Machado-Neto et al. Applied Cancer Research (2017) 37:25
DOI 10.1186/s41241-017-0033-9

Applied Cancer Research

RESEARCH ARTICLE Open Access

SIVA, a target of p53, is downregulated in myelodysplastic syndromes

João Agostinho Machado-Neto[1,2*], Paula de Melo Campos[1], Patricia Favaro[1,3], Mariana Lazarini[1,3], Renata Scopim-Ribeiro[1,2], Irene Lorand-Metze[1], Fernando Ferreira Costa[1], Sara Terezinha Olalla Saad[1] and Fabiola Traina[1,2*]

Abstract

Background: *SIVA* is a transcriptional target of p53 that plays a potential role in the development and progression of cancer. In this study, we analyzed *SIVA1* and *SIVA2* expression, and its association with clinical features and *TP53* and *MDM2* expression in bone marrow cells from healthy donors and myelodysplastic syndrome (MDS) patients.

Methods: Fifty-five untreated patients with MDS and 22 healthy donors were included. Gene expression was evaluated by quantitative PCR. For statistical analysis, Mann–Whitney test, Spearman correlation analysis and Log-rank (Mantel-Cox) were used, as appropriate. A p value <0.05 was considered statistically significant.

Results: *SIVA1* and *SIVA2* transcripts were significantly decreased in bone marrow samples from MDS patients compared to healthy donors, and positively correlated with *MDM2* and *TP53* expression in MDS patients (all $p < 0.05$). *MDM2* expression was also downregulated in bone marrow samples from MDS patients compared to healthy donors ($p < 0.05$). However, *SIVA1*, *SIVA2*, *MDM2* and *TP53* expressions did not impact on MDS outcomes.

Conclusions: *SIVA1* and *SIVA2* transcripts are downregulated in bone marrow samples from MDS patients.

Keywords: SIVA1, SIVA2, Myelodysplastic syndromes, TP53, MDM2

Background

Apoptosis resistance and genomic instability are hallmarks of cancer cells [1, 2]. The p53 tumor suppressor protein is a transcription factor that regulates several signaling pathways involved in the cell response to stress, suppressing malignant transformation by cell cycle arrest, DNA repair, induction of apoptosis and initiation of senescence [3]. Deregulation of p53 is a common event in hematological malignancies. In acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), strong p53 protein expression has been associated with *TP53* mutations [4–7] and *TP53* mutations have been associated with poor prognosis [8–11]. In low-risk MDS patients, high p53 protein expression is an independent predictor of transformation into AML [4].

* Correspondence: jamachadoneto@gmail.com; ftraina@fmrp.usp.br
[1]Hematology and Hemotherapy Center-University of Campinas, Hemocentro-Unicamp, Instituto Nacional de Ciência e Tecnologia do Sangue, Rua Carlos Chagas, 480, Campinas, SP, CEP 13083-878, Brazil
Full list of author information is available at the end of the article

SIVA is a transcriptional target of p53 that was initially described as a proapoptotic protein and acts on both extrinsic and intrinsic apoptotic pathways [12, 13]. Two alternatively-spliced transcript variants encoding distinct proteins have been described, *SIVA1* and *SIVA2*. MDM2 is a negative regulator of p53 and may modulate the expression of *SIVA* through regulation of the stability and activation of p73 and E2F1 transcription factors, which represent a p53-independent mechanism of *SIVA* regulation [13, 14].

SIVA1 binds to BCL2 and BCL-XL, and abrogates their anti-apoptotic activity [15, 16]. SIVA modulates BAX oligomerization, binds to XIAP, and balances NFκB and JNK signaling, promoting apoptosis [17, 18]. In acute lymphoblast leukemia cell lines, both SIVA isoforms play an important role in the apoptotic pathway, induced through CD27 antigen by activation of BID, with a consequent release of cytochrome C and activation of caspases 9 and 3 [19]. In leukemia cell lines, SIVA1 also binds to and inhibits Stathmin 1 activity, preventing tumor growth [20]. In contrast to the tumor

suppression functions initially described for SIVA, recent studies indicate that the conditional knockout of *SIVA1* reduced tumorigenesis in KRAS-driven lung cancer murine model [21] and high *SIVA1* expression was associated with worse survival rates in AML patients [22]. In the present study, we characterized *SIVA1* and *SIVA2* expressions in healthy controls and MDS patients, and their correlation with clinical features, as well as the expression of SIVA-related genes: *TP53* and *MDM2*.

Methods

Bone marrow samples

Bone marrow samples collected from 55 untreated patients with MDS and 22 healthy donors from related bone marrow transplantation (median age 33 years [range 18–56]) were analyzed. Patient's characteristics are described in Table 1. The present study was approved by the Ethics Committee of the University of Campinas in accordance with the Helsinki Declaration. Written informed consent was obtained from all healthy donors and MDS patients who participated in this study.

Table 1 Patients' characteristics

Patients	Number
MDS	55
Gender	
Male/Female	32/23
Age (years), median (range):	69 (16–90)
WHO classification	
RA/RARS/RCMD	3/4/31
RAEB-1/RAEB-2	10/7
IPSS-R	
Very low/Low	7/25
Intermediate/High/Very high	8/9/4
Not available	3
Cytogenetic risk[a]	
Very good/good	2/42
Intermediate	6
Poor /very poor	0/2
No growth	3
BM blast (%)	
< 5%	38
≥ 5 and <10%	10
≥ 10 and <20%	7

Abbreviations: *MDS* myelodysplastic syndromes, *WHO* World Health Organization, *RA* refractory anemia, *RARS* refractory anemia with ringed sideroblasts, *RCMD* refractory cytopenia with multilineage dysplasia, *RAEB-1* refractory anemia with excess blast-1, *RAEB-2* refractory anemia with excess blast-2, *BM* bone marrow

[a]In MDS cohort, karyotype findings included very low risk: –Y (n = 1), del(11q) (n = 1); low risk: normal (n = 46), intermediate risk: +8 (n = 2); −7 (n = 1), other (n = 3); high risk: 3 abnormalities (n = 0), and very high risk: >3 abnormalities (n = 2)

Patients who attended the clinic between 2005 and 2013 and signed the informed consent for the study were included. Diagnosis was made by clinical data, peripheral blood counts, bone marrow (BM) cytology and histology and cytogenetics. Deficiency anemias, autoimmune diseases and viral infections were excluded [23]. The cases were classified by the WHO 2008 criteria and risk stratification was made according to IPSS-R [24].

Quantitative polymerase chain reaction (qPCR)

Total RNA was obtained from total bone marrow cells, after removal of erythrocytes by hemolysis, using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Genomic DNA was eliminated using DNAse I treatment (Invitrogen). cDNA was obtained from 1 μg of RNA using RevertAid™ First Strand cDNA Synthesis Kit (MBI Fermentas, St. Leon-Rot, Germany). A total of 120 ng of cDNA was used for gene expression analysis by quantitative PCR (qPCR) in the ABI 7500 Sequence Detection System (Applied Biosystem, Foster City, CA, USA) using specific primers for *SIVA1*, *SIVA2*, *TP53*, *MDM2* and *HPRT1*. Primer sequences and concentrations are described in Table 2. *HPRT1* was used as the reference gene. The relative gene expression was calculated using the equation $2^{-\Delta\Delta CT}$ [25]. A negative 'No Template Control' was included for each primer pair. The dissociation protocol was performed at the end of each run to check for non-specific amplification. Three replicas were run on the same plate for each sample.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 5 (GraphPad Software, Inc., San. Diego, CA, USA) or SAS System for windows 9.2 (SAS Institute, Inc., Cary, NC, USA). Mann–Whitney test was used for measured factors; Spearman correlation analysis was used for ranking correlation tests and Log-rank (Mantel-Cox) was used to estimate overall survival (OS) and event free survival (EFS). OS was defined from time of sampling to

Table 2 Primer sequences and concentrations

Gene	Sequence	Concentration
SIVA1	FW: 5′- TCTTCGAGAAGACCAAGCG –3′	300 nM
	RV: 5′- TGCCCAAGGCTCCTGATC –3′	
SIVA2	FW: 5′- CAGGAGGTCTTCGACCCA –3′	600 nM
	RV: 5′- AGTCCACGAGGCCACACA –3′	
TP53	FW: 5′- GGCGCACAGAGGAAGAGAAT –3′	150 nM
	RV: 5′- GGAGAGGAGCTGGTGTTGTTG –3′	
MDM2	FW: 5′- TTCGAGCCTAGCAATGATCTAGAA –3′	150 nM
	RV: 5′- AAACCCACACAACAAATTGCAA –3′	
HPRT1	FW: 5′- GAACGTCTTGCTCGAGATGTG –3′	150 nM
	RV: 5′- TCCAGCAGGTCAGCAAAGAAT-3′	

date of death or last seen. For MDS patients, EFS was defined as time of sampling to date of progression to high-risk MDS or AML with myelodysplasia-related changes, or date of death. A p value <0.05 was considered as statistically significant.

Results

SIVA1 and *SIVA2* transcripts are downregulated in bone marrow cells from MDS patients

SIVA1 and *SIVA2* transcripts were significantly decreased in bone marrow samples from MDS patients compared to cells from healthy donors (*SIVA1*: median 0.71 [range 0.00–10.28] versus (vs.) 2.18 [0.23–25.88], $p < 0.0001$, Fig. 1a; *SIVA2*: 0.85 [0.04–18.14] vs. 4.69 [0.81–35.53], respectively, $p < 0.0001$, Fig. 1b). No difference was observed on *SIVA1* and *SIVA2* expression when MDS patients were stratified by IPSS-R into very low/low vs. intermediate/high/very high ($p > 0.05$, Additional file 1: Figure S1). Similar results were observed when MDS patients were stratified by WHO 2008 classification (refractory anemia (RA)/refractory anemia with ringed sideroblasts (RARS)/refractory cytopenia with multilineage dysplasia (RCMD) vs. refractory anemia with excess blast-1 (RAEB-1)/refractory anemia with excess blast-2 (RAEB-2) group; $p > 0.05$, Additional file 2: Figure S2. Spearman correlation analysis showed a significant positive correlation between *SIVA1* and *SIVA2* expression in normal ($r = 0.74$, $p < 0.0001$, Fig. 1c) and MDS ($r = 0.75$, $p < 0.0001$, Fig. 1d) bone marrow samples, indicating a similar regulation for both isoforms of SIVA in hematopoietic cells.

SIVA1 and *SIVA2* expression correlates with *MDM2* and *TP53* expression in MDS bone marrow cells

MDM2 expression was downregulated in bone marrow cells from MDS patients compared to healthy donors (1.08 [0.18–10.07] vs. 1.59 [0.24–5.52], $p = 0.03$, Figure 2a). *TP53* expression was similar between MDS patients and

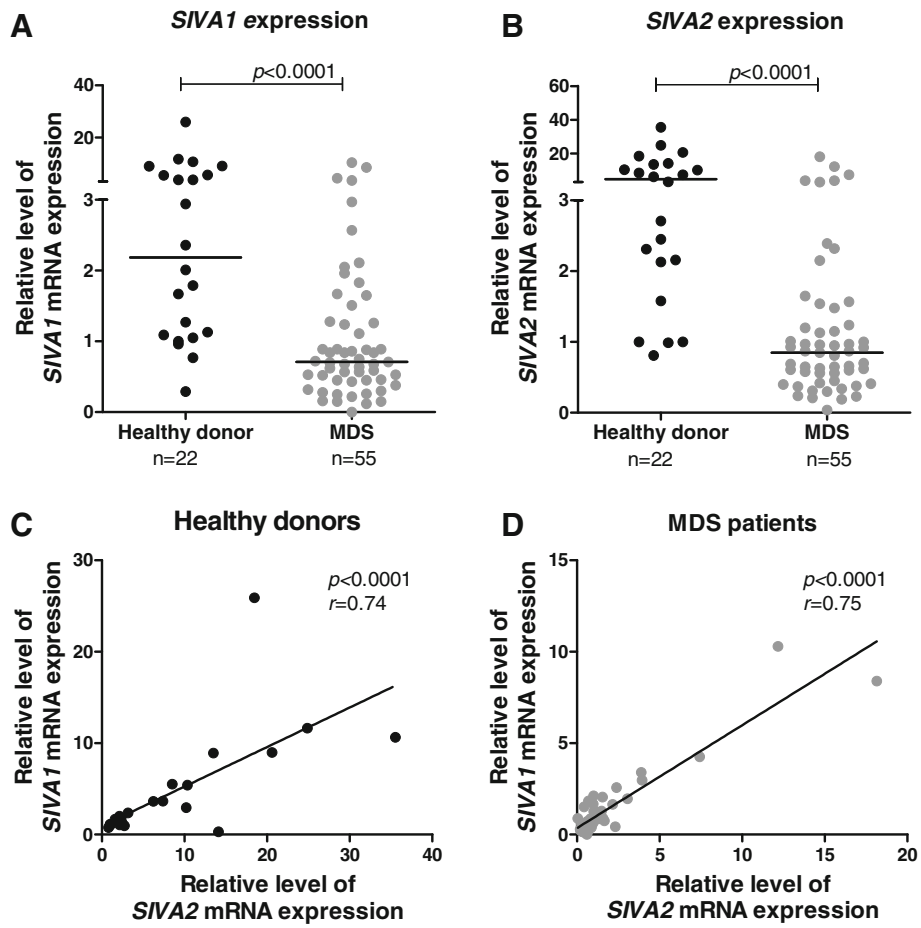

Fig. 1 *SIVA1* and *SIVA2* expression in bone marrow cells from healthy donors and patients with myelodysplastic syndromes (MDS). *SIVA1* (**a**) and *SIVA2* (**b**) mRNA expression in total bone marrow cells from healthy donors and MDS patients. Horizontal lines indicate medians. The numbers of subjects studied and p values are indicated; *Mann–Whitney* test. Correlation analysis between *SIVA1* expression with *SIVA2* expression in total bone marrow cells from healthy donors (**c**) and MDS patients (**d**). The p and r values are indicated; Spearman correlation test

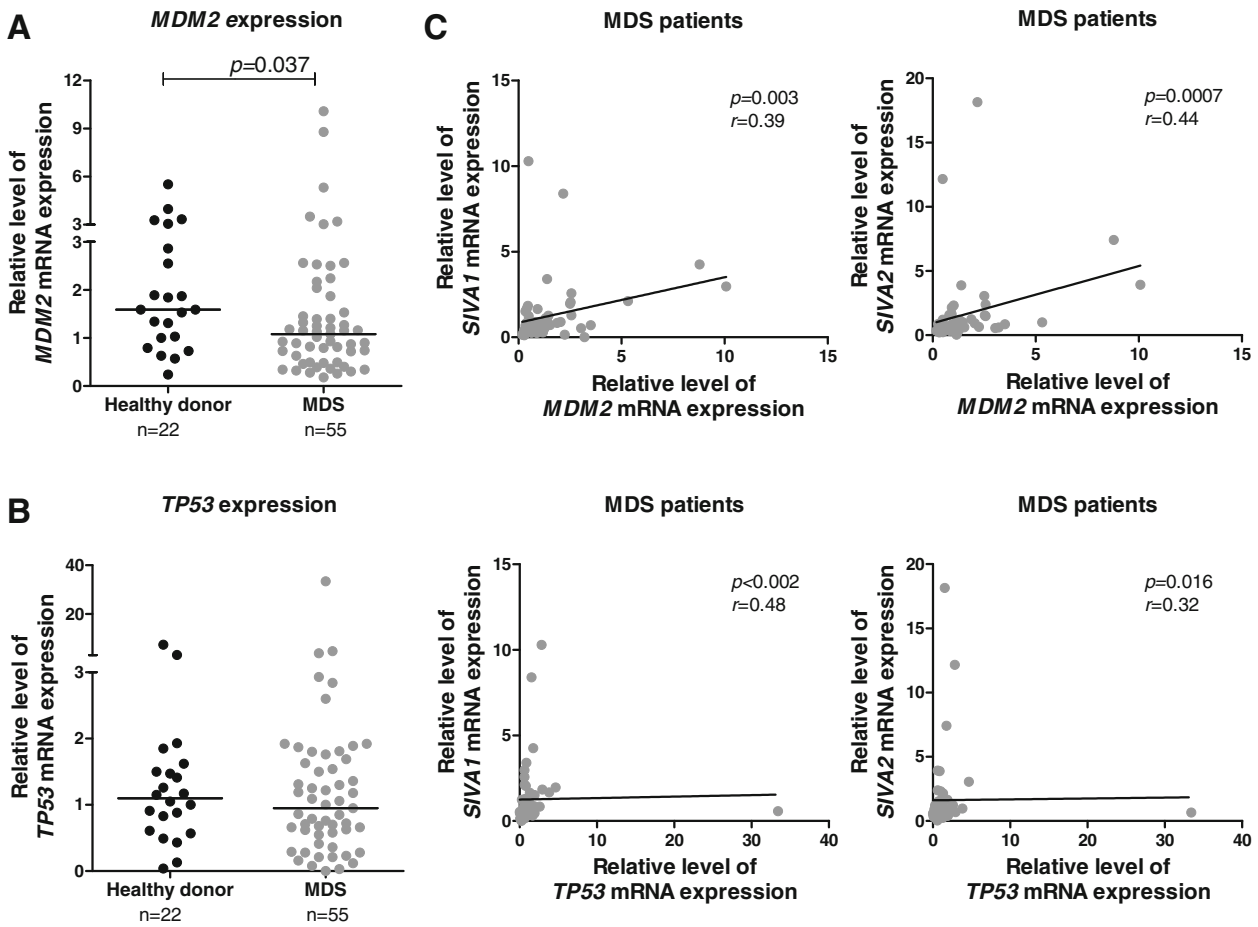

Fig. 2 *TP53* and *MDM2* expression and their correlation with *SIVA1* and *SIVA2* levels in bone marrow cells from patients with myelodysplastic syndromes (MDS). *MDM2* (**a**) and *TP53* (**b**) mRNA expression in total bone marrow cells from healthy donors and MDS patients. *Horizontal lines* indicate medians. The numbers of subjects studied and *p* values are indicated; *Mann–Whitney* test. **c** Correlation analysis between *SIVA1* or *SIVA2* with *MDM2* and *TP53* expression in total bone marrow cells from MDS patients. The *p* and *r* values are indicated; Spearman correlation test

healthy donors (*TP53*: 0.95 [0.00–33.41] vs. 1.10 [0.04–7.32], Fig. 2b). *TP53* expression was significantly increased in the IPSS-R intermediate/high/very-high risk MDS compared to the IPSS-R very low/low risk groups (1.25 [0.16–33.41] vs. 0.72 [0.00–4.65], $p = 0.03$; Additional file 1: Figure S1), and no differences were observed for *MDM2* expression ($p > 0.05$). No difference was observed in *MDM2* and *TP53* expression when MDS patients were stratified by WHO 2008 classification into RA/RARS/RCMD group vs. RAEB-1/RAEB-2 group ($p > 0.05$, Additional file 2: Figure S2). *MDM2* and *TP53* expressions were positively correlated with *SIVA1* and *SIVA2* in bone marrow samples from MDS patients (*MDM2/SIVA1*: $r = 0.39$, $p = 0.003$; *MDM2*/*SIVA2*: $r = 0.44$, $p = 0.0007$; *TP53*/*SIVA1*: $r = 0.48$, $p < 0.002$; *TP53*/*SIVA2*: $r = 0.32$, $p = 0.02$; Figure 2c). In healthy donors, *SIVA1* and *SIVA2* expression correlated only with *MDM2* expression, but not with *TP53* expression (Additional file 3: Figure S3). In our cohort of MDS patients, the factors that were significantly associated with EFS and OS were gender, WHO 2008 classification and IPSS-R by univariate analysis. Male gender and RAEB1/2 classification negatively impact on EFS and OS by multivariate analysis (Table 3).

Discussion

Herein, we analyzed the expression of *SIVA1* and *SIVA2* in normal and MDS bone marrow samples, and their correlation with *MDM2* and *TP53* expression. Regarding *SIVA* expression in MDS, our results are in agreement with a previous microarray study that showed a downregulation of *SIVA* in bone marrow mononuclear cells from MDS patients, when compared to healthy donors [26], and provide further evidence of the participation of SIVA in hematological malignancies.

We also observed a downregulation of *MDM2* in MDS patients. Pellagatti and colleagues [27], using microarray analysis, reported that the ATM signaling pathway is

Table 3 Univariate and multivariate analyses of survival outcomes for MDS patients

Factor	Univariate analysis						Multivariate analysis					
	Event Free Survival			Overall Survival			Event Free Survival			Overall Survival		
	Hazard Ratio[b]	(95% C.I.)	*p*	Hazard Ratio[b]	(95% C.I.)	*p*	Hazard Ratio[b]	(95% C.I.)	*p*	Hazard Ratio[b]	(95% C.I.)	*p*
Gender												
Male vs. female	1.92	0.97–3.80	0.06	2.26	1.09–4.59	0.02	3.07	1.44–6.58	0.002	3.29	1.48–7.35	0.002
Age at sampling	1.01	0.99–1.04	0.28	1.01	0.99–1.04	0.31	-	-	-	-	-	-
WHO 2008 classification												
RAEB-1/RAEB-2 vs. others	5.12	2.58–10.17	<0.0001	3.95	1.94–8.06	0.002	8.54	3.66–19.93	<0.0001	6.03	2.58–14.09	0.0004
Risk Stratification by IPSS-R[a]												
Intermediate/High/Very high vs. Very low/Low	2.17	1.18–4.34	0.01	2.04	1.04–4.01	0.04	-	-	-	-	-	-
SIVA1 expression	1.07	0.87–1.32	0.52	1.05	0.85–1.30	0.62	-	-	-	-	-	-
SIVA2 expression	1.05	0.94–1.17	0.35	1.03	0.92–1.14	0.59	-	-	-	-	-	-
MDM2 expression	0.80	0.63–1.01	0.06	0.79	0.62–1.02	0.07	-	-	-	-	-	-
TP53 expression	1.02	0.97–1.08	0.46	1.02	0.96–1.09	0.43	-	-	-	-	-	-

Abbreviations: *MDS* myelodysplastic syndromes, *WHO* World Health Organization, *RAEB-1* refractory anemia with excess blast-1, *RAEB-2* refractory anemia with excess blast-2, *R-IPSS* Revised International Prognostic Scoring System

[a]Metaphase cytogenetic was not available in three patients

[b]Hazard ratios >1 indicate that the first factor has the poorer outcome

deregulated in high-risk MDS, which included downregulation of *MDM2*. The positive correlation between *SIVA* transcripts and *MDM2* may be related to the fact that both genes are transcription targets of p53 [13, 28], suggesting a defective transcriptional activity of p53 protein. SIVA1 binds to and regulates p53 stability by acting as an adapter protein between p53 and MDM2 [29, 30], and SIVA1 acts as an ubiquitin ligase for ARF and indirectly regulates p53 stability [31]. Given that there is a reduced expression of *SIVA1* in bone marrow samples from MDS, herein identified, further studies are necessary to verify whether SIVA1 downregulation may be involved in aberrant p53 signaling pathway reported in MDS cells [32].

Conclusion

In conclusion, we demonstrated that SIVA expression is impaired in MDS. The downregulation of *SIVA* and its correlation with *MDM2* may be due to defective p53 transcriptional machinery in this disease. Future studies are necessary to verify the effects of SIVA in hematopoietic cells and their participation in the malignant phenotype.

Additional files

Additional file 1: Figure S1. *SIVA1*, *SIVA2*, *MDM2*, *TP53* and *BCL2* expression in bone marrow cells from myelodysplastic syndromes (MDS) stratified by Revised International Prognostic Scoring System (IPSS-R). *SIVA1* (A), *SIVA2* (B), *MDM2* (C) and *TP53* (D) mRNA expression in total bone marrow cells from MDS patients stratified by IPSS-R into very low/low risk group and intermediate/high/very high risk group. Horizontal lines indicate medians. The numbers of subjects studied and *p* values are indicated; *Mann–Whitney* test. (PDF 32 kb)

Additional file 2: Figure S2. *SIVA1*, *SIVA2*, *MDM2* and *TP53* expression in bone marrow cells from myelodysplastic syndromes (MDS) stratified by World Healthy Organization (WHO) 2008 classification. *SIVA1* (A), *SIVA2* (B), *MDM2* (C) and *TP53* (D) mRNA expression in total bone marrow cells from MDS patients stratified by WHO classification into refractory anemia (RA)/refractory anemia with ringed sideroblasts (RARS)/refractory cytopenia with multilineage dysplasia (RCMD) group and refractory anemia with excess blast-1 (RAEB-1)/refractory anemia with excess blast-2 (RAEB-2) group. Horizontal lines indicate medians. The numbers of subjects studied are indicated. (PDF 31 kb)

Additional file 3: Figure S3. *TP53* and *MDM2* expressions and their correlation with *SIVA1* and *SIVA2* levels in bone marrow cells from healthy donors. Correlation analysis between *SIVA1* or *SIVA2* with *MDM2* or *TP53* expression in total bone marrow cells from healthy donors. The *p* and *r* values are indicated; Spearman correlation test. (PDF 25 kb)

Abbreviations

AML: Acute myeloid leukemia; BAX: BCL2-associated X protein; BCL2: B cell leukemia/lymphoma 2; BCL-XL: BCL2-like 1; BID: BH3 interacting domain death agonist; BM: Bone marrow; EFS: Event free survival; HPRT1: Hypoxanthine phosphoribosyltransferase 1; IPSS-R: Revised International Prognostic Scoring System; JNK: c-Jun N-terminal kinase; MDM2: MDM2proto-oncogene; MDS: Myelodysplastic syndromes; NFκB: Nuclear factor kappa B; OS: Overall survival; p53: Protein 53; q-PCR: Quantitative polymerase chain reaction; RA: Refractory anemia; RAEB-1: Refractory anemia with excess blast-1; RAEB-2: Refractory anemia with excess blast-2; RARS: Refractory anemia with ringed sideroblasts; RCMD: Refractory cytopenia with multilineage dysplasia; SIVA: SIVA1 apoptosis inducing factor; TP53: Tumor protein 53; WHO: World Health Organization; XIAP: X-linked inhibitor of apoptosis.

Acknowledgments

The authors would like to thank Raquel S. Foglio and Andy Cumming for English review, and Tereza Salles for her valuable technical assistance.

Funding

This work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Availability of data and materials

Please contact author for data requests.

Authors' contributions

JAM-N performed all the experiments, statistical analyses, patient database, manuscript preparation, completion and final approval. PMC, PF, ML and RS-R participated in the interpretation of manuscript data, clinical data collection, manuscript editing, and final approval. IL-M, FFC and STOS participated in revised the diagnoses, patient follow up, manuscript editing and final approval. FT participated in the overall design of the study and experiments, statistical analyses, patient follow up, manuscript preparation, editing, completion and final approval. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the University of Campinas in accordance with the Helsinki Declaration. Written informed consent was obtained from all healthy donors and MDS patients who participated in this study.

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Author details

[1]Hematology and Hemotherapy Center-University of Campinas, Hemocentro-Unicamp, Instituto Nacional de Ciência e Tecnologia do Sangue, Rua Carlos Chagas, 480, Campinas, SP, CEP 13083-878, Brazil. [2]Currently at Department of Internal Medicine, University of São Paulo at Ribeirão Preto Medical School, Ribeirão Preto, São Paulo, Brazil. [3]Currrently at Department of Biological Sciences, Federal University of São Paulo, Diadema, São Paulo, Brazil.

Received: 3 May 2017 Accepted: 6 June 2017
Published online: 15 June 2017

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
2. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene. 2007;26:1324–37.
3. Kruse JP, Gu W. Modes of p53 regulation. Cell. 2009;137:609–22.
4. Saft L, Karimi M, Ghaderi M, Matolcsy A, Mufti GJ, Kulasekararaj A, et al. p53 protein expression independently predicts outcome in patients with lower-risk myelodysplastic syndromes with del(5q). Haematologica. 2014;99:1041–9.
5. Loghavi S, Al-Ibraheemi A, Zuo Z, Garcia-Manero G, Yabe M, Wang SA, et al. TP53 overexpression is an independent adverse prognostic factor in de novo myelodysplastic syndromes with fibrosis. Br J Haematol. 2015;171:91–9.
6. Duarte FB, Goncalves RP, Barbosa MC, Rocha Filho FD, de Jesus Dos Santos TE, Dos Santos TN, et al. Tumor suppressor p53 protein expression: prognostic significance in patients with low-risk myelodysplastic syndrome. Rev Bras Hematol Hemoter. 2014;36:196–201.
7. Bektas O, Uner A, Buyukasik Y, Uz B, Bozkurt S, Eliacik E, et al. Clinical and pathological correlations of marrow PUMA and P53 expressions in myelodysplastic syndromes. APMIS. 2015;123:445–51.

8. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364:2496–506.
9. Christiansen DH, Andersen MK, Pedersen-Bjergaard J. Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol. 2001;19:1405–13.
10. Padua RA, Guinn BA, Al-Sabah AI, Smith M, Taylor C, Pettersson T, et al. RAS, FMS and p53 mutations and poor clinical outcome in myelodysplasias: a 10-year follow-up. Leukemia. 1998;12:887–92.
11. Quintas-Cardama A, Hu C, Qutub A, Qiu YH, Zhang X, Post SM, et al. p53 pathway dysfunction is highly prevalent in acute myeloid leukemia independent of TP53 mutational status. Leukemia. 2017;31:1296–305.
12. Prasad KV, Ao Z, Yoon Y, Wu MX, Rizk M, Jacquot S, et al. CD27, a member of the tumor necrosis factor receptor family, induces apoptosis and binds to Siva, a proapoptotic protein. Proc Natl Acad Sci U S A. 1997;94:6346–51.
13. Fortin A, MacLaurin JG, Arbour N, Cregan SP, Kushwaha N, Callaghan SM, et al. The proapoptotic gene SIVA is a direct transcriptional target for the tumor suppressors p53 and E2F1. J Biol Chem. 2004;279:28706–14.
14. Ray RM, Bhattacharya S, Johnson LR. Mdm2 inhibition induces apoptosis in p53 deficient human colon cancer cells by activating p73- and E2F1-mediated expression of PUMA and Siva-1. Apoptosis. 2011;16:35–44.
15. Chu F, Barkinge J, Hawkins S, Gudi R, Salgia R, Kanteti PV. Expression of Siva-1 protein or its putative amphipathic helical region enhances cisplatin-induced apoptosis in breast cancer cells: effect of elevated levels of BCL-2. Cancer Res. 2005;65:5301–9.
16. Xue L, Chu F, Cheng Y, Sun X, Borthakur A, Ramarao M, et al. Siva-1 binds to and inhibits BCL-X(L)-mediated protection against UV radiation-induced apoptosis. Proc Natl Acad Sci U S A. 2002;99:6925–30.
17. Resch U, Schichl YM, Winsauer G, Gudi R, Prasad K, de Martin R. Siva1 is a XIAP-interacting protein that balances NFkappaB and JNK signalling to promote apoptosis. J Cell Sci. 2009;122:2651–61.
18. Barkinge JL, Gudi R, Sarah H, Chu F, Borthakur A, Prabhakar BS, et al. The p53-induced Siva-1 plays a significant role in cisplatin-mediated apoptosis. J Carcinog. 2009;8:2.
19. Py B, Slomianny C, Auberger P, Petit PX, Benichou S. Siva-1 and an alternative splice form lacking the death domain, Siva-2, similarly induce apoptosis in T lymphocytes via a caspase-dependent mitochondrial pathway. J Immunol. 2004;172:4008–17.
20. Machado-Neto JA, Lazarini M, Favaro P, de Melo CP, Scopim-Ribeiro R, Franchi Junior GC, et al. ANKHD1 silencing inhibits Stathmin 1 activity, cell proliferation and migration of leukemia cells. Biochim Biophys Acta. 1853; 2015:583–93.
21. Van Nostrand JL, Brisac A, Mello SS, Jacobs SB, Luong R, Attardi LD. The p53 target Gene SIVA enables non-small cell lung cancer development. Cancer Discov. 2015;5:622–35.
22. Park IK, Blum W, Baker SD, Caligiuri MA. E3 ubiquitin ligase Cbl-b activates the p53 pathway by targeting Siva1, a negative regulator of ARF, in FLT3 inhibitor-resistant acute myeloid leukemia. Leukemia. 2017;31:502–5.
23. Reis-Alves SC, Traina F, Harada G, Campos PM, Saad ST, Metze K, et al. Immunophenotyping in myelodysplastic syndromes can add prognostic information to well-established and new clinical scores. PLoS One. 2013;8:e81048.
24. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454–65.
25. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(−Delta Delta C(T)) method. Methods. 2001;25:402–8.
26. Bar M, Stirewalt D, Pogosova-Agadjanyan E, Wagner V, Gooley T, Abbasi N, et al. Gene expression patterns in Myelodyplasia underline the role of apoptosis and differentiation in disease initiation and progression. Transl Oncogenomics. 2008;3:137–49.
27. Pellagatti A, Cazzola M, Giagounidis A, Perry J, Malcovati L, Della Porta MG, et al. Deregulated gene expression pathways in myelodysplastic syndrome hematopoietic stem cells. Leukemia. 2010;24:756–64.
28. Manfredi JJ. The Mdm2-p53 relationship evolves: Mdm2 swings both ways as an oncogene and a tumor suppressor. Genes Dev. 2010;24:1580–9.
29. Du W, Jiang P, Li N, Mei Y, Wang X, Wen L, et al. Suppression of p53 activity by Siva1. Cell Death Differ. 2009;16:1493–504.
30. Mei Y, Wu M. Multifaceted functions of Siva-1: more than an Indian god of destruction. Protein Cell. 2012;3:117–22.
31. Wang X, Zha M, Zhao X, Jiang P, Du W, Tam AY, et al. Siva1 inhibits p53 function by acting as an ARF E3 ubiquitin ligase. Nat Commun. 2013;4:1551.
32. Zhang L, McGraw KL, Sallman DA, List AF. The role of p53 in myelodysplastic syndromes and acute myeloid leukemia: molecular aspects and clinical implications. Leuk Lymphoma. 2017;58:1777–90.