ORIGINAL ARTICLE

Vol. 39 (1): 95-102, January - February, 2013
doi: 10.1590/S1677-5538.IBJU.2013.01.12

Expression profile of microrna-145 in urothelial bladder cancer

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ABSTRACT

Purpose: Bladder cancer (BC) is the second most common malignancy of the urinary tract, with high mortality. The knowledge of the molecular pathways associated with BC carcinogenesis is crucial to identify new diagnostic and prognostic biomarkers. MicroRNAs (miRNAs) are short non-coding RNA molecules that play important roles in the regulation of gene expression by acting directly on mRNAs. miR-145 has been considered as a tumor suppressor, which targets the c-MYC, MUC-1 and FSCN1 genes. Our aim was to evaluate the expression profile of miR-145 in low-grade non-invasive and high-grade invasive bladder urothelial carcinomas.

Materials and Methods: We studied 30 specimens of low-grade, non-invasive pTa and 30 of pT2/pT3 high-grade invasive UC obtained by transurethral resection or radical cystectomy, followed over a mean time of 16.1 months. Normal controls were represented by five samples of normal bladder biopsy from patients who underwent retropubic prostatectomy to treat BPH. miRNA extraction and cDNA generation were performed using commercial kits. Analysis was performed by qRT-PCR, and miR-145 expression was calculated using the $2^{-\Delta\Delta ct}$ method; we used RNU-43 and RNU-48 as endogenous controls.

Results: miR-145 was under-expressed in 73.3% and 86.7% of pTa and pT2/pT3, respectively, with expression means of 1.61 for the former and 0.66 for the last. There were no significant differences in miR-145 expression and histological grade, tumor stage, angiolymphatic neoplastic invasion and tumor recurrence.

Conclusion: miR-145 is under-expressed in low-grade, non-invasive and high-grade invasive urothelial bladder carcinoma and may play an important role in the carcinogenesis pathway, being an interesting candidate diagnostic marker.

ARTICLE INFO

Key words:
MicroRNAs; MIRN145 microRNA, human [Supplementary Concept]; Urinary Bladder; Diagnostic Techniques, Urological; Biological Markers

Int Braz J Urol. 2013; 39: 95-102

Submitted for publication:
January 01, 2011

Accepted after revision:
November 09, 2011

INTRODUCTION

Bladder cancer (BC) is the second most common malignancy of the urinary tract, and approximately 383,300 new cases are estimated to be diagnosed in 2011 (1). Ninety percent of BC are urothelial carcinomas (UC), previously known as transitional cell carcinomas, and the majority are papillary low-grade, non-muscle invasive cancers that recur in up to 80% of cases but rarely progress to muscle invasion (2,3). In contrast, 10 to 20% of tumors are muscle invasive at diagnosis, and 50% of patients die from metastatic disease (4).

The molecular pathways underlying the two main distinct types of UC, low-grade non-muscle invasive UC and high-grade muscle invasive UC (2,5) have been investigated to identify new potential markers for diagnosis, disease mo-

nitoring, prognosis and the development of new targeted therapies (2,6).The most common genetic alteration of BC associated with low-grade and low-stage is an activating mutation of the fibroblast growth factor receptor 3 (FGFR3) gene (6,7), whereas mutations in p53, retinoblastoma (RB1) and PTEN have been identified as being characteristic of the carcinogenesis pathway for high--grade invasive BC (7-9).

The FGFR3 gene belongs to the growth factor receptor family related to the tyrosine kinase signaling pathway, which plays an important role in embryogenesis, development, angiogenesis, wound healing, tissue homeostasis and tumorigenesis, by regulating the processes of cellular proliferation, migration and apoptosis (7). Mutations are the primary phenomenon related to FGFR3 dysfunction by allowing ligand-independent operation (7,10).

P53, RB1 and PTEN are traditional tumor suppressor genes that work together and trigger BC carcinogenic pathways through several mechanisms, ranging from missense mutation and subsequently loss-of-function (9). Moreover, PTEN gene is another tumor suppressor and play roles in cell proliferation, migrations and invasion trough PI3K/AKT/mTOR carcinogenic pathway (3,9). Despite PTEN is related to development of non--invasive tumors, it is much more associated with promoters pathways and progression of invasive neoplasias. Other events are also related to alterations in protein expression, including DNA methylation, histone acetylation and abnormalities in the expression of microRNAs that contribute to the development and progression of BC.

MicroRNAs (miRNAs) are members of small single-stranded regulatory RNAs (21-25 nucleotides) that can suppress translation or promote degradation of mRNAs, thereby regulating the expression of target genes, including transcription factors, oncogenes and tumor suppressor genes. MicroRNAs have been reported to be differentially expressed in several types of cancers. Currently, there are more than 1400 miRNAs identified in humans, and up to 30% of genes are thought to be regulated by miRNAs (11). MicroRNAs are involved in cell development, differentiation, apoptosis, tissue homeostasis and several metabolic pathways (12-15) and have been related to carcinogenesis by acting as negative regulators of genes related to cancer, as exemplified by the effects of miR-15a and miR-16-1 on BCL2 mRNA, miR-143 and miR-let7c on RAS mRNA as well as miR-21 on p53 mRNA (16-19).

miR-145 is located in chromosome 5q32 and is widely established as a tumor suppressor. Several studies have validated miR-145 as an inhibitor of cellular proliferation, apoptosis, invasiveness and metastasis, as it is down-regulated in an array of cancers including those of the colorectum, lung, breast and prostate (20-22). In colorectal cancer, it was firstly demonstrated that down-regulation of miR-145 is involved with malignancies where miR-145 may play a role in tumor initiation (23,24). In BC, a Japanese group previously showed under-expression of miR-145 that normally targets the oncogenes KRT-7 and FSCN1 (25,26). However, they have not related miR-145 expression with important prognostic factors or performed any follow-up. Our aim is to study the expression profile of miR-145 in low--grade, non-invasive and high-grade invasive BC, speculating on its potential role as a prognostic or diagnostic marker.

MATERIALS AND METHODS

Patients

Specimens of 30 low-grade, non-invasive, staged pTa and 30 high-grade invasive, staged pT2/pT3 urothelial carcinomas obtained from patients who underwent transurethral resection or radical cystectomy were the subject of the study. Seventy-three percent of patients were male, and the mean age was 66.5 years, ranging from 41 to 86 years. As a control, we used normal bladder tissue from five patients who underwent retropubic prostatectomy to treat benign prostatic hyperplasia. All patients provided informed consent, and the study design was approved by the Institutional Board of Ethics, Protocol #0176/10.

A 1 cm^2 fragment of tumor tissue was immediately frozen and stored at -80°C for molecular studies. The remaining tissue was fixed in 10% formalin, routinely processed and stained with hematoxylin and eosin for histological examination.

Only low-grade, non-invasive pTa and high-grade invasive pT2/pT3 tumors were included in the study. For tumor grading, we used the WHO/ISUP 2004 and for staging AJCC/TNM 2010 classifications. The mean follow-up time was 16.1 months.

miRNA extraction and amplification

MiR-145 was isolated using a mirVana Kit® (Applied Biosystems, CA, USA) according to the manufacturer's instructions, and the concentration was determined by 260/280 nm absorbance using a Nanodrop® ND-1000 spectrophotometer (Thermo Scientific). miRNA cDNA was generated using a Taqman MicroRNA Reverse Transcription Kit® (Applied Biosystems, CA, USA). miRNA reactions were incubated at 16°C for 30 min, 42°C for 30 min and 85°C for 5 min. The cDNA was stored at -20°C until further use.

For miRNA amplification, a Taqman Reagent Kit® (Applied Biosystems, CA, USA) and the 7500 Fast Real-Time PCR System® (Applied Biosystems, CA, USA) were used.

Expression profiles of miR-145 were obtained by relative quantification determined by the $2^{-\Delta\Delta ct}$ method. The formula includes the following mathematic sentences: $\Delta\Delta CT = dCT_1 - dCT_2$, where dCT_1 = CT of miRNA-target, (tumor sample) - CT of mean of endogenous control (tumor sample), and dCT_2 = CT of mean of normal controls (normal bladder samples) - CT of mean of endogenous control (normal bladder samples). The final result is obtained by application of $2^{-\Delta\Delta ct}$ method and findings greater and smaller than 1 are considerate over and under-expressed, respectively.

The reactions were conducted in duplicate, and RNU-43 and RNU-48 were used as endogenous controls. Endogenous RNUs are miRNAs produced by cell machinery and they do not play roles over cellular functions and show a stable behavior. Thus, they were used to stardardize the values in mathematic formula.

Statistical analysis

Mann-Whitney U tests, ANOVA and T tests were used to compare miR-145 expression levels with tumor grade, stage and angiolymphatic invasion, respectively. The distribution of the expression levels of miR-145 was skewed; therefore, the data were log-transformed for analyses. The results are presented as the geometric means at a 95% confidence interval (95% CI). The number 1 in logarithmic graphics represent normal bladder samples and the expression levels are represented at times, for overexpression (greater than 1) or underexpression (smaller than 1).

RESULTS

miR-145 was under-expressed in 73.3% (22/30) and 86.7% (26/30) of pTa and pT2/pT3, respectively, as presented in Figure-1. Although both groups showed miR-145 under-expressed, we can observe that levels of under-expression were more evident in pT2/pT3 group. Furthermore, when we consider samples over-expressed (8/30 for pTa and 4/30 for pT2/pT3), the levels of over-expression were greater in low-grade, non-invasive pTa group, when compared with high-grade invasive pT2/pT3 tumors.

Expression values of miR-145 in pTa, pT2/pT3 and normal bladder controls are represented in Table-1. The mean and median expression of

Figure 1 - Expression levels (fold-change) of miR-145 in pTa and pT2/pT3 tumors.

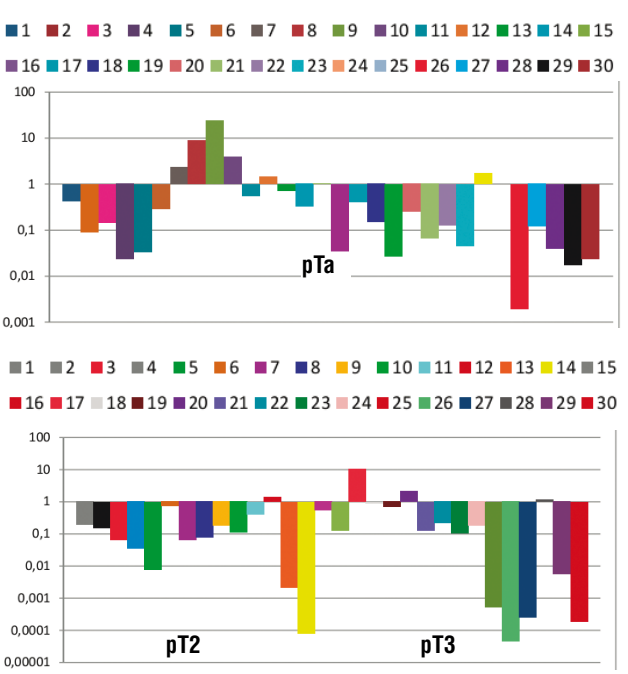

Table 1 - pTa, pT2/pT3 and controls dCTs and expression values for both tumor groups. dCT = miR-145 amplification value - mean of RNU-43 and RNU-48 amplification value. Final expression values were obtained by $2^{-\Delta\Delta}ct$ method .

pTa Samples	Avg dCT	Expression Value	pT2/pT3 Samples	Avg dCT	Expression Value	Normal Bladder Sample	Avg dCT
1	1.241	0.422	**1**	2.956	0.129	**1**	1.193
2	3.460	0.090	**2**	-3.358	10.25	**2**	-0.713
3	2.793	0.144	**3**	0.142	0.906	**3**	0.337
4	5.436	0.023	**4**	0.566	0.675	**4**	2.655
5	4.885	0.033	**5**	-1.058	2.080	**5**	-3.477
6	1.793	0.288	**6**	2.983	0.126		
7	-1.187	2.275	**7**	2.218	0.215		
8	-3.177	9.037	**8**	2.416	0.187		
9	-4.590	24.06	**9**	2.708	0.153		
10	-1.982	3.947	**10**	3.934	0.065		
11	0.856	0.552	**11**	4.866	0.034		
12	-0.515	1.428	**12**	7.073	0.008		
13	0.490	0.711	**13**	3.278	0.103		
14	1.621	0.324	**14**	0.482	0.715		
15	-0.031	1.021	**15**	3.983	0.063		
16	4.814	0.035	**16**	3.736	0.075		
17	1.295	0.407	**17**	2.503	0.176		
18	2.755	0.148	**18**	2.485	0.178		
19	5.222	0.026	**19**	3.196	0.109		
20	2.010	0.248	**20**	1.284	0.410		
21	3.938	0.065	**21**	10.871	0.0005		
22	2.980	0.126	**22**	-0.489	1.402		
23	4.476	0.044	**23**	14.465	4E-05		
24	-0.768	1.701	**24**	11.927	0,0003		
25	-0.001	1.000	**25**	-0.216	1.160		
26	9.003	0.001	**26**	7.520	0.005		
27	3.056	0.120	**27**	8.858	0.002		
28	4.665	0.039	**28**	13.608	8E-05		
29	5.819	0.017	**29**	12.383	0.0001		
30	5.397	0.023	**30**	0.895	0.537		

miR-145 was 1.61 and 0.2 (0.002 - 24.07) in pTa and 0.66 and 0.13 (4.4E-05 - 10.25) in pT2/pT3, respectively. We observed no significant differences when we compared miR-145 expression in pTa and pT2/pT3 when considering grade (p = 0.27), stage (p = 0.48) and angiolymphatic invasion (p = 0.89). Additionally, there was no difference regarding tumor recurrence (Table-2).

cause its negative regulation of target mRNAs involved in control of cell cycle, apoptosis, invasiveness and metastasis, exerting a fundamental role in cellular and tissue homeostasis (22-24,28).

The first report of miR-145 under-expression was performed by Michael et al. (23) in a study suggesting that these alterations could be involved in the initiation of colorectal cancer. These

Table 2 - Comparison of miR-145 by grade, stage, angiolymphatic invasion and tumor recurrence.

	Low grade (30)	High grade (30)	pTa (30)	pT2-3 (30)	Angiolymphatic tumor embolization		Tumor recurrence	
miR-145	1.61	0.66	1.61	0.66	Yes (16)	No (44)	Yes (29)	No (31)
Mean	0.20	0.13	0.20	0.13	1.03	1.41	0.43	1.93
Median	0.002	4.4-5	0.002	4.4-5	0.12	0.15		
Min	24.07	10.25	24.07	10.25	4.4-5	8.0-5		
Max					10.25	24.07		
P value	0.27		0.48		0.89		0.44	

DISCUSSION

Although we did not detect any differences in miR-145 expression between low- and high--grade tumors, our results show that this miRNA is under-expressed in both urothelial carcinomas; the lowest miRNA levels were detected in the second group (86.7%). We did not include pT1 and Cis tumors because they have genetic molecular profiles that harbor both the carcinogenic pathway of pTa, as of the pT2/pT3.

In BC, miR-145 can silence a large number of genes and has been involved in bladder carcinogenesis. Ichimi et al. (27) have previously shown miR-145 under-expression in BC by microarray and qRT-PCR, but they did not characterize the relationship between miR-145 expression with histological grading, staging or tumor behavior.

MiR-145 is located on chromosome 5q32 and is considered a tumor suppressor miRNA be-

findings were confirmed by Shi et al. (24) who showed that miR-145 under-expression was associated with malignant tumors.

Accumulating evidence suggest that microRNAs could be key players in regulation of tumor cell invasion and metastasis. Sachdeva and Mo (27) have shown in breast cancer cells lines that miR-145 targets Mucin 1 (MUC-1) gene, involved in initiation, invasiveness and tumor dissemination. Another miR-145 target is c-MYC (22). miR-145 inhibits c-MYC, a negative regulator of p21, and loss of miR-145 expression could be involved in a failure of c-MYC regulation, lowering levels of p21 and increasing cellular proliferation rate. C-MYC over-expression could also stimulate CDK-4/6 and cyclin D1, promoting RB1 phosphorylation, which would also trigger mitosis and cellular proliferation. The other role of miR-145 is to enhance p53 function by MDM-2 indirect inhibition (6). P53 gene is one of the main indirect targets of miR-145 and is

directly related to the high-grade invasive BC carcinogenesis pathway. In 2009, Sachdeva et al. (22) observed that, under physiological conditions, higher levels of p53 due to cellular stress leads to increased levels of miR-145 through p53 response element (p53RE). P53 can also trigger the enzymatic machinery of microRNAs, mainly the RNase III Drosha, promoting higher expression levels of several microRNAs including miR-145. Loss of p53 function through mutations could generate a lack of production and consequent under-expression of miR-145 (28).

Spizzo et al. (29) demonstrated a tumor suppressor role of miR-145, preventing cell growth and inducing apoptosis through stimulation of p53, by transfecting miR-145 into breast cancer cell lines. This experiment could suggest a therapeutic use of miR-145 in tumors.

The FSCN1 gene is another target of miR-145. The protein product of this gene is required to form protrusions of the cellular membrane and cytoplasmic movements related to migration. In malignant neoplasms, FSCN1 activity has been correlated to high-grade disease, extensive invasion, metastasis and poor prognosis (30). Chiyomaru et al. (26) concluded that there is an association between FSCN1 oncogene over-expression due to miR-145 under-expression in BC, which leads to a more aggressive phenotype. The authors found a positive correlation between high tumor stage and low levels of miR-145. However, we did not find a relationship between miR-145 expression and tumor grade, stage or angiolymphatic tumor embolization.

We also investigated the levels of miR-145 with tumor recurrence and found no association between both groups. Here, we can make the case that miR-145 is important to tumor carcinogenesis and triggers low-grade, non-invasive pTa tumorigenesis through the lack of control of AKT. We also speculate that miR-145 is involved in our cases of high-grade invasive pT2/pT3 carcinomas through MUC-1, c-MYC, p53 and FSCN1 deregulation.

The casuistic was limited, and groups greater than 30 samples are wished. Maybe this fact could really be related to absence of statistical differences. Another limitation was a short follow-up.

CONCLUSIONS

MiR-145 is a well-characterized tumor suppressor miRNA. We hypothesize that lack of protector role promoted by this miRNA over probable target genes PI3K/AKT, FSCN1, MDM2, c-Myc and MUC-1 could be involved in carcinogenic process of low-grade, non-invasive and high-grade invasive urothelial carcinomas, triggering their carcinogenesis. Since we found miR-145 widely under-expressed in both tumor groups, we speculate its use as a possible diagnostic marker. These findings should be tested in experimental models.

ABREVIATIONS

BC: Bladder Cancer
miR and miRNA: micro RNA
qRT-PCR: quantitative transcriptase reverse polymerase chain reaction
cDNA: complementar DNA
UC(s): urothelial carcinoma(s)
mRNA: messenger RNA
FGFR3: fibroblast growth factor receptor 3
ISUP: International Society of Urological Pathology
RB1: retinoblastoma gene
PTEN: phosphatase and tensin homolog gene
WHO: World Health Organization

ACKNOWLEDGEMENTS

Sponsor by: FAPESP 10/50824-1

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Recently discovered, the micro RNAs have been extensively studied in recent years in several malignancies. This paper brings relevant new information about the role of a micro RNA in two extremes of urothelial BC: the low grade pTa and the high grade invasive ones (pT2/3). The result shows a reduced action of this miR as in low risk pTa, as in invasive BC. Theorically, target therapies that improve or regenerate the actions of miR145 could be planned in the future if these findings are validated.

The authors did not investigate pT1 and in situ (CIS) BC, justifying that these tumors have different carcinogenic pathways.

Meanwhile, I think it would be interesting to test miR145 in pT1 and in CIS, to be sure that this micro RNA is really not involved in the carcinogenic process of these high risk non-muscle invasive bladder tumors. Some of pT1 tumors e.g., presents as recurrence after the treatment of pTa lesions and CIS can co exist side by side of some papillary lesions. Are theses lesions independent?

In the future, other interesting issue concerning recurrent non-muscle invasive BCs might to investigate if intravesical BCG instillations could influence (restore?) the miR145 expression.

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