HOXC10 is significantly overexpressed in colorectal cancer

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Abstract. Colorectal cancer (CRC) is one of the most common types of cancer in world and has a high rate of mortality. The majority of cases of CRC are sporadic; however, factors such as age, a family history of inflammatory diseases, diet, lifestyle and genetics increase the risk. *HOX* genes and lncRNAs are two classes of genes, and alterations in the expression levels of these genes are significantly associated with numerous different types of cancer. In the present study, the expression levels of *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* in tumor tissues were compared with normal healthy tissues in patients with CRC. Paired tumor and normal tissues were collected from 39 patients with CRC, and reverse transcription-quantitative PCR was used the expression of *HOXC-AS3*, *HOXC13* and *HOXC10* in the tumor tissues compared with the respective normal tissues. Expression of these genes were increased in the tumor tissues compared with normal tissues; however, the difference was only significant for *HOXC10*. Additionally, there was a strong and significant correlation between the expression of *HOTAIR* and *HOXC13*, a moderate and significant correlation between the expression of *HOTAIR* and *HOXC13-AS*, and between *HOXC13* and *HOXC13-AS* genes. The expression of *HOXC10* was significantly higher in tumor tissues compared with the normal tissues; whereas the upregulation of *HOXC-AS3* and *HOXC13* were not significant. Only the correlation between the expression of *HOTAIR* and *HOXC13* was strong and significant. As *HOXC10* expression was significantly upregulated in the tumor tissues relative to normal tissues, it may serve as a biomarker for the diagnosis of CRC and as a potential therapeutic target.

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer (1) and 880,792 CRC-associated deaths were reported

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in 2018 (2). The prevalence of CRC is 9.2% in women and 10% in men, and it is the second most common type of cancer in women and third most common type of cancer in men (3). In ~90% of cases, CRC is sporadic, and patients do not have any family history of the disease (4). Risk factors for CRC include age (higher in individuals >50 years), and a family history of inflammatory bowel disease (3.7% risk for CRC) and Crohn's disease (2.5% risk for CRC) (5-7). Diet and lifestyle may increase the risk of CRC (8), such as smoking (9,10), consumption of red meat (11,12) and low levels of physical activity (13).

Mutations in various genes, alterations in DNA methylation and chromosomal instability have been identified as genetic causes of CRC. Analysis of gene expression profiles of cancer cells serves an important role in the diagnosis and treatment of patients with cancer and may result in improved insight into the dysregulated mechanisms associated with specific types of cancer. *HOX* genes are involved in the regulation of different cellular processes, including differentiation, angiogenesis, signaling, apoptosis, mobility and metastasis (14,15). *HOXC* genes (*HOXC4*, *HOXC5*, *HOXC6*, *HOXC8*, *HOXC9*, *HOXC10*, *HOXC11*, *HOXC12* and *HOXC13*) are members of the *HOX* family of genes and are located on chromosome 12q13.3 (16), and *HOXC13* is involved in the growth and formation of hair and nails (17,18).

Three long non-coding RNAs (lncRNAs), *HOTAIR*, *HOXC13-AS* and *HOXC-AS3* are located on the antisense strand of the *HOXC* gene cluster (Fig. 1). *HOTAIR* is a polyadenylated RNA that binds to certain protein complexes, such as PRC2, and regulates the conformation of chromatin (19-21). *HOXC10*, *HOXC-AS3*, *HOXC13* and *HOXC13-AS* are located in close proximity to the oncogenic lncRNA, *HOTAIR*. Thus, it was hypothesized that there may be an association between these genes with *HOTAIR* and development of cancer. In the present study, the expression levels of these genes were assessed using reverse transcription-quantitative (RT-q) PCR in tumor tissues and matching healthy adjacent tissues in patients with CRC.

Materials and methods

Patients and tissue samples. A total of 39 pairs of tumor tissue and healthy adjacent tissue was obtained from patients. The median age of patients was 54 years old (range, 30-79 years) and included 20 males and 19 females. Tissues were obtained from patients with CRC following surgery and immediately stored in liquid nitrogen. The present study was approved by

the Ethics Committee of Shahid Chamran University of Ahvaz (Ahvaz, Iran) and written informed consent was obtained from all patients.

RT-qPCR. A total of 50 mg frozen tissue from each patient was crushed and homogenized. Total RNA was extracted using TRIzol® Reagent (Invitrogen; Thermo Fisher Scientific, Inc.) and RNA was dissolved in diethyl pyrocarbonate. The RNA concentration of each sample was measured using a NanoDrop™ 2000/c spectrophotometer (Thermo Fisher Scientific, Inc.) and stored at -80°C. RNA integrity was assessed using electrophoresis on a 1% agarose gel containing SafeStain (CinnaGen), and the 28S, 18S and 5S bands were observed. Extracted RNAs were treated using DNaseI (Takara Bio, Inc.). Primescript™ RT reagent kit (Takara Bio, Inc.) was used for reverse transcription of RNA to cDNA. A total of 1 μl random hexamers (100 μM) and 1 μl oligo(dT) primer (50 μM) were added to 1 μg DNase treated RNA and RNase free water was added to a final volume of 5 μl and incubated at 65°C for 5 min. Subsequently, 1 μl reverse transcriptase enzyme (1 U/μl) and 4 μl 5X buffer was added, and RNase free H$_2$O was added to a final volume of 20 μl and incubated at 37°C for 30 min for cDNA synthesis, followed by incubation at 80°C for 5 sec to inactivate the enzyme and cDNA was stored at -20°C. For qPCR, the following reagents were mixed as follows: 10 μl SYBR Premix Ex Taq II (2X) (Takara Bio, Inc.), 0.5 μl each forward and reverse primers (10 pmol each; Macrogen, Inc.), 2 μl cDNA and 7 μl DNase free water. The primer sequences used are presented in Table I. *β-actin* was used as the loading control. The thermocycling conditions were: 95°C for 30 sec; 40 cycles of 95°C for 5 sec and 60°C for 32 sec; and a dissociation stage of 95°C for 15 sec, 60°C for 60 sec and 95°C for 1 sec. Relative expression of *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* was measured using the 2$^{-\Delta\Delta Cq}$ method (22) for the 39 pairs of the tumor tissues and marginal normal tissues in patients with CRC. *β-actin* was used as the reference gene.

Data analysis. All analysis was performed using GraphPad Prism version 5 (GraphPad Software, Inc.). Differences between two groups were compared using a Wilcoxon test. A Spearman's rank correlation coefficient was used for correlation analysis of relative gene expression with clinical parameters.

Results

Comparison of expression of HOX genes between tumor and normal tissues. Expression of HOX expression of *HOXC-AS3* and *HOXC13* in the tumor tissues was upregulated compared with the marginal normal tissues with a fold change of 4.65 and 2.47, respectively. Although *HOXC-AS3* and *HOXC13* were upregulated in the tumor tissues, statistical analysis showed the difference was not significant (P=0.144 and P=0.78, respectively; Fig. 2). However, expression of *HOXC10* was significantly upregulated in the tumor tissues compared with the marginal normal tissues with a fold change of 2.07 (P=0.0001; Fig. 2). Comparison of the expression of *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* in the tumor and normal tissues is shown in Fig. 2.

Table I. Sequence of primers used in this study.

Genes	Primer sequences (5'-3')
HOXC10	F: CCAGACACCTCGGATAACG
HOXC10	R: GGCACCTCTTCTTCCTTCC
HOXC13	F: TCTCCCTTCCCAGACGTGGT
HOXC13	R: CGCTCAGAGAGGTTCGTGGT
HOTAIR	F: GAAAGGTCCTGCTCCGCTTC
HOTAIR	R: TCCTCTCGCCGCCGTCTG
HOXC-AS3	F: CGATAGGCGGCTTTGG
HOXC-AS3	R: CGTCTTGTGTGCTGGTTTCC
HOXC13-AS	F: CGGACATCGGAGCACTATG
HOXC13-AS	R: CGGCTGGTCTTCTTGAGG
β-actin	F: ATTGGCAATGAGCGGTTC
β-actin	R: TGAAGGTAGTTTCGTGGATG

F, forward; R, reverse.

Correlation between the expression of genes. To determine the correlation coefficients, the fold change ratio of each gene was used. There was a significant positive correlation between expression of *HOTAIR* and *HOXC13* (r=0.75, strong correlation; P=0.00000004); between *HOTAIR* and *HOXC13-AS* (r=0.57, moderate correlation; P=0.001); and between *HOXC13* and *HOXC13-AS* (r=0.43, moderate; P=0.006). There was positive correlation between *HOTAIR* and *HOXC10* (r=0.306, moderate; P=0.058), and between *HOTAIR* and *HOXC-AS3* (r=0.384, moderate; P=0.016). There was a significantly negative correlation between *HOXC10* and *HOXC-AS3* (r=-0.331, moderate; P=0.039).

Association between gene expression and clinicopathological features. The association between the expression of the five genes with clinicopathological characteristics of the patients was calculated. Statistical analysis showed that there was no significant association between sex, histological grade, tumor size (cm), Tumor-Node-Metastasis (TNM) stage (23), lymphatic invasion, vascular invasion and the expression of *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* or *HOXC13-AS* in the patients with CRC (all P>0.05; Table II).

Discussion

In 2012, ~1.4 million new cases of CRC were diagnosed. By 2035, it is estimated that there will be >2.4 million new cases of colorectal cancer (24). In the present study, the expression levels of *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* in matching normal and tumor tissues from 39 patients with CRC were assessed using RT-qPCR. *HOXC10*, *HOXC-AS3*, *HOXC13*, and *HOXC13-AS* are located in proximity to the oncogenic lncRNA *HOTAIR*. Thus, it was hypothesized that there may be an association between these genes and *HOTAIR* in carcinogenesis. To evaluate this hypothesis, the correlation between the expression of these five genes with *HOTAIR*, and the association between these genes and certain clinicopathological characteristics were calculated. The results showed that the expression of *HOTAIR* was not
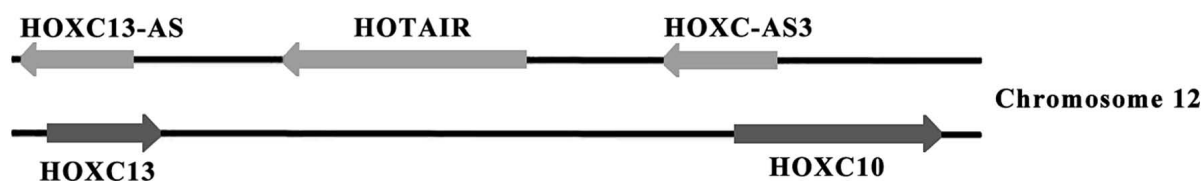
Figure 1. *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* are located on the sense or antisense strands of chromosome 12.
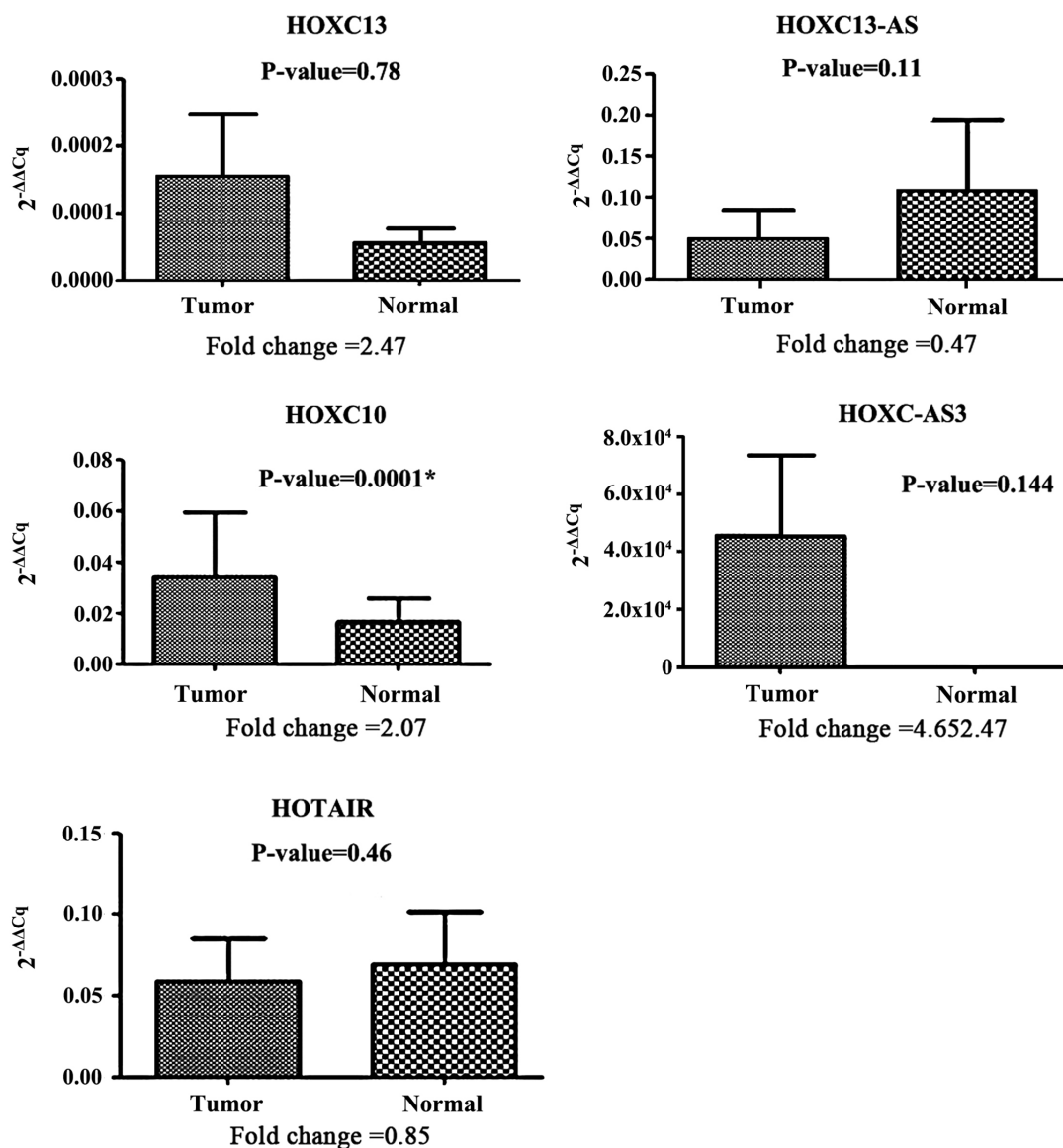

Figure 2. Comparison of the expression of *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* in paired tumor and normal tissues. Only the expression levels of *HOXC10* were significantly different between the two tissues. *P=0.0001.

significantly altered in tumor tissues compared with marginal normal tissues, contrasting with previous studies which reported a significant increase in the expression of *HOTAIR* in CRC (25-29). Kogo *et al* (30) studied 100 pairs of tumor and normal CRC samples and reported that there was no significant increase in expression of *HOTAIR*. Svoboda *et al* (31) also reported that the relative expression of *HOTAIR* between the tumor and adjacent normal tissue was not significantly different in patients with CRC. These differences may be related to the ethnicity of the individuals studied, their lifestyle, diet or other

lifestyle factors. Upregulation of *HOXC13* has been reported in odontogenic tumors, liposarcoma, metastatic melanoma, esophageal squamous cell carcinoma, lung adenocarcinoma and ameloblastoma (32-37). However, the expression levels of *HOXC13* in CRC was not significantly altered in the present study. Tatangelo *et al* (38) reported a significant upregulation in the expression of *HOXC13* and *HOTAIR* in right (proximal) side of CRCs tissues.

Overexpression of *HOXC13-AS* has been reported in nasopharyngeal carcinoma (39). To the best of our knowledge,

Table II. Association between expression of the selected genes and clinicopathological characteristics.

Characteristics	n	*HOXC13*	*HOXC13-AS*	*HOTAIR*	*HOXC10*	*HOXC-AS3*
Sex		0.66	0.37	0.56	0.42	0.83
Male	20					
Female	19					
Histological grade		0.3	0.57	0.4	0.07	0.57
≤2	33					
>2	6					
Tumor size, cm		0.078	0.81	0.74	0.32	0.66
≤5	20					
>5	19					
TNM stage		0.16	0.28	0.22	0.85	0.06
≤3	20					
>3	19					
Lymphatic invasion		0.41	0.66	0.6	0.81	0.36
Yes	20					
No	19					
Vascular invasion		0.53	0.42	0.83	0.6	0.15
Yes	19					
No	20					

TNM, Tumor-Node-Metastasis staging system.

the present study is the first to evaluate the expression of *HOXC13-AS* in CRC, and the results showed that there was no significant difference in the expression of *HOXC13-AS* between normal and cancer tissues.

Studies have shown that the expression of *HOXC10* is significantly increased in thyroid cancer, breast carcinoma and lung cancer (40-43). Kim *et al* (44) reported that expression of *HOXC10* was upregulated in gastric cancer. They showed that upregulation of *HOXC10* increases proliferation and migration of gastric cancer cells (44). In the present study the expression levels of *HOXC10* in CRC were assessed and the results showed that the relative expression in the tumor tissues was significantly higher compared with marginal normal tissues in CRC (P=0.0001). Zhang *et al* (45) showed that expression of *HOXC-AS3* was upregulated in gastric cancer tissues compared with normal tissues, but in the present study, expression of *HOXC-AS3* was not changed significantly altered in tumor tissues of patients with CRC compared with normal tissues. To the best of our knowledge, the present study is the first to assess the expression of *HOXC-AS3* in patients with CRC.

The association between the expression *HOXC10*, *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* with clinicopathological characteristics, including sex, histological grade, tumor size (cm), TNM stage, lymphatic invasion and vascular invasion were calculated. Although there was no significant relationship between any of the genes evaluated and any of the clinicopathological characteristics, the correlation coefficients were positive for all the clinical parameters and expression data, suggesting that, whilst an association may exist it is not strong and not statistically significant. Therefore, upregulation

of the studied genes may have weak or moderate effects on these characteristics. For protein coding genes, it may be possible that the expression levels of the protein products may be directly correlated with these characteristics. Additionally, upregulated genes may affect the initiation and progression of tumorigenesis, including increasing proliferation and reducing apoptosis (46).

To determine the correlation coefficient, the fold change ratio of each gene was used. There was a strong and significant correlation between the expression of *HOTAIR* and *HOXC13*; and a moderate but significant correlation between the expression of *HOTAIR* and *HOXC13-AS*, and between *HOXC13* and *HOXC13-AS*.

The correlation between the expression of *HOTAIR* and *HOXC10* and between the expression of *HOTAIR* and *HOXC-AS3* were moderate but not significant. There was a moderate negative correlation between the expression of *HOXC-AS3* and *HOXC10* and this difference was significant.

HOTAIR and *HOXC13* appeared to exhibit similar expression pattern as there was a strong correlation between them. The results of the present study suggest that these genes may affect expression of each other expression in cis; however, additional functional studies are required to determine whether this is the case. Due to the significant upregulation of *HOCX10* in the tumor tissues, it may be used as a biomarker for the diagnosis and treatment of CRC.

Future studies should use larger cohorts and evaluate the expression of the studied genes in the serum and blood of patients. Additionally, the expression of these genes in other types of cancer and the expression of other HOX family genes in CRC should be assessed. To determine whether HOTAIR

influences expression of any of the HOX family genes, HOTAIR expression should be knocked down and the expression of surrounding genes assessed.

In conclusion the present study showed that *HOXC10* expression was significantly higher in CRC samples compared with the normal adjacent tissues, but expression of *HOXC-AS3*, *HOTAIR*, *HOXC13* and *HOXC13-AS* did not differ significantly. Based on these results, HOXC10 may be considered as a biomarker for diagnosis of CRC. Additionally the expression of *HOTAIR* and *HOXC13* were strongly correlated and thus may share a regulatory mechanism of expression or one of these genes may regulate the expression of the other. Further functional studies are required to elucidate the mechanism underlying this correlation.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

MZ and HG conceived and designed the study; MG and ME acquired, analyzed and interpreted the data; ME, MG, MZ and HG participated in drafting the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of Shahid Chamran University of Ahvaz (Ahvaz, Iran) and written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108, 2005.
2. International Agency for Research on Cancer WHO. Cancer today. IARC Web site. https://gco.iarc.fr/today/. Accessed Jan 21, 2019.
3. Stewart BW and Wild CP (eds): World Cancer Report 2014. IARC Nonserial Publication, Lyon, pp630, 2014.
4. Bogaert J and Prenen H: Molecular genetics of colorectal cancer. Ann Gastroenterol 27: 9-14, 2014.
5. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, *et al*: Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American cancer society, the US multi-society task force on colorectal cancer, and the American college of radiology. CA Cancer J Clin 58: 130-16, 2008.
6. Eaden JA, Abrams KR and Mayberry JF: The risk of colorectal cancer in ulcerative colitis: A meta-analysis. Gut 48: 526-535, 2001.
7. Canavan C, Abrams KR and Mayberry J: Meta-analysis: Colorectal and small bowel cancer risk in patients with crohn's disease. Aliment Pharmacol Ther 23: 1097-1104, 2006.
8. Robertson DJ: ABC of colorectal cancer. Gastroenterology 143: 868-886, 2012.
9. Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB and Maisonneuve P: Smoking and colorectal cancer: A meta-analysis. JAMA 300: 2765-2778, 2008.
10. Liang PS, Chen TY and Giovannucci E: Cigarette smoking and colorectal cancer incidence and mortality: Systematic review and meta-analysis. Int J Cancer 124: 2406-2415, 2009.
11. Bastide NM, Pierre FH and Corpet DE: Heme iron from meat and risk of colorectal cancer: A meta-analysis and a review of the mechanisms involved. Cancer Prev Res (Phila) 4: 177-184, 2011.
12. Santarelli RL, Pierre F and Corpet DE: Processed meat and colorectal cancer: A review of epidemiologic and experimental evidence. Nutr Cancer 60: 131-144, 2008.
13. Martinez-Useros J and Garcia-Foncillas J: Obesity and colorectal cancer: Molecular features of adipose tissue. J Transl Med 14: 21, 2016.
14. Grier DG, Thompson A, Kwasniewska A, McGonigle GJ, Halliday HL and Lappin TR: The pathophysiology of HOX genes and their role in cancer. J Pathol 205: 154-171, 2005.
15. Shah N and Sukumar S: The Hox genes and their roles in oncogenesis. Nat Rev Cancer 10: 361-371, 2010.
16. Apiou F, Flagiello D, Cillo C, Malfoy B, Poupon MF and Dutrillaux B: Fine mapping of human HOX gene clusters. Cytogenet Cell Genet 73: 114-115, 1996.
17. Godwin AR and Capecchi MR: Hoxc13 mutant mice lack external hair. Genes Dev 12: 11-20, 1998.
18. Kulessa H, Turk G and Hogan BL: Inhibitionof Bmp signaling affects growth and differentiation in the anagen hair follicle. EMBO J 19: 6664-6674, 2000.
19. Woo CJ and Kingston RE: HOTAIR lifts noncoding RNAs to new levels. Cell 129: 1257-1259, 2007.
20. Chu C, Qu K, Zhong FL, Artandi SE and Chang HY: Genomic maps oflong noncoding rna occupancy reveal principles of rna-chromatin interactions. Mol Cell 44: 667-668, 2011.
21. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, *et al*: Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464: 1071-1076, 2010.
22. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods 25: 402-408, 2001.
23. Galli F, Ruspi L, Marzorati A, Lavazza M, Di Rocco G, Boni L, Dionigi G and Rausei S. N staging system: Tumor-node-metastasis and future perspectives. Transl Gastroenterol Hepatol 2: 4, 2017.
24. Pauler FM, Koerner MV and Barlow DP: Silencing by imprinted noncoding RNAs: Is transcription the answer? Trends Genet 23: 284-292, 2007.
25. Xue Y, Ma G, Gu D, Zhu L, Hua Q, Du M, Chu H, Tong N, Chen J, Zhang Z and Wang M: Genome-wide analysis of long noncoding RNA signature in human colorectal cancer. Gene 556: 227-234, 2015.
26. Yang XD, Xu HT, Xu XH, Ru G, Liu W, Zhu JJ, Wu YY, Zhao K, Wu Y, Xing CG, *et al*: Knockdown of long non-coding RNA HOTAIR inhibits proliferation and invasiveness and improves radiosensitivity in colorectal cancer. Oncol Rep1 35: 479-487, 2016.
27. Dou J, Ni Y, He X, Wu D, Li M, Wu S, Zhang R, Guo M and Zhao F: Decreasing lncRNA HOTAIR expression inhibits human colorectal cancer stem cells. Am J Transl Res 8: 98-108, 2016.
28. Lu X, Liu Z, Ning X, Huang L and Jiang B: The long noncoding RNA HOTAIR promotes colorectal cancer progression by sponging miR-197. Oncol Res 26: 473-481, 2018.
29. Huang X and Lu S: MicroR-545 mediates colorectal cancer cells proliferation through up-regulating epidermal growth factor receptor expression in HOTAIR long non-coding RNA dependent. Mol Cell Biochem 431: 45-54, 2017.

30. Kogo R, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, *et al*: Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is associated with poor prognosis in colorectal cancers. Cancer Res 71: 6320-6326, 2011.
31. Svoboda M, Slyskova J, Schneiderova M, Makovicky P, Bielik L, Levy M, Lipska L, Hemmelova B, Kala Z, Protivankova M, *et al*: HOTAIR long non-coding RNA is a negative prognostic factor not only in primary tumors, but also in the blood of colorectal cancer patients. Carcinogenesis 35: 1510-1515, 2014.
32. Zhong M, Wang J, Gong YB, Li JC, Zhang B and Hou L: Expression of HOXC13 in ameloblastoma. Zhonghua Kou Qiang Yi Xue Za Zhi 42: 43-46, 2007 (In Chinese).
33. Hong YS, Wang J, Liu J, Zhang B, Hou L and Zhong M: Expressionof HOX C13 in odontogenic tumors. Shanghai Kou Qiang Yi Xue 16: 587-591, 2007 (In Chinese).
34. Cantile M, Scognamiglio G, Anniciello A, Farina M, Gentilcore G, Santonastaso C, Fulciniti F, Cillo C, Franco R, Ascierto PA and Botti G: Increased HOXC13 expression in metastatic melanoma progression. J Transl Med 10: 91, 2012.
35. Cantile M, Galletta F, Franco R, Aquino G, Scognamiglio G, Marra L, Cerrone M, Malzone G, Manna A, Apice G, *et al*: Hyperexpression of HOXC13, located in the 12q13 chromosomal region, in welldifferentiated and dedifferentiated human liposarcomas. Oncol Rep 30: 2579-2586, 2013.
36. Luo J, Wang Z, Huang J, Yao Y, Sun Q, Wang J, Shen Y, Xu L and Ren B: HOXC13 promotes proliferation of esophageal squamous cell carcinoma via repressing transcription of CASP3. Cancer Sci 109: 317-329, 2018.
37. Yao Y, Luo J, Sun Q, Xu T, Sun S, Chen M, Lin X, Qian Q, Zhang Y, Cao L, *et al*: HOXC13 promotes proliferation oflung adenocarcinoma via modulation of CCND1 and CCNE1. Am J Cancer Res 7: 1820-183, 2017.
38. Tatangelo F, Di Mauro A, Scognamiglio G, Aquino G, Lettiero A, Delrio P, Avallone A, Cantile M and Botti G: Posterior HOX genesand HOTAIR expression in the proximal and distal colon cancer pathogenesis. J Transl Med 16: 350, 2018.
39. Gao C, Lu W, Lou W, Wang L and Xu Q: Long noncoding RNA HOXC13-AS positively affects cell proliferation and invasion in nasopharyngeal carcinoma via modulating miR-383-3p/HMGA2 axis. J Cell Physiol 234: 12809-12820, 2019.
40. Feng X, Li T, Liu Z, Shi Y and Peng Y: HOXC10 up-regulation contributes to human thyroid cancer and indicates poor survival outcome. Mol Biosyst 11: 2946-2954, 2015.
41. Ansari KI, Hussain I, Kasiri S and Mandal SS: HOXC10 is overexpressed in breast cancer and transcriptionally regulated by estrogen via involvement of histone methylases MLL3 and MLL4. J Mol Endocrinol 48: 61-75, 2012.
42. Sadik H, Korangath P, Nguyen NK, Gyorffy B, Kumar R, Hedayati M, Teo WW, Park S, Panday H, Munoz TG, *et al*: HOXC10 expression supports the development of chemotherapy resistance by fine tuning DNA repair in breast cancer cells. Cancer Res 76: 4443-4456, 2016.
43. Tang XL, Ding BX, Hua Y, Chen H, Wu T, Chen ZQ and Yuan CH: Hoxc10 promotes the metastasis of human lung adenocarcinoma and indicates poor survival outcome. Front Physiol 8: 557, 2017.
44. Kim J, Bae DH, Kim JH, Song KS, Kim YS and Kim SY: HOXC10 overexpression promotes cell proliferation and migration in gastric cancer. Oncol Rep 42: 202-212, 2019.
45. Zhang E, He X, Zhang C, Su J, Lu X, Si X, Chen J, Yin D Han L and De W: A novel long noncoding RNA HOXC-AS3 mediates tumorigenesis of gastric cancer by binding to YBX1. Genome Biol 19: 154, 2018.
46. Bhatlekar S, Fields JZ and Boman BM: HOX genes and their role in the development of human cancers. J Mol Med 92: 811-823, 2014.