involved in leukemogenesis. In addition, high *HMGN2* expression, but not *HMGN5* expression, was an independent favorable prognostic factor for EFS and OS, suggesting that *HMGN2* has a stronger effect in AML than other HMGN family members.

In multivariate analysis, we also found that age ≥ 60 years had a poor effect on EFS and OS, consistent with the fact that older AML patients generally have less favorable prognosis due to higher mutation burden, poorer baseline performance status and higher incidence of comorbidities [22]. We identified that *DNMT3A* mutation was also an independent risk indicator for EFS, in line with a previous finding that *DNMT3A* mutation is related to inferior disease-free survival and a trend toward shorter OS in cytogenetically normal AML [23]. AML and normal BM samples from the Gene Expression Omnibus dataset GSE138702 were performed to analyze the protein expression of *HMGN2* and *HMGN5*, and the results are shown in [Supplementary Figure 1](#). Low expression of *HMGN2* protein was observed in AML ($p = 0.02793$). There was a statistically insignificant difference in the expression of *HMGN5* protein between AML patients and healthy donors ($p > 0.05$). The expression level of *HMGN5* protein in AML was slightly lower than in normal controls. We speculate that the possible reason is that *HMGN5* antagonizes antioncogenes: when the expression of antioncogenes increased, the expression of *HMGN5* increased to antagonize them, while when the expression of antioncogenes decreased, the expression of *HMGN5* also decreased. These findings require further validation.

Based on our results and the studies of *HMGN2* and *HMGN5* in solid tumors, we speculate that *HMGN2* and *HMGN5* may play opposite roles in AML. In our follow-up research, we will overexpress *HMGN2* and *HMGN5* in AML cell lines by lentivirus. MTT assay, trypan blue counting, Transwell assay and flow cytometry will be performed to examine the influence of *HMGN2* and *HMGN5* overexpression on cell proliferation, viability, migration and apoptosis *in vitro*, then nude mice will be used to establish a subcutaneous heterotopic transplantation tumor model to investigate the effect of *HMGN2* and *HMGN5* overexpression on AML cell growth *in vivo*. Moreover, we would analyze the potential signal pathway related to *HMGN2* and *HMGN5* by gene ontology analysis and Kyoto Encyclopedia of Genes and Genomes analysis. We speculate that *HMGN2* overexpression would block AML development by inhibiting cell proliferation and migration and promoting apoptosis, while high *HMGN5* expression would show the opposite effect. In this study we preliminarily explored the prognostic value of the HMGN family, especially *HMGN2* and *HMGN5*, in AML. At present there is no direct evidence showing a link between gene expression and major mutations in AML, thus we would also perform chromatin immunoprecipitation and other experimental techniques to further screen the main target genes of *HMGN2/5* and investigate whether they are primary or passenger events.

In conclusion, high expression of *HMGN5* indicates adverse prognosis in AML, while highly expressed *HMGN2* predicts good prognosis, but the prognostic effects on survival can be offset by allo-HSCT. In general, *HMGN2* is an independent favorable prognostic indicator in AML. To illustrate the function of *HMGNs* in leukemogenesis, further studies are necessary. The limitation of our study is the small sample size, and larger prospective cohorts need to be used to validate the results.

Summary points

- Acute myeloid leukemia (AML) is a highly heterogeneous malignant tumor.
- High expression of *HMGN2* is an independent favorable prognostic factor in AML patients.
- High expression of *HMGN5* is an independent risk prognostic factor in AML patients.
- Event-free survival and overall survival are higher in AML patients with higher expression of *HMGN2*.
- Event-free survival and overall survival are lower in AML patients with higher expression of *HMGN5*.
- Allogeneic hematopoietic stem cell transplantation could overcome the prognostic effect of *HMGN2* and *HMGN5*.
- *HMGN2* may act as a tumor suppressor gene in solid tumors and chronic lymphocytic leukemia, while *HMGN5* plays the opposite role in solid tumors.
- *HMGN2/5* might also play the opposite role in the pathogenesis of AML.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0555

Author contributions

W Cui and Yuna Liu wrote and revised the paper. L Fu, T Zeng and Yan Liu designed and revised the paper. Y Tan and X Peng drew the figures and tables. L Cui, Z Cheng and Y Dai performed the literature search. All authors read and approved the final manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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