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Brief communication

MEL1S, not MEL1, is overexpressed in myelodysplastic syndromes patients with t(1;3)(p36;q21)

Zhijian Xiao [a,b,*], Meirong Zhang [a], Xuping Liu [c], Yue Zhang [b], Lin Yang [b], Yushu Hao [a]

[a] *Department of Clinical Hematology, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, PR China*
[b] *State Key Laboratory of Experiment Hematology, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, PR China*
[c] *Laboratory of Cytogenetics, Institute of Hematology and Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, PR China*

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Abstract

Balanced chromosomal translocations rarely occur in myelodysplastic syndromes (MDS). We describe here in three further Chinese patients with myelodysplastic syndromes (MDS) whose cytogenetic analysis showed t(1;3)(p36;q21). We detected the expression pattern of MEL1 and MEL1s in BM of two healthy subjects and the three patients, and found that the expression of MEL1s was overexpressed in MDS patients with t(1;3)(p36;q21). Our findings combined previous observations reported in literature support that MDS patients with t(1;3)(p36;q21) should be a new specific subset of MDS. Imbalance of a complete MEL1 message with a PR domain and a short MEL1 message lacking a PR domain (MEL1S) might be involved in the pathogenesis of these patients.

Keywords: Myelodysplastic syndromes; t(1 ;3)(p36 ;q21); MEL1; MEL1S

Balanced chromosomal translocations rarely occur in myelodysplastic syndromes (MDS). In the mid-1980s, Moir et al. [1] first reported the t(1;3)(p36;q21) in three cases of MDS. Until now, 18 MDS patients with t(1;3) have been reported [2]. Clinicopathological features of t(1;3)(p36;q21) positive MDS included normal or elevated platelet counts, hyperplasia with dysplasia of megakaryocytes, poor response to chemotherapy, and poor prognosis.

The MEL1 gene, which was mapped to human chromosome 1p36, was originally isolated as the gene that was transcriptionally activated by t(1;3)(p36;q21) in acute myeloid leukemia [3]. MEL1 gene encodes two types of transcripts, full-length MEL1 and short-form MEL1s [4]. The MEL1 gene that retains the PR domain is highly homologous to MDS1/EVI1, whereas the MEL1s gene is an alternatively spliced transcript of MEL1 gene, which lacks the PR domain as observed in EVI1. Mochizuki et al. [3] reported that MEL1 is expressed in leukemia cells with t(1;3) but not in other cell lines or bone marrow (BM), spleen, and fetal liver, suggesting that MEL1 is specifically in the t(1;3)(p36;q21)-positive MDS/AML. The same group [4] reported that the 150 kDa translation product of MEL1S was detected mainly in the t(1;3)(p36;q21)-positive AML cells by immunoblot analysis. Moreover, overexpression of MEL1S blocked granulocytic differentiation induced by G-CSF in IL-3-dependent murine myeloid L-G3 cells, while MEL1 could not block the differentiation, overexpression of MEL1S could be one of the causative factors in the pathogenesis of t(1;3) AML has be

* Corresponding author. Tel.: +86 22 27307938x3184; fax: +86 22 27306542.
E-mail address: zjxiao@hotmail.com (Z. Xiao).

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Table 1
Major clinical and hematologic findings of the patients

	Case 1	Case 2	Case3
Sex/age (y)	M/70	M/59	F/51
Diagnosis	RAEB-II	RCMD	RCMD
Prior exposure history	No	No	No
Peripheral blood			
Hemoglobin (g/l)	61	60	71
MCV (fl)	103.9	127.0	111.0
WBC ($\times 10^9$/l)	5.0	5.15	4.3
ANC ($\times 10^9$/l)	2.15	2.88	2.28
Platelets ($\times 10^9$/l)	214	169	424
Bone marrow			
Cellularity	Normocellular	Increase	Increase
Dyserythropoiesis	Present	Present	Present
Ringed sideroblasts (%)	15%	1%	8%
Megakaryocytes			
Number	Increased	Increased	Increased
Dysmegakaryopoisis	Marked	Marked	Marked
Dysgranolopoiese	Present	Present	Present
Karyotype (no. of karyotype)	47, XY, t(1;3)(p36;q21),+13[6]/45–46, XY, t(1;3)(p36;q21), −13 [CP4]	46, XY, t(1;3)(p36;q21)[8]/44–45, XY, t(1;3)(p36;q21), −14, −20, −21 [CP3]	46, XX, t(1;3)(p36;q21) [11]/46, XX [4]
Evolution (month)	AML-M4 (15)	Stable	Stable
Survival (months from diagnosis)	16	21+	6+

suggested [4]. In order to distinguish the expression pattern of MEL1 and MEL1s, Lahortiga et al. [5] designed two sets of primers specific for cMEL (MEL1 plus MELs) and MEL1, respectively. Using the primers, they analysed the expression of MEL1 and cMEL by RT-PCR separately on CD34 + cells, bone marrow (BM) and peripheral of a healthy donor, normal uterus, and in BM of a patient with MDS (RAEB-2). They found that in normal BM, expression of cMEL was stronger than the expression of only MEL1, and in the patient sample, both amplification had the same intensity, suggesting that MEL1s could be underexpressed.

We describe herein three further Chinese patients with myelodysplastic syndromes (MDS) whose cytogenetic analysis showed t(1;3)(p36;q21) (Table 1 and Fig. 1A). The hematologic findings in our cases confirmed the previous such patients observations reported in English literatures that this translocation is associated with macrocytic anemia, normal or elevated platelet counts, hyperplasia with dysplasia of megakaryocytes, and poor prognosis, the majority of patients transform into AML-M1 or -M4 type with a short preleukemic phase. Using the same primers and PCR conditions, we detected the expression pattern of MEL1 and MEL1s in BM of two healthy subjects and the three patients, we found that the expression of cMEL was a little stronger than the expression of only MEL1 (cMEL:MEL1 were 1:1.35 and 1:1.15, respectively) in normal BM (Fig. 1B), but the expression of cMEL was significantly stronger than the expression of only MEL1 (cMEL:MEL1 were 1:2.14 and 1:2.23, respectively) in case 1 and case 2, and in case 3, only the expression of MEL1s was detected (Fig. 1B),

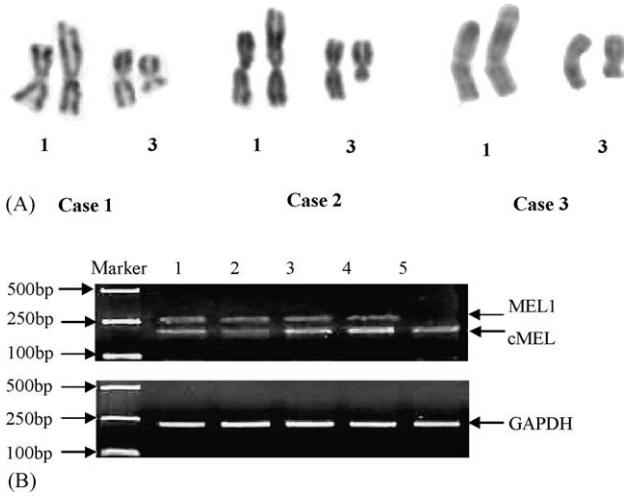

Fig. 1. (A) Partial karyotypes of the patients showing t(1;3)(p36;q21). (B) Expression of MEL1 and cMEL. Bone marrow mononuclear cells from healthy subjects and MDS patients with t(1;3)(p36;q21) were separated by centrifugation with the Ficoll–Hypaque (Union Stem Cell and Gene Engineering Company; China). Total RNA was extracted using the TRIzol reagent (Invitrogen Life Technologies, Carlsbad, CA). 2.5 μg RNA was used to synthesize cDNA using the Superscript First-Strand Synthesis System (Invitrogen Life Technologies, Inc.) in a final volume of 50 μl of random primer (GIBCOBRL). RT-PCR was performed using the primers and the conditions as reported [5]. Transcript of the GAPDH gene were used as a control. PCR products were recovered using QIA quick Gel Extraction Kit (QIAGEN) and sequenced using BigDye terminator cycle sequencing ready reaction Kit (PE). Line 1 and line 2, two healthy subjects; line 3, case 1; line 4, case 2; line 5, case 3.

suggesting MEL1s was overexpressed in MDS patients with t(1;3)(p36;q21).

In conclusion, our findings combined previous observations reported in literature support that MDS patients with t(1;3)(p36;q21) should be a new specific subset of MDS. These patients showed macrocytic anemia, normal or elevated platelet counts, hyperplasia with dysplasia of megakaryocytes, and poor prognosis. Imbalance of a complete MEL1 message with a PR domain and a short MEL1 message lacking a PR domain (MEL1S) might be involved in the pathogenesis of these patients.

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