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ORIGINAL ARTICLE

Analysis of Aurora kinase A expression in CD34$^+$ blast cells isolated from patients with myelodysplastic syndromes and acute myeloid leukemia

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Abstract Aurora kinase A, also known as aurora A, is a serine/threonine kinase that plays critical roles in mitosis entry, chromosome alignment, segregation, and cytokinesis. Overexpression of aurora A has been observed in many solid tumors and some hematopoietic neoplasms, but little is known about its expression in myeloid diseases. Because cytogenetic abnormalities play an essential role in the pathogenesis of myeloid malignancies, we hypothesized that aurora A deregulation may be involved in myelodysplastic syndromes and acute myeloid leukemia and contribute to the chromosomal instability observed in these diseases. We assessed aurora A mRNA levels in CD34$^+$ bone marrow blasts from nine patients with acute myeloid leukemia, 20 patients with myelodysplastic syndromes, and five normal patients serving as controls. CD34$^+$ blasts were isolated from bone marrow aspirate specimens using magnetic activated cell separation technology. RNA was extracted from purified CD34$^+$ cells, and quantitative real-time reverse transcriptase polymerase chain reaction for aurora A was performed. Immunocytochemical analyses for total aurora A, phosphorylated aurora A, Ki-67, and activated caspase 3 were performed on cytospin slides made from purified CD34$^+$ cells in myelodysplastic syndrome patients using standard methods. Aurora A mRNA and protein levels were correlated, as was aurora A mRNA level, with blast counts, cytogenetic abnormalities, and International Prognostic Scoring System score. We found that CD34$^+$ cells in myelodysplastic syndromes and acute myeloid leukemia expressed aurora A at significantly higher levels (P=0.01 and P=0.01, respectively) than normal CD34$^+$ cells. Aurora A mRNA levels correlated with total and phosphorylated protein levels (P=0.0002 and P=0.02, respectively). No significant correlation was found between aurora A mRNA level and blast count, blast viability, cytogenetic abnormalities, or the International Prognostic Scoring System score in patients with myelodysplastic syndromes. We conclude that aurora A is up-regulated in CD34$^+$ blasts from myeloid neoplasms.

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Introduction

Aurora kinases are a family of serine/threonine kinases that includes three members designated as aurora A, B, and C [1–3]. Aurora A (AA) is localized at the centrosome during interphase, translocated to mitotic spindles in the early mitotic phase, and degraded after the metaphase–anaphase transition. Activation of AA is required for mitotic entry, centrosome maturation, centrosome separation, and chromosome alignment [1–3]. Aurora B localizes to the inner centromere during prometaphase and metaphase and then to the spindle midzone microtubules in late anaphase/telophase and in the midbody during cytokinesis. Its main role is to insure normal chromosomal alignment and cytokinesis [1–3]. Aurora C is associated with aurora B in regulating mitotic chromosome dynamics in mammalian cells [4].

Aurora A overexpression has been observed in several solid tumors, including colon, breast, prostate, and gastric cancers [5–8]. The expression level of AA correlated with clinical stage in patients with prostate cancer [9]. Information regarding the expression of aurora kinase expression in hematologic neoplasia is limited. A group from Japan studied aurora A and B expression in leukemia cell lines and mononuclear cells isolated from leukemia patients and found aberrant expression of aurora kinases in numerous hematological malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia, and chronic myeloid leukemia [10, 11]. Furthermore, aberrant expression accompanied by high proliferation of neoplastic cells was inhibited by selective aurora kinase inhibitors, suggesting that aurora kinases play important roles in the growth and proliferation of hematologic neoplasms [10, 11]. These studies were substantiated by data published recently by a Chinese group [12].

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies that are thought to be hematological stem cell disorders. Myelodysplastic syndromes are characterized by inefficient hematopoiesis, and patients present clinically with cytopenia in one or more lineages. Bone marrow aspiration and biopsy show hypercellular but dysplastic hematopoiesis [13]. Although approximately half of MDS patients have cytogenetic abnormalities, the pathogenesis of MDS and the roles of the genetic abnormalities in tumorigenesis remain to be defined. To our knowledge, the expression of aurora kinases in MDS has not been assessed.

The goal of the current study was to investigate the level of aurora A expression in MDS and AML and to correlate the results with clinicopathologic and cytogenetic features.

Materials and methods

Patients and specimen sources

With informed consent from patients and approval from the institutional review board of The University of Texas M. D. Anderson Cancer Center, we obtained peripheral blood, bone marrow aspirate, aspirate clot, and trephine biopsy specimens from a total of 34 patients, including nine with AML, 20 with MDS, and five with no evidence of hematologic neoplasia used as reference controls. The patient characteristics are shown in Table 1. The control specimens were obtained from one patient with colon cancer without bone marrow involvement and four patients with anemia in whom the possibility of MDS was excluded. The diagnoses of AML and MDS were reviewed and confirmed by hematopathologists at M. D. Anderson Cancer Center according to World Health Organization criteria [13]. All cases were newly diagnosed and had not undergone any treatment; these cases were chosen randomly from patients evaluated by the Department of Hematopathology at M. D. Anderson Cancer Center during 2007.

$CD34^+$ mononuclear cell enrichment

Bone marrow mononuclear cells were isolated from anticoagulated bone marrow aspirate specimens by density gradient centrifugation using a commercially available system according to the manufacturer's specifications (Miltenyi Biotec, Auburn, CA, USA). A $CD34^+$ cell isolation kit that contained isolation buffer [phosphate-buffered saline (PBS) pH 7.2, 0.5% bovine serum albumin, and 2 mM ethylene diamine tetraacetic acid], a magnetic activated cell separation (MACS) column and separator, and a PhycoErythrin-conjugated CD34 antibody was used for the cell separation. $CD34^+$ cells were labeled with magnetic microbeads, retained in the MACS column while passing through a magnetic field, and eluted with elution buffer after removal from the magnetic field. A small sample of purified $CD34^+$ blasts were diluted with PBS and assessed using an automatic cell counter to detect the cell number and viability (Vi-Cell, Beckman Coulter, Fullerton, CA, USA). A portion of the eluate was used to make cytospin slides; the remainder was subjected to centrifugation at $300\times g$ for 10 min and the supernatant discarded.

Real-time reverse transcriptase polymerase chain reaction

Total RNA was extracted from $CD34^+$ mononuclear cells using the standard Trizol method (Invitrogen, Carlsbad, CA, USA). cDNA was prepared with the Quantitect RT Kit (Qiagen, Valencia, CA, USA) according to the manufac-

Table 1 Clinical characteristics and test results of patients

No.	Age (years)	Sex	Diagnosis	BM Blast %	Cytogenetics	IPSS score	ddCt AA mRNA
1	65	M	Colon cancer staging	0	NA	NA	0.17
2	38	F	Renal carcinoma history, R/O MDS	4	46, XX	NA	0.41
3	57	F	Anemia, R/O MDS	3	46, XX	NA	0.20
4	86	M	Anemia, R/O MDS	1	46, XY	NA	0.55
5	65	M	Anemia, R/O MDS	3	46, XY	NA	0.36
6	70	M	AML, NOS (WHO); AMML, M4 (FAB)	31	complex	NA	0.71
7	41	M	AML, NOS (WHO); AML, M6a (FAB)	22	complex	NA	0.19
8	82	M	AML, NOS (WHO)	33	complex	NA	1.05
9	76	M	AML, NOS (WHO); AML, M0 (FAB)	92	47, XY, + 13	NA	1.72
10	43	M	AML with inv (16) (WHO); AML, M4Eo (FAB)	30	46, XY, t(16;16) (p13.1;q22)	NA	2.31
11	75	M	AML arising from MDS (WHO); M6a (FAB)	27	complex	NA	0.99
12	71	M	AML arising from MDS (WHO); M4 (FAB)	75	46, XY, add (4) (P16), -7	NA	0.96
13	68	M	AML with multilineage dysplasia	21	46, XY, inv (7) (q22q34)	NA	0.87
14	59	F	AML, therapy related (WHO)	23	complex	NA	1.00
15	68	M	RCMD (WHO)	2	46, XY	0	1.1
16	62	M	RCMD (WHO)	0	46, XY	0.5	0.81
17	48	F	RCMD (WHO)	1	46, XX	0	0.67
18	67	M	RCMD (WHO)	3	NA	NA	0.91
19	63	M	RCMD (WHO)	4	complex	1	1.11
20	83	M	RCMD (WHO)	2	46, XY	0	0.20
21	72	M	RCMD RS (WHO)	2	47, XY, + 19	1	1.26
22	65	M	RCMD RS (WHO)	3	46, XY	0	0.33
23	34	F	MDS, therapy related (WHO)	5		2	0.61
24	68	M	MDS, therapy related (WHO)	2	complex	1.5	1.08
25	40	M	MDS, therapy related (WHO)	8	complex	2	0.39
26	79	M	RAEB1 (WHO)	5	46, XY	1	0.76
27	71	M	RAEB1 (WHO)	8	46, XY	0	0.51
28	64	M	RAEB2 (WHO)	18	complex	2.5	0.39
29	67	M	RAEB2 (WHO)	13	46, XY	1.5	0.62
30	77	M	RAEB2 (WHO)	12	45, XY, -Y	1.5	0.44
31	77	M	CMML-1(WHO)	8	46, XY	0.5	0.48
32	70	M	CMML-2 (WHO)	12	45, X, -Y	2	0.98
33	76	M	CMML-2 (WHO)	18	46, XY, I (17) (q10)	2.5	2.17
34	72	M	MDS/MPD, NOS (WHO)	8	46, XY	1	0.84

IPSS International Prognostic Scoring System; *ddCt AA* aurora kinase A gene expression fold change compared to a reference sample, which was read as 1; *NA* not applicable; *MDS* myelodysplastic syndromes; *AML* acute myeloid leukemia; *NOS* not otherwise specified; *WHO* World Health Organization; *AMML* acute myelomonocytic leukemia; *FAB* French-American-British system; *RCMD* refractory cytopenia with multilineage dysplasia; *RS* ringed sideroblasts; *RAEB* refractory anemia with excess blasts; *MPD* myeloproliferative disease; *R/O* rule out; *CMML* chronic myelomonocytic leukemia

turer's instructions. Aurora A cDNA was amplified using Taqman Universal PCR Mastermix (Applied Biosystems, Foster City, CA, USA) and the aurora A assay kit on demand (catalog number Hs01597773_mH, Applied Biosystems). Human β-actin mRNA was used as an internal control, assayed using Taqman Universal PCR Mastermix with concentrations of forward primer (CCCTGGCACC CAGCAC) and reverse primer (GCCGATCCACACG GAGTAC) of 400 nM each and probe (fam-ATCAAGAT CATTGCTCCTCCTGAGCGC-bhq) of 100 nM. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) was performed in an automatic MX3000P real-time PCR thermal cycler (Stratagene, La Jolla, CA, USA). The relative gene expression levels were normalized by β-actin signal to eliminate the differences in total RNA amount and reverse transcription efficiency. Relative RNA level was reported via standard delta delta Ct (δδ Ct). cDNA purified from normal $CD34^+$ hematopoietic progenitor cells was used as calibrator sample (Allcells, LLC, Emeryville, CA, USA).

Immunocytochemical analysis

Immunocytochemical analysis was performed using a cytospin preparation of $CD34^+$ -enriched mononuclear cells according to standard procedures. Antibodies specific for the following proteins were tested: total AA and phosphorylated (at threonine 288, active form) AA (pAA; Abcam, Cambridge, MA, USA), CD34 (Biocare Medical, Concord, CA, USA), and Ki-67 plus caspase 3 prediluted double stain antibody (Biocare Medical). Expression of AA and pAA was arbitrarily classified as low level if less than 50% of blasts were positive and as high level if 50% or more blasts were positive.

Cytogenetics and international prognostic scoring system score

Standard conventional cytogenetics with G-band karyotyping was performed at our institution using bone marrow aspirate specimens as described previously [14]. Fluorescence in situ hybridization was performed if clinically indicated for the diagnoses of AML and MDS. Patients with MDS were assigned an International Prognosis Scoring System (IPSS) score, which is used clinically to predict prognosis in MDS [15]. This score integrates the bone marrow aspirate blast count, cytogenetic risk factors, and severity of cytopenias into a score and classifies patients as low risk (score 0), intermediate risk (0.5–2), or high risk (≥2.5). The IPSS scores are shown in Table 1.

Statistics

To compare the expression level of AA in different groups (AML versus MDS versus control), the Kruskal–Wallis rank sum test was used. To correlate AA mRNA levels with immunocytochemical staining, the Spearman correlation coefficient was computed. For correlations between AA mRNA and blast count, complexity of cytogenetics, or IPSS score, the Spearman correlation coefficient method was used.

Results

AA mRNA expression levels in AML and MDS

Use of RT-PCR revealed that, in five control patients, AA mRNA levels ranged from 0.17 to 0.55. In MDS patients, the median AA mRNA level was 0.99 (range, 0.2 to 2.17). In AML patients, the median AA mRNA level was 0.76 (range, 0.19 to 2.31). Compared with controls, AA mRNA levels were significantly higher in both AML (P=0.01) and MDS patients (P=0.01; Fig. 1). There was no significant difference in AA mRNA levels between AML and MDS patients.

Immunocytochemical stains

To validate that the purified mononuclear cells had numerous blasts, anti-CD34 antibody was used for immunostaining. Figure 2a, b shows that most (~80%) of the mononuclear cells isolated from control (Fig. 2a) or MDS patients (Fig. 2b) were blasts immunoreactive with CD34.

Immunostains for total AA showed weak to no staining in normal control specimens (Fig. 2c) and stronger cytoplasmic staining in MDS patient specimens (Fig. 2d). Similarly, immunostains for pAA showed weak to no stain in normal controls (Fig. 2e) and stronger cytoplasmic staining in MDS cases (Fig. 2f). Ki-67 stain highlighted a small proportion of proliferative $CD34^+$ cells in both normal control and MDS cases, and no statistically significant difference existed between the two groups (dark brown nuclear stain, Fig. 2g). Active caspase 3 stained the cells undergoing apoptosis red. Only a small number of cells stained red, and no statistically significant difference existed between the control and MDS groups (Fig. 2h).

Correlation of AA mRNA and protein in MDS

AA mRNA levels correlated with total AA protein levels, as assessed by immunocytochemical staining in MDS patients (r=0.78, P=0.002; Fig. 3). Furthermore, AA mRNA levels correlated with active phosphorylated AA protein levels, as assessed by immunocytochemical staining in MDS patients (P=0.02; not shown).

Conventional cytogenetic results in MDS patients

Table 1 shows the demographics and clinical characteristics of all subjects. Table 2 shows the detailed cytogenetic changes in MDS patients. Among the 20 MDS patients, half had a normal karyotype, and the others showed various abnormalities, including five patients with complex karyotypes (three or more abnormalities). Two patients had abnormalities involving chromosome 20, where the gene for AA is located (20q13.2), one with monosomy 20 and the other with del(20)(q11.2q13.3).

Correlation of AA mRNA with blast counts and viability, cytogenetic risk factors, and IPSS score

No significant correlation was found in MDS patients between AA mRNA levels and bone marrow blast counts (P=0.50), blast cell viability (P=0.38), cytogenetic risk factors (P=0.45), or IPSS score (P=0.51) (Table 3).

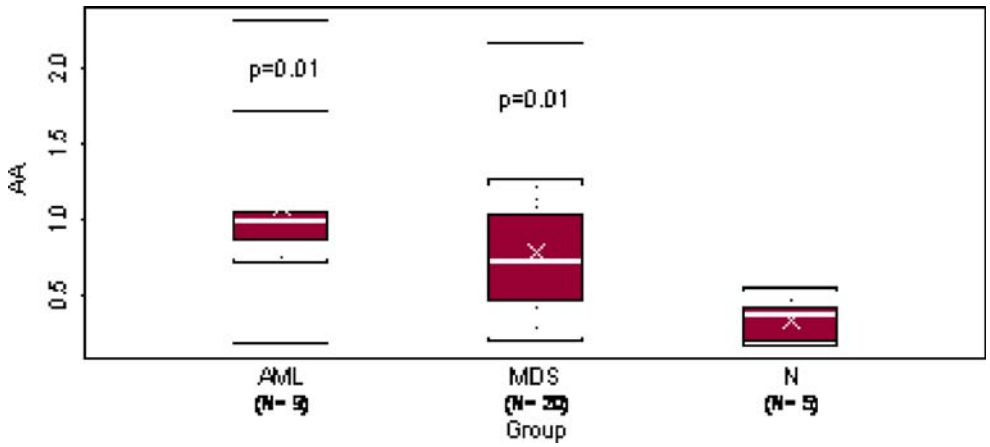

Fig. 1 AA mRNA levels in both AML and MDS patients

Discussion

Our study showed deregulated aurora A expression in $CD34^+$ blasts cells isolated from patients with untreated myelodysplastic syndromes and acute myeloid leukemia. We found that AA mRNA was expressed at significantly higher levels in both AML and MDS patients than in controls. Furthermore, AA mRNA expression correlated strongly with both total AA and phosphorylated (active) AA protein, as assessed by immunocytochemical staining of $CD34^+$ cells. Although AA protein is known to localize in centrosomes and mitotic spindles at the G_2 to M phase transition, immunocytochemical staining has shown that most cells are positive for AA in a diffuse, cytoplasmic pattern, regardless of their cell cycle status [8, 16, 17]. The current study revealed dual cytoplasmic and nuclear staining for AA in AML and MDS, but the staining patterns were different: the cytoplasmic staining was diffuse, whereas the nuclear staining had a punctate pattern. To our knowledge, no previous study has investigated AA expression in MDS or has correlated nuclear or cytoplasmic staining with mRNA levels.

Our results showed good correlation between AA mRNA and cytoplasmic AA protein levels, further strengthened by the strong correlation found between the AA

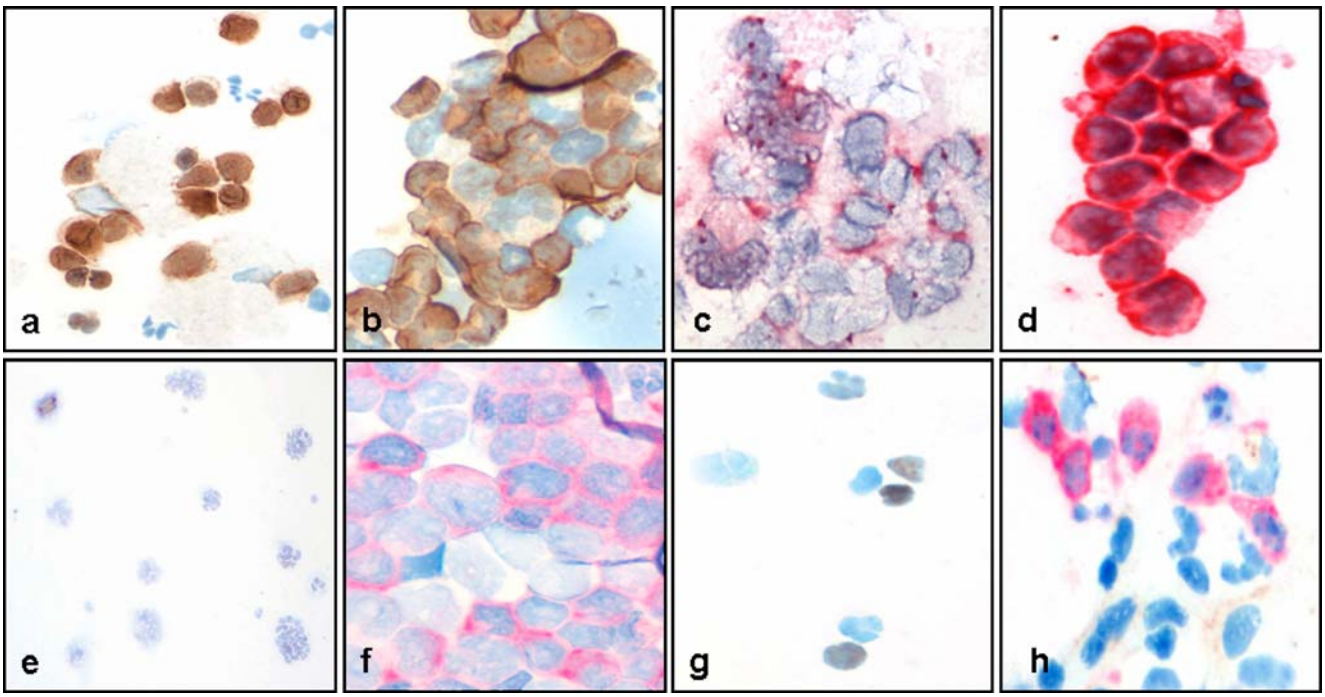

Fig. 2 Immunocytochemical stains. Mononuclear $CD34^+$ cells isolated from control (**a**) or MDS patients (**b**); total AA in normal control specimens (**c**) and in MDS patient specimens (**d**); pAA in normal controls (**e**) and in MDS cases (**f**); proliferative Ki-67^+ cells (**g**) and apoptotic active caspase 3^+ cells (**h**) in MDS cases

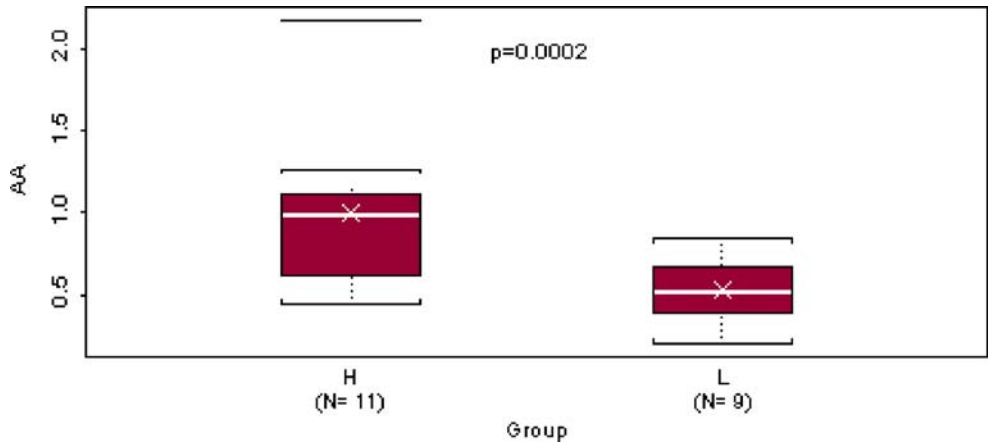

Fig. 3 AA mRNA levels correlated with total AA protein levels

mRNA and cytoplasmic phosphorylated AA protein. Our findings are consistent with those in a recently published study showing high-level expression of AA in $CD34^+$ blasts in AML patients [12].

Table 2 Detailed cytogenetic profiles in MDS patients

No.	Diagnosis	Cytogenetics
1	RCMD (WHO)	46, XY
2	RCMD (WHO)	46, XY
3	t-MDS (WHO)	45, XY, 6q-, -7, 12p-
4	RCMD (WHO)	46, XY
5	t-MDS (WHO)	45,XY,del(5)(q22q35),dic(6;21)(p25;p11.2)[18] 45,XY,del(5)(q22q35),del(6)(q13q25),del(7)(q22q34),-20[2]
6	RCMD (WHO)	NA
7	RCMD (WHO)	46,XY,del(5)(q22q35),del(11)(q23)[6] 46,XY,del(5)(q22q35),del(11)(q23),del(20)(q11.2q13.3)[9]
8	RCMD RS (WHO)	47, XY, + 19
9	RCMD RS (WHO)	46, XY
10	RAEB1 (WHO)	46, XY
11	RAEB1 (WHO)	46, XY
12	RCMD (WHO)	46, XY
13	RAEB2 (WHO)	43,XY,del(5)(q13q35),add(11)(q23),-13,psu dic(15;22)(p12;p12),-18[16] 44,idem, + psu dic(15;22)[2]
14	MDS/MPD, NOS (WHO)	46, XY
15	CMML (WHO)	46, XY, I (17) (q10)
16	RAEB2 (WHO)	46, XY
17	RAEB2 (WHO)	45, XY, -Y
18	CMML-1	46, XY
19	t-MDS	45, XY, t(3;8) (q26.2;q24.1), -7
20	CMML-2	45, X, -Y

MDS myelodysplastic syndromes; *NOS* not otherwise specified; *WHO* World Health Organization; *RCMD* refractory cytopenia with multilineage dysplasia; *RS* ringed sideroblasts; *RAEB* refractory anemia with excess blasts; *MPD* myeloproliferative disease; *R/O* rule out; *CMML* chronic myelomonocytic leukemia

Our results did not show a significant correlation of AA mRNA with bone marrow blast counts, viability of $CD34^+$ blast cells, cytogenetic abnormalities, IPSS score, proliferation index assessed by Ki-67 stain, or apoptotic activity assessed by active caspase 3 staining. Several hypotheses may explain these findings. First, AA may be important in the initiation of MDS but not in its progression. If AA plays an important role in early-stage MDS and its level remains high in later stages, this level may remain high regardless of disease severity, a theory supported by our results. The exact mechanism for the pathogenesis of MDS is not known, but a "multifactorial and multistep" theory is well accepted [18], which states that genetic damage or instability occurs early in the development of the disease. The genetic damage could be hereditary, as in pediatric MDS, or acquired from irradiation, chemotherapy, immunomodulation, or inflammation. The fact that most adult MDS patients are elderly (mean age close to 70 years) suggests that environmental factors play an important role.

Second, MDS is a heterogeneous combination of syndromes with various pathogenic pathways. Our limited number of study subjects with various subtypes of MDS may have made identification of correlations more difficult. Third, AA levels may be associated with genetic changes in MDS, although our current studies did not detect this association. Conventional cytogenetic analysis is very useful for studying genomic changes but is neither specific

Table 3 Correlation analysis of AA mRNA in MDS patients

	AA mRNA	
	Coefficient	*P* value
Blast.count	−0.15	0.50
Blast.viability	0.21	0.38
Cytogenetics	0.18	0.45
IPSS	0.16	0.51
Total.cell.viability	−0.23	0.36

nor adequately sensitive to detect changes that probably occur at the molecular level in MDS. Among the 20 MDS patients that we assessed, either the whole chromosome 20 or the locus where the AA gene is located (20q13.2) was deleted in two. However, the AA mRNA levels were paradoxically higher in these two patients than were levels in the controls. It seems likely that genetic events that cannot be detected by conventional cytogenetic methods led to AA overexpression in these two patients, although abnormalities at the transcriptional and translational levels also may occur.

Our finding that AA mRNA levels in AML patients are significantly higher than in the controls agrees with those of other studies [11, 12]; however, AA mRNA levels in AML patients were not significantly different from those in MDS patients. The up-regulation of AA in both AML and MDS patients suggests the importance of AA in the pathogenesis of myeloid neoplasms and as a potential target for drug development. Some AA inhibitors have demonstrated promising antiproliferative activity in in vitro studies and are being explored as potential anticancer agents in clinical trials [12].

One possible limitation of our study was the unbalanced male-to-female ratio in both the AML and MDS groups (men to women, 8:1 in the AML group and 18:2 in the MDS group). It is known that both sexes have similar incidences of AML and MDS. The uneven sex ratios were not caused by selection bias because our patient selection was based on whether patients had received previous therapy.

In summary, we found increased AA expression in $CD34^{+}$ cells derived from both AML and MDS patients, with AA mRNA levels correlating to protein levels but not to clinicopathologic or cytogenetic findings.

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

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