Marked upregulation of Survivin and Aurora-B kinase is associated with disease progression in the myelodysplastic syndromes

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ABSTRACT

Background
Myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis. Survivin is a member of the inhibitor of apoptosis family and suppresses apoptosis. Survivin also functions as a subunit of the chromosomal passenger complex for regulating mitosis with Aurora-B. Survivin and Aurora-B play an important role in maintaining genome stability. The aim of this study was to determine the role of Survivin and Aurora-B kinase in disease progression and prognosis of myelodysplastic syndromes.

Design and Methods
We evaluated the expression levels of these two genes in CD34$^+$ cells prepared from 64 patients with myelodysplastic syndrome or leukemic blasts from 50 patients with *de novo* acute myeloid leukemia using quantitative real-time PCR.

Results
Survivin and Aurora-B expression levels were highly correlated with the type of myelodysplastic syndrome, were much higher in refractory anemia with excess blasts-1, refractory anemia with excess blasts-2, and secondary acute myeloid leukemia following myelodysplastic syndrome than in normal control, and increased during disease progression. There was a significant correlation between these expression levels and the International Prognostic Scoring System. Interestingly, these levels were remarkably higher in patients with secondary acute myeloid leukemia following myelodysplastic syndromes than in those with *de novo* acute myeloid leukemia.

Conclusions
This is the first report showing that high levels of Survivin and Aurora-B kinase expression in CD34$^+$ cells are distinctive molecular features of high-risk myelodysplastic syndromes and secondary acute myeloid leukemia following myelodysplastic syndrome. Marked upregulation of Survivin and Aurora-B kinase may contribute to genetic instability and disease progression of myelodysplastic syndromes. Our data may explain why patients with high-risk myelodysplastic syndromes frequently show complex chromosomal abnormality.

Key words: Survivin, Aurora-B kinase, myelodysplastic syndromes, MDS.

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Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by peripheral cytopenias despite normal or hypercellular bone marrow (BM)[1] which could evolve into an overt acute myeloid leukemia (AML). Underlying excessive apoptosis or an apoptosis-associated phenotype of BM cells, including clonal CD34 precursors, have been found to be a possible explanation for the ineffective hematopoiesis, especially in early cases of myelodysplastic syndrome.[2-5] Several prognostic factors have been reported to be involved in disease progression of MDS.[6-9] However, specific genes that contribute to MDS progression are still not completely understood.[10]

Deregulation of programmed cell death contributes to leukemogenesis and to blast cell survival. Cells resistant to apoptosis are prone to accumulate genetic aberrations, acquire the capacity to survive independently from growth factor stimulation and escape from immune system control.[11] Survivin, a member of the inhibitor of apoptosis (IAP) family, is a bifunctional protein that acts as a suppressor of apoptosis[12] and plays a central role in mitosis.[13,14] Survivin is transiently expressed during embryonic development but is barely detectable in normal, differentiated adult tissue.[12] However, Survivin is over-expressed in a number of different tumor tissues indicating that it has a role in carcinogenesis.[12,15] A high level of Survivin expression correlates with poor outcome in a variety of solid tumors.[16-18] Similarly, in malignant hematologic diseases, overexpression of Survivin correlates with reduced overall survival in patients with T-cell leukemia[19] as well as those with diffuse large B-cell lymphoma.[20] However, it remains unclear whether Survivin expression plays an important role during MDS progression.

Besides its role as an IAP, Survivin functions as a subunit of the chromosomal passenger complex (CPC) and together with the other CPC subunits such as Aurora-B, INCENP, and Borealin regulates cell division.[13,21-24] The activity of Aurora-B kinase is stimulated by Survivin binding and phosphorylation.[23] Aurora-B is the enzymatic core of the complex, whereas Survivin and INCENP dictate the timing and localization of the kinase activity.[13] CPC corrects attachment errors between chromosomes and the mitotic spindle, regulates the quality-control of mitotic spindle checkpoint, and ensures the correct completion of cytokinesis.[25,26] In solid tumor cells, high expression of Aurora-B and INCENP, as well as that of Survivin, has been observed.[27] However, no studies have reported the impact of abnormal expression of Survivin and Aurora-B kinase in $CD34^+$ cells during the clinical course of MDS. The aim of our study was to determine the clinical significance of Survivin and Aurora-B kinase expression in MDS and s-AML. We have demonstrated for the first time that high levels of Survivin and Aurora-B kinase expression are distinctive molecular features of high-risk MDS and s-AML. Marked upregulations of Survivin and Aurora-B Kinase may contribute to genetic instability and may be involved in disease progression of MDS.

Design and Methods

Patients

After obtaining informed consent from patients and approval from the institutional review board of The University of Fukui Hospital, bone marrow (BM) samples from 114 patients (64 MDS, 50 *de novo* AML) were tested for Survivin and Aurora-B kinase expression. Of the 64 MDS patients, 36 were male and 28 female; median age was 71 years (range 33-87 years); there were 11 patients with refractory anemia (RA), 3 with RA with ringed sideroblasts (RARS), 9 with refractory cytopenia with multilineage dysplasia (RCMD), 2 with RCMD with ringed sideroblasts (RCMD-RS), 10 with refractory anemia with excess of blasts-1 (RAEB-1), 11 with RAEB-2, and 18 with secondary AML (s-AML) that had evolved from MDS. Patients with *de novo* AML were classified as M0 (n=4), M1 (n=7), M2 (n=12), M3 (n=7), M4 (n=8), M5 (n=6), M6 (n=4) and M7 (n=2). Cytogenetic analysis identified the karyotype of t(8;21) (n=5), t(15;17) (n=7), inv(16) (n=4), –5/del(5) (n=2), -7/del(7) (n=3), $^+$21(2) and normal (n=11). Complex karyotypes were found by cytogenetic analysis in 15% of patients with *de novo* AML. Eight samples from age-matched healthy volunteers were used as controls.

Sample collection and $CD34^+$ cell enrichment

Bone marrow mononuclear cells were isolated by density gradient centrifugation using HISTOPAQUE 1077 (Sigma). Cells were washed twice in magnetic-activated cell separation (MACS) buffer (phosphate-buffered saline supplemented with 0.5% bovine serum albumin and 2 mM ethylenediaminetetraacetic acid, EDTA). After incubation with immunoglobulin (Ig) Fc receptor blocking reagent and hapten-conjugated anti-CD34 antibody (Miltenyi Biotec, Bergisch Gladbach, Germany) for 15 min at 4°C, cells were washed twice and resuspended in 500 μL MACS buffer. Magnetically labeled cells were passed through a positive selection column (LS column; Miltenyi Biotec) in a magnetic field. After 2 column washes, the retained cells were eluted with 1 mL MACS buffer. The eluate was passed through a fresh column, washed twice, and eluted in 500 μL MACS buffer. Average number of isolated $CD34^+$ cells from low-risk MDS was 2.4×10^5. Purity of CD34 cells was determined by flow cytometry and was 85-99% with no difference in purity between samples from different patient and control groups. Representative FACS plot for CD34 expression are shown in *Online Supplementary Figure S1*.

Real-time quantitative polymerase chain reaction (RQ-PCR)

Total RNA was isolated using BIO ROBOT EZ1 (Qiagen, Hilden, Germany). The amount of RNA was measured by photometry. Reverse transcription of total RNA was performed using the High Capacity cDNA Reverse Transcription kit (Applied Biosystems, Foster City, CA, USA). Quantitative PCR was performed using TaqMan real-time PCR methods. The StepOne Plus PCR System and TaqMan Gene Expression Assays (Applied Biosystems, Foster City, CA, USA) were used for the quantification of all genes according to the manufacturer's instructions. The assay IDs were: BIRC5 (Survivin) Hs03043574_m1; Aurora-B, Hs00177782_m1. GAPDH, Hs02786624_g1. The relative mRNA expression of Survivin or Auroa-B kinase was calculated using the comparative threshold method (Ct-method) with GAPDH for normalization.[28] Human leukemia HL-60 cells were used as positive controls for Survivin and Aurora-B kinase expression. The Survivin or Aurora-B kinase expression level in normal CD34 cells from 7 healthy donors was investigated. Measurable amounts of Survivin or Aurora-B kinase were found in all CD34 samples isolated from healthy controls. Mean value of expression level of Survivin or Aurora-B kinase in normal CD34 cells was defined as 1. All experiments were performed in triplicate.

Statistical methods

Mann-Whitney U tests were used to estimate the statistical significance of the differences observed between groups. $P<0.05$ was considered statistically significant. The correlation between Survivin or Aurora-B kinase expression and IPSS score was investigated by means of Spearman's correlation coefficient.

Results

Survivin and Aurora-B kinase expression in refractory anemia and refractory cytopenia with multilineage dysplasia

The degree of Survivin expression was higher in patients with RA and RCMD than in controls (Figure 1A and B). The median expression of Survivin was 1.5-fold higher in CD34 cells isolated from MDS RA patients than in normal CD34 cells (Figure 1B). The RCMD patients have significantly higher levels of Survivin transcript than RA patients (P=0.042) (Figure 1B). This value is significantly higher not only than the value in RA patients, but also than that in normal controls (P=0.011). In addition, we investigated the expression of Aurora-B kinase in RA and RCMD (Figure 1C and D). RA patients show 1.3-fold higher levels of Aurora-B kinase transcript than normal controls. The RCMD patients showed an even higher expression (2.3-fold) of Aurora-B kinase (Figure 1D). The median value of expression (2.3-fold) of Aurora-B kinase in RCMD patients is significantly higher not only than the value in normal controls (P=0.031) but also than that in RA patients (P=0.049) (Figure 1D). In addition, patients with RARS (n=3) and RCMD-RS (n=2) show increased expression of Survivin (1.7-fold and 3.3-fold, respectively) and Aurora-B kinase (1.5-fold and 2.4-fold, respectively) compared to that in normal controls. However, our study included only a small number of patients with RARS with RCMD-RS, and more samples are required to confirm this.

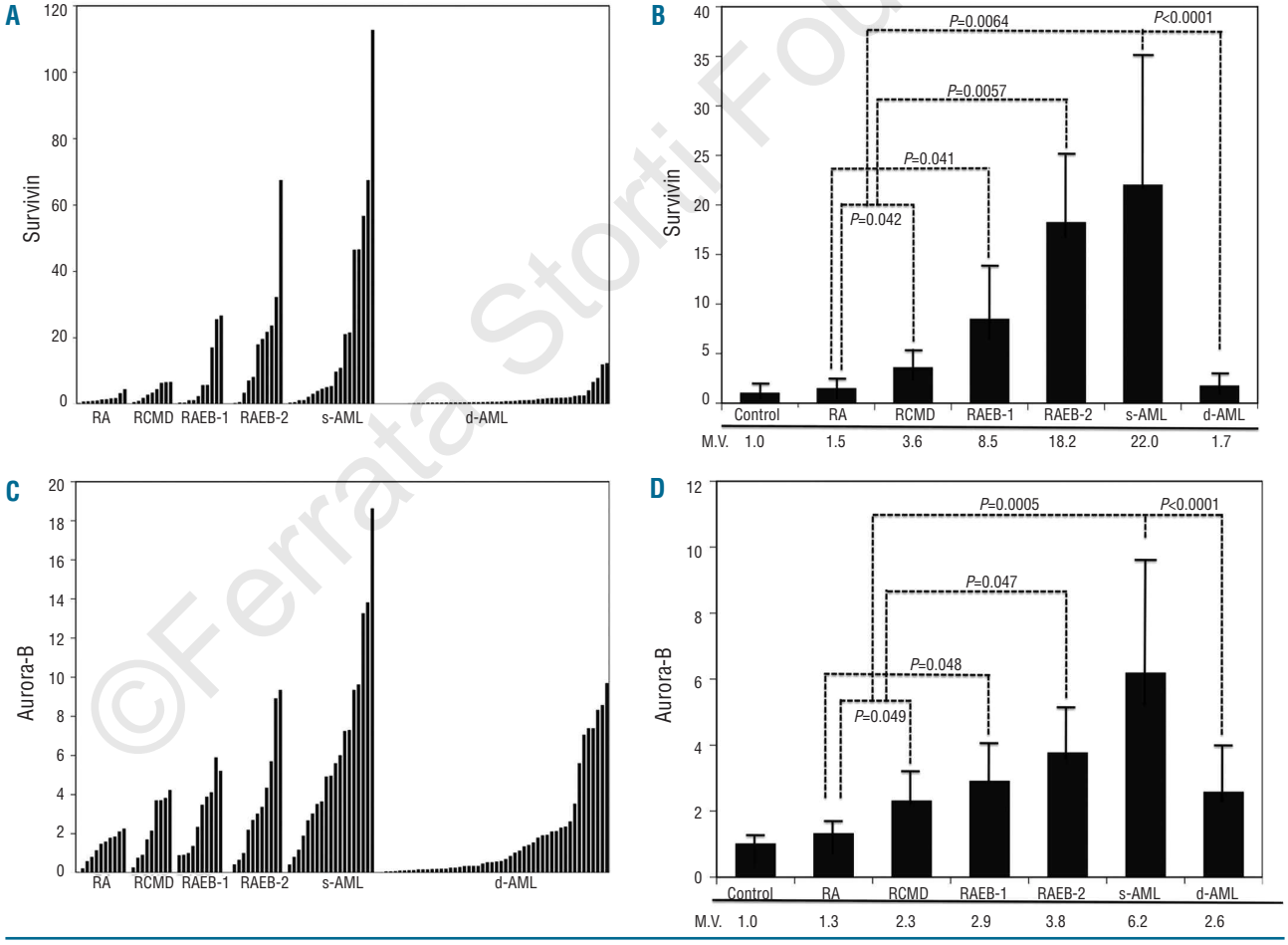

Figure 1. Expression of Survivin and Aurora-B kinase in MDS, s-AML and *de novo* AML (d-AML). (A) Survivin expression evaluated by real-time quantitative polymerase chain reaction (RQ-PCR) in the samples from patients with RA, RCMD, RAEB-1, RAEB-2, secondary acute myeloid leukemia (s-AML) and *de novo* AML (d-AML). CD34 cells were isolated using a Mac bead column as described in Design and Methods. (B) Mean values of Survivin expression evaluated by RQ-PCR in the samples from normal volunteers, RA, RCMD, RAEB-1, RAEB-2, s-AML and *de novo* AML (d-AML). M.V.: mean expression value. (C) Aurora-B kinase expression evaluated by RQ-PCR in the samples from patients with RA, RCMD, RAEB-1, RAEB-2, s-AML and *de novo* AML (d-AML). CD34 cells were isolated using a Mac bead column as described in *Design and Methods* section. (D) Mean values of Aurora-B expression evaluated by RQ-PCR in the samples from normal volunteers, RA, RCMD, RAEB-1, RAEB-2, s-AML and *de novo* AML (d-AML). M.V.: mean expression value.

Survivin and Aurora-B kinase expression in RAEB-1, RAEB-2 and in s-AML

Survivin expression was markedly increased in the samples obtained from patients with RAEB-1 and RAEB-2 (Figure 1A). The median expression of Survivin mRNA was 8.5-fold higher in CD34 cells from RAEB-1 patients and 18.2-fold higher in CD34 cells from RAEB-2 patients than in normal CD34 cells (P=0.038 and P=0.0046, respectively) (Figure 1B). These values are significantly higher not only than the values in normal controls but also than those in RA and RCMD patients (Figure 1B). Furthermore, we examined the levels of Survivin in the samples isolated from 18 patients with s-AML. The median expression of Survivin mRNA was 22-fold higher in leukemic blast cells from s-AML patients than in normal controls (P=0.0057) (Figure 1B). These values are significantly higher than those in the combined group with RA and RCMD (P=0.0064) (Figure 1B). In addition, we determined the expression of Aurora-B kinase in RAEB-1, RAEB-2, and s-AML. Aurora-B kinase showed higher expression preferentially in patients with RAEB-1, RAEB-2, and s-AML than in patients with RA and RCMD (Figure 1C). These differences in Aurora-B kinase expression were statistically significant (Figure 1D). The expression profiles of Aurora-B kinase were similar to those of Survivin.

Cytogenetic analysis revealed complex karyotypes in 39% of patients in the combined group of RAEB-1, RAEB-2, and s-AML. In these patients, mean values of expression of Survivin and Aurora-B kinase were significantly higher (3.6-fold and 2.3-fold, respectively) than those in patients with normal karyotype (P<0.003 and P<0.01).

Correlations between the expression levels of Survivin or Aurora-B kinase and the IPSS Score in myelodysplastic syndromes

Spearman's correlation coefficient analysis in all MDS patients showed that there was a strong correlation between the expression levels of Survivin and the risk categories of the patients defined according to the IPSS (P<0.0001) (Figure 2A). Expression levels of Aurora-B kinase in MDS patients were also strongly correlated with the IPSS risk categories (P=0.0002) (Figure 2B).

Survivin and Aurora-B kinase expression in de novo acute myeloid leukemia

We investigated the expression of Survivin in blast cells isolated from 50 patients with *de novo* AML. Unexpectedly, the level of Survivin expression in *de novo* AML was lower than that in MDS (Figure 1A and B). The median expression of Survivin mRNA was 1.7-fold higher than that in normal CD34 cells (Figure 1B); however, this is not statistically significant. Median expression of Survivin in de novo AML was significantly lower than that in s-AML (P<0.0001) (Figure 1B). Comparison of Survivin expression between patients with normal karyotype and those with complex karyotypes showed no statistical difference. In addition, no significant association was observed between Survivin expression and specific chromosomal abnormalities, including t(8;21), t(15;17), inv16, +21, –5/del(5q) and –7/del(7q). There was no statistical difference in Survivin expression levels between French-American-British (FAB) classified subgroups. Median expression of Aurora-B kinase in *de novo* AML was significantly lower than that in s-AML (P<0.0001) (Figure 1D). No correlation was observed between Aurora-B expression and specific cytogenetics. No significant difference was observed in Aurora-B expression among various FAB groups.

Correlation between expression levels of Survivin and Aurora-B kinase in patients with myelodysplastic syndromes and s-AML

There may be some correlation between the expression levels of Survivin and Aurora-B kinase in each patient with MDS and s-AML (*Online Supplementary Figure S2*). Both Survivin and Aurora-B kinase are subunits of the chromosomal passenger complex (CPC) which plays an important role during mitosis as the mitotic spindle checkpoint.[25,26,29] We performed regression analysis to examine whether there is any correlation between the expression levels of Survivin and Aurora-B kinase. Our results showed that expression of Aurora-B kinase was significantly correlated

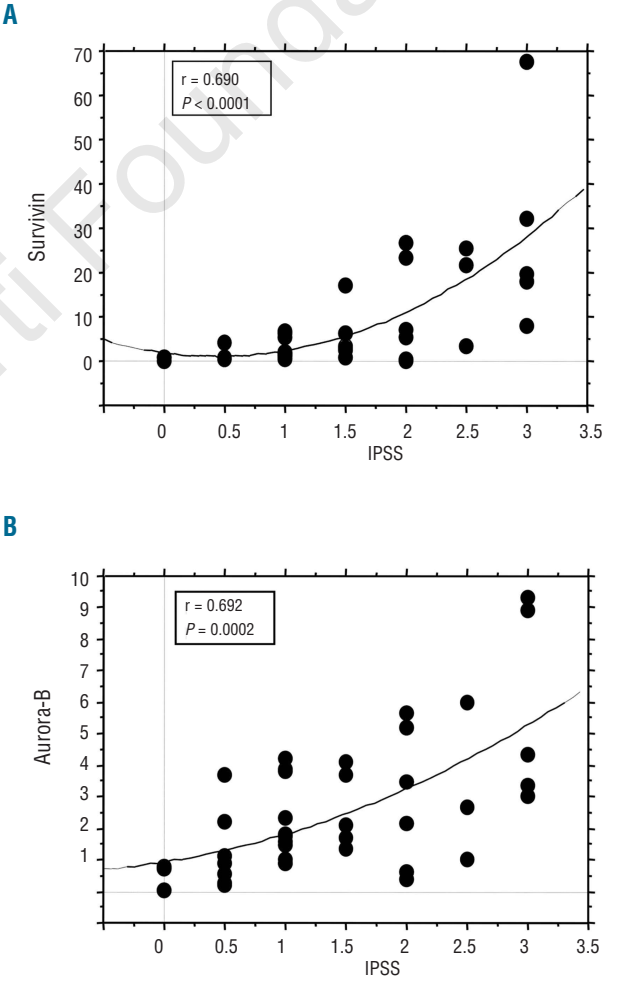

Figure 2. Correlations between the levels of Survivin or Aurora-B kinase expression and the IPSS Score in MDS. (A) Survivin expression was correlated with IPSS score in patients with MDS. R = 0.690 and P<0.0001 indicates a significant correlation between the 2 parameters (Survivin expression and IPSS score). (B) Aurora-B kinase expression was correlated with IPSS score in patients with MDS. R = 0.692 and P=0.0002 indicates a significant correlation between the 2 parameters (Aurora-B kinase expression and IPSS score). The correlation between the Survivin or Aurora-B kinase expression and IPSS was evaluated by the Spearman's correlation coefficient.

with Survivin expression in MDS and s-AML (Figure 3). However, there was no such correlation in patients with *de novo* AML (*data not shown*).

Follow up of Survivin and Aurora-B kinase expression during myelodysplastic syndromes progression

Survivin and Aurora-B kinase expression levels were evaluated in 4 MDS patients at different time points during clinical follow up. These 4 patients included one patient with RA, one patient with RCMD and 2 patients with RAEB-1 (Figure 4 and Table 1). Patient 1 with RCMD and Patient 2 with RA were treated with only supportive therapies such as transfusion. These patients subsequently developed acute leukemia. These 2 patients showed a marked increase in the levels of Survivin transcript expression at disease progression. At first observation, Patient 2 showed del(7)(q22q36) as a cytogenetic abnormality (Table 1). At the time of leukemic progression, a marked increase (58-fold) in Survivin expression was observed (Figure 4) with additional cytogenetic abnormalities such as del(5)(q23q34) and der(17)t(5;17) (Table 1). Patient 3 with RAEB-1 was treated with low-dose cytarabine. However, no improvement was observed. This patient developed acute leukemia with an apparent increase in expression of Survivin and Aurora-B (Figure 4). Patient 4 with RAEB-1 developed acute leukemia. At that time, this patient was treated with combination chemotherapy including cytarabine and aclarubicin. Survivin and Aurora-B kinase returned to normal levels in one s-AML patient who achieved a complete remission; however, after five months this patient relapsed. High levels of Survivin were subsequently detected (Figure 4). These data indicate that longitudinal monitoring of Survivin and Aurora-B kinase levels may reflect disease status in MDS patients.

Discussion

To date there have been no studies that have examined whether expression of Survivin and Aurora-B kinase is increased in CD34$^+$ cells isolated from MDS patients during disease progression. In this study, we measured Survivin and Aurora-B kinase expression in a series of MDS patients and *de novo* AML patients using a sensitive RQ-PCR method. Our data show that expression of Survivin and Aurora-B kinase are directly correlated with the type of MDS, being higher in a statistically significant manner in RA with respect to RAEB-2 and to s-AML. In addition, we found that expression of Survivin or Aurora-B kinase is strongly correlated with IPSS, the risk scoring system for MDS. Interestingly, we found that levels of Survivin and Aurora-B kinase were markedly higher in patients with s-AML than patients with *de novo* AML.

It is well known that Survivin overexpression is associated with a poor outcome in various cancers.[26] The fact that Survivin acts as an inhibitor of effector caspases 3/7 and blocks the mutual downstream events of apoptosis pathways[30] means that Survivin is a key factor in the response to chemotherapy. Patients with high-risk MDS and secondary AML are particularly resistant to standard chemotherapy compared to patients with *de novo* AML, suggesting that these entities are biologically distinct from *de novo* AML. However, the specific gene responsible for the pathological differences between secondary leukemia following MDS and *de novo* AML has still not been clarified. In the present study, we found that marked upregulation of Survivin was associated with disease progression of MDS. In particular, patients with high-risk MDS and secondary AML showed a significant increase in Survivin expression, which may contribute to the anti-cancer drug resistance and may explain why high-risk MDS and s-AML patients have a poor prognosis.

Only 2 studies on expression of Survivin in a series of adult patients with *de novo* AML have been reported.[31,32] Adida *et al.*[31] reported that Survivin was detected in 75 (60%) out of 125 *de novo* AML patients with data available from immunohistochemical analysis. No significant difference was observed in complete remission rate or overall survival between Survivin-positive and Survivin-negative AML patients.[31] In addition, Wagner *et al.*[32] reported that the expression of Survivin did not correlate with complete

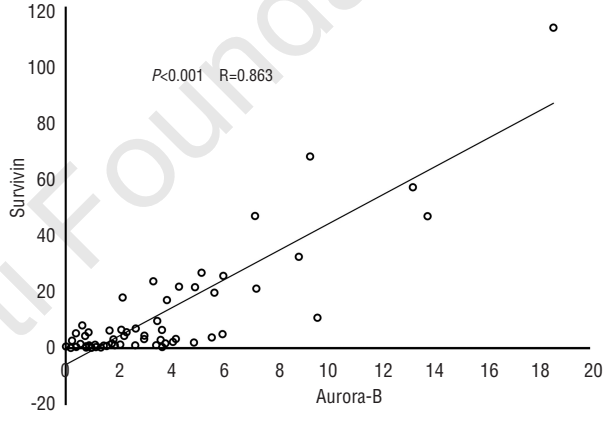

Figure 3. Correlation between the expression levels of Survivin and Aurora-B kinase in patients with MDS and s-AML. Regression analysis performed between Survivin and Aurora-B kinase expression in patients with MDS and s-AML R value = 0.863 indicates a good correlation between the two parameters considered.

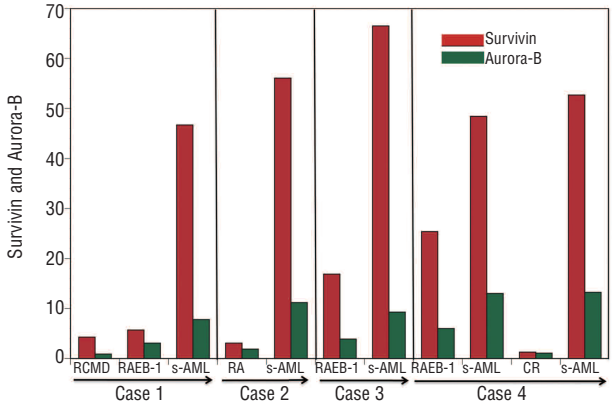

Figure 4. Survivin and Aurora-B kinase expression levels during follow up of 4 patients with MDS. In all cases, a marked increase in Survivin and Aurora-B kinase expression was noted in parallel with disease progression. Survivin or Aurora-B kinase expression was evaluated by RQ-PCR as described in *Design and Methods*.

Table 1. Cytogenetic data for 4 patients with MDS. Data for these 4 patients were identical to those of patients with clinical follow up (Figure 4).

Case 1		
	RCMD	46XY [15] /46XY, del(20)(q11q13)[5]
	RAEB-1	46XY, t(1;17)(q21:q21), del(20)(q11q13)[7] / 46XY[13]
	s-AML	46XY, t(1;17)(q21:q21), del(20)(q11q13)[20]
Case 2		
	RA	46,XY, del(7)(q22q36),
	s-AML	46,XY, del(5)(q23q34), del(7)(q22q36), der(17)t(5;17)(p11;p11)
Case 3		
	RAEB-1	45, X. -Y, der(1;7)(q10;p10)
	s-AML	47, X, -Y, +1. der(1;7)(q10;p10), del(5)(q31q32). r(6), +8. +8 [18]
Case 4		
	RAEB-1	46, XY, -7, der(7)t(1;7)(q22:q23), del(20)(q13)[17] / 46XY[3]
	s-AML	46, XY, -7, der(7)t(1;7)(q22:q23), del(20)(q13)[20]
	CR	46, XY
	s-AML	46, XY, -7, der(7)t(1;7)(q22:q23), del(20)(q13)[15] / 46, XY, -8, del(7)(q22:q36), del(20)(q13), der(8)t(1;8)(q23;q24) [5]

remission rate or overall survival in adult AML patients. In our present study, we observed that the median expression of mRNA of Survivin in AML patients was 1.7-fold higher than that in normal CD34 cells; however, this is not statistically significant. Most *de novo* AML patients do not show significant Survivin upregulation. Gianelli *et al.*[33] reported that MDS patients belonging to the low or INT1 (IPSS) risk groups had higher levels of Survivin mRNA than those belonging to INT2 or high IPSS. Their results are not consistent with our data. However, Gianelli *et al.* did not examine the expression of this gene using isolated $CD34^+$ cells. They used BM mononuclear cells. Therefore, it is difficult to make a comparison between their results and ours. Invernizzi *et al.*[34] analyzed the expression of Survivin by immunocytochemistry in bone marrow cells from patients with chronic myelomonocytic leukemia (CMML). They found that Survivin levels were higher in patients with CMML than in MDS and AML ($P<0.0001$) but were similar to those found in MPD.[34] In the present study, we did not examine Survivin expression in CMML because of the extremely small number of patients in this category.

Aurora-B kinase is over-expressed in various solid tumors.[29,35,36] This kinase plays an integral part in the mitotic spindle checkpoint and monitors the biorientation in the spindle-kinetochord attachment needed for precise separation of chromosomes during metaphase.[25,29] Disruption of Aurora-B function at the protein or gene level has been shown to impair mitotic spindle checkpoint.[29] Nguyen *et al.* reported that a stable mutant of Aurora-B induces tetraploidy and aneuploidy in normal murine epithelial cells.[37] In addition, they found that overexpression of Aurora-B kinase induces premature chromosome separation and generation of tetraploid and aneuploid cells which, in turn, facilitates genomic instability and tumor development in a xenograft model.[38] This is particularly interesting because patients with MDS, especially high-risk patients, frequently show aneuploidy and genetic instability.[39] In the present study, we demonstrated for the first time that Aurora-B kinase expression was increased during disease progression of MDS. It is intriguing to consider that increased expression of Aurora-B kinase may be involved in genetic instability and aneuploidy in MDS.

Our results indicate that high levels of Survivin and Aurora-B kinase expression may be associated with complex karyotypic abonormalities in MDS. Survivin expression increased when the patients had additional chromosomal abnormalities during disease progression (Table 1). For example, Patient 3 had a complex karyotype including ring chromosome and del(5) during progression to overt leukemia. At that time, a clear increase in Survivin expression was observed. Both Survivin and Aurora-B kinase genes are located on chromosome 17. However, abnormalities of chromosome 17 are not always associated with increased Survivin and Aurora-B expression in MDS. Hoffman *et al.*[40] demonstrated that introduction of the wild-type *p53* gene into *p53*-null human lung cancer cells resulted in a significant decrease in Survivin gene expression. They also found that wild-type p53 repressed promoter activity in the Survivin gene by binding to this promoter.[40] In contrast, mutations of the *p53* gene may be involved in the upregulation of Survivin.[41,42] Mutations of the *p53* tumor suppressor gene can be detected in high-risk MDS.[43] Patients carrying *p53* mutations frequently have a complex karyotype.[44,45] Therefore, it could be hypothesized that a high level of Survivin expression may be caused by mutant *p53* in patients with high-risk MDS. In the present study, however, we did not examine the status of the *p53* gene in each MDS patient and further studies are required to explore this hypothesis.

Several *in vitro* studies on the functional correlation between Survivin and Aurora-B have been reported. However, there has been no study into the expression of Survivin and Aurora-B in clinical hematologic malignancies. Here, we compared the expression of Survivin with that of a subunit of CPC complex, Aurora-B. Our data clearly indicate that the amount of Aurora-B kinase was significantly correlated with Survivin expression in MDS and s-AML, but not in *de novo* AML. Aurora-B kinase activity is stimulated by binding and phosphorylation of

Survivin.[24] These findings lead to the hypothesis that interaction between Survivin and Aurora-B may be involved in development of a malignant tumor. However, the pathophysiological meaning of the upregulation of Survivin and Aurora-B kinase expression in high-risk MDS remains unclear. Further investigation will be required to clarify this phenomenon.

Currently, both Survivin and Aurora-B kinase are considered attractive molecular targets for cancer treatment. Our present data clearly indicate that high levels of Survivin and Aurora-B kinase expression are distinctive molecular features of high-risk MDS and s-AML, emphasizing the potential of these genes as molecular targets in their treatment.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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