# Variation in Sp1 binding sites correlates with expression of survivin in breast cancer

QING XU, MEI LIU, NINGZHI XU and HONGXIA ZHU

Laboratory of Cell and Molecular Biology and State Key Laboratory of Molecular Oncology, Cancer Institute and Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, P.R. China

Received October 17, 2013; Accepted November 26, 2013

DOI: 10.3892/mmr.2014.2371

**Abstract.** Survivin is the smallest member of the inhibitor of apoptosis (IAP) family and is deregulated in breast cancer, where it is associated with a poor overall prognosis. It is well established that survivin overexpression predominately occurs at the transcriptional level. Numerous transcription factors bind to specific sequences in the promoter regions of genes and are involved in transcriptional regulation. Specificity protein (Sp) 1 binding sites have been found in the promoter region of the survivin gene. The present study aimed to investigate whether variations in Sp1 binding sites affect survivin expression. Nested polymerase chain reaction followed by DNA sequencing were performed to analyze the survivin gene promoter region in 42 breast cancer tissue samples. Furthermore, survivin expression was assessed using immunohistochemistry. High survivin protein expression was found in 66.7% (28/42) of breast cancer tissue samples. In addition, 15 variations in seven Sp1 binding sites were detected in 12 samples and Sp1 binding site variation was found to be associated with low survivin expression in the 42 samples. These findings suggested that variations in Sp1 binding sites may be associated with survivin expression.

## Introduction

Survivin, encoded by the human baculoviral IAP repeat containing 5 (BIRC5) gene, is the smallest member of the inhibitor of apoptosis (IAP) family and is involved in several distinct molecular processes, including cell division, intracellular signaling and apoptosis (1). Survivin is rarely expressed in normal human tissues, but is widely expressed in the majority of cancer types, including neuroblastoma, melanoma and hepatocellular carcinoma, as well as brain, esophageal, laryngeal, gastric, colorectal, bladder, renal, uterine, ovarian, lung, breast and pancreatic cancer. Moreover, survivin is associated with increased tumor aggression and poorer clinical outcome (2,3). Due to the high global expression of survivin in cancer, survivin has been proposed to be a molecular target for anticancer therapy (4-7).

The expression of survivin in breast cancer has attracted much research attention. Over the past year, several studies have investigated survivin mRNA and protein expression in breast cancer, as well as the correlation between survivin expression and clinicopathological factors and prognosis in patients with breast cancer. Survivin has been reported to be expressed in numerous types of breast cancer and overexpression of survivin has been associated with a poor overall prognosis (8-14).

The mechanisms underlying survivin overexpression in cancer have yet to be elucidated; however, survivin expression has been proposed to be regulated primarily at the transcriptional level (15). Genetic variation in the survivin promoter region may be responsible for survivin expression, particularly the -31G/C single-nucleotide polymorphism (SNP), which has been shown to affect survivin expression, thereby influencing overall susceptibility to cancer (16,17). The -31G/C SNP is located at the cell cycle-dependent element/cell cycle homology (CDE/CHR) repressor region and mediates survivin expression through functional disruption of binding at the CDE/CHR repressor motif (18). However, -31 G/C polymorphism has not been found to be associated with survivin expression in breast cancer (19). Analysis of the putative promoter region of BIRC5 has revealed that the ubiquitous transcription factor specificity protein (Sp) 1 may be responsible for the constitutive survivin expression in tumors (20,21). Furthermore, numerous other transcription factors, including retinoblastoma protein, p53, signal transducer and activator of transcription 3, c-Myc, E2F, Krüppel-like factor (KLF) 5 and KLF4, may be involved in the regulation of survivin expression (22,23). Among these transcription factors, Sp1 has attracted the most research attention. Sp1 has been proposed to be the predominant reason

*Correspondence to:* Dr Hongxia Zhu, Laboratory of Cell and Molecular Biology and State Key Laboratory of Molecular Oncology, Cancer Institute and Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan Nanli, PO Box 2258, Beijing 100021, P.R. China
E-mail: drhxzhu@cicams.ac.cn

*Abbreviations:* IAP, inhibitor of apoptosis; BIRC5, human baculoviral IAP repeat containing 5; Sp1, specificity protein 1

*Key words:* survivin, Sp1 binding sites, promoter region, breast cancer

for constitutive survivin expression in tumors (20,21). There are at least seven potential Sp1 binding sites in the core promoter region of survivin, according to the canonical or close to canonical sequence (G/T)(G/A)GGCG(G/T)(G/A)(G/A)(C/T), with at least three of the Sp1 binding sites reported to be functionally active (20-22). Furthermore, other transcription factors, including KLF4, have been found to regulate survivin expression through direct interaction with Sp1 (23,24).

Thus, Sp1 may be the key to understanding survivin expression in cancer. *In vitro* assays have revealed that Sp1 mutation may decrease survivin promoter activity, as well as survivin expression (22). The present study aimed to investigate whether Sp1 binding sites vary in breast cancer tissues and to analyze the correlation between Sp1 binding site variations and survivin expression.

## Materials and methods

*Tissue sample collection and immunohistochemistry*. Breast cancer tissue samples were obtained from Loudi Central Hospital (Loudi, China). All samples were confirmed by pathologists. Paraffin-embedded samples were cut into 4-mm sections and immunohistochemistry was performed using a standard streptavidin peroxidase (SP) method. Slides were dewaxed using xylene and rehydrated with serial dilutions of ethanol. Antigen retrieval was then performed and endogenous peroxidase activity was blocked using 3% hydrogen peroxide and nonspecific staining was blocked using 10% normal goat serum (Vector Laboratories Inc., Burlingame, CA, USA). Slides were incubated with anti-survivin antibodies diluted 1:100 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) at 4˚C in a humidified chamber overnight, followed by incubation with biotin-conjugated secondary antibodies (ZSGB-BIO, Beijing, China) for 30 min and incubation with streptavidin peroxidase for 15 min. 3,3'-diaminobenzidine tetrachloride (DAB; ZSGB-BIO) was added to the slides to detect peroxidase activity. Sections were then dehydrated using alcohol and cleared using xylene. The slides were assessed by two individual investigators. Survivin immunoreactivity was scored between 0 and 4 based on the color and percentage of cells showing distinct nuclear and/or diffuse cytoplasmic immunohistochemical staining. Informed consent was obtained from all patients prior to sample collection and the protocol was approved by the Institutional Review Board of Loudi Central Hospital (Loudi, China).

*DNA extraction, nested polymerase chain reaction (PCR) and DNA sequencing*. Genomic DNA was extracted from three paraffin-embedded sections representative of breast cancer tissues. The DNA was then isolated using a DNA Extraction from Paraffin-Embedded Tissue kit (Takara Bio, Inc., Shiga, Japan) according to the manufacturer's instructions. The concentration and purity of the extracted DNA was assessed using spectroscopy with a NanoDrop® ND-1000 spectrophotometer (Nanodrop Technologies Inc., Wilmington, DE, USA). Nested PCR analysis was performed to detect Sp1 binding sites in the survivin gene promoter region. The primer sequences were as follows: External primers: SurO1, forward 5'-CGCGTTCTTTGAAAGCAGTCGAG-3' and SurO2, reverse 5'-GAAGGGCCAGTTCTTGAATGTAGAG-3', which were used for the first round of PCR; and internal primers: SurI1, forward 5'-GCTAGGTGTGGGCAGGGACGAGCTG-3' and SurI2, reverse 5'-GATTCAAATCTGGCGGTTAATGG-3', which were used to amplify a 207 bp fragment in a final volume of 50 $\mu$l. A total of 5 $\mu$l PCR product was separated on a 1.5% agarose gel and stained with ethidium bromide, followed by analysis under ultraviolet (UV) light. Amplified products which were observed as clear bands were sequenced in duplicate in the forward and reverse directions using a BigDye® Terminator sequencing kit (Applied Biosystems, Inc., Foster City, CA, USA) and an ABI Prism 3730XL DNA Analyzer (Applied Biosystems, Inc.) according to the manufacturer's instructions. Sequences were compared against the archived sequence of the human survivin gene in GenBank (http://www.ncbi.nlm.nih.gov/genbank/).

*Statistical analysis*. All statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL, USA) for windows. The $\chi^2$ test was performed to analyze the correlation between Sp1 binding site mutations in the survivin gene promoter region and survivin expression in breast cancer tissues. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Survivin expression in 42 breast cancer tissues detected using immunohistochemistry*. Survivin expression was analyzed in 42 patients with breast cancer using immunohistochemistry. Samples were scored between 0 and 4 based on survivin expression. The numbers of samples exhibiting survivin expression with a score of 0, 1, 2, 3 and 4 were 7 (16.7%), 7 (16.7%), 12 (28.6%), 12 (28.6%) and 4 (9.5%), respectively. Scores of 0 and 1 were defined as 'low expression' and scores of 2-4 were defined as 'high expression'. Among the 42 tissue samples, 14 tissues exhibited low survivin expression, while 28 samples had high survivin expression.

*Analysis of Sp1 binding site variation in the survivin gene promoter region*. In order to compare nucleotide sequences, survivin gene promoter fragments were amplified from the genomic DNA isolated from the 42 breast cancer tissue samples using nested PCR. The intended sequence was 207 bp long, containing seven Sp1 binding sites from -34 to -240 upstream of the translation initiation site of the survivin gene (Fig. 1A). The PCR products were separated on a 1.5% agarose gel. PCR fragments which exhibited single clear bands under UV light were sequenced (samples 1, 3 and 4; Fig. 1B). In total, 15 variations on seven Sp1 binding sites were observed in 12 samples. No Sp1 binding site variations were found in the other 30 samples. Among these variations, Sp1 binding site E, which is located at the 'Sp1-complex' (21), was observed to have the greatest mutation frequency, while the Sp1 binding site A exhibited no variation (Table I).

*Correlation between variation in Sp1 binding sites in the survivin gene promoter region and survivin expression*. In order to analyze the correlation between variation in Sp1 binding sites in the survivin gene promoter region and survivin expression, $\chi^2$ tests were performed and a significant correlation was observed ($P<0.05$, Table II). As shown in Fig. 2, case 1 was a sample which exhibited no Sp1 binding

Table I. Variations in Sp1 binding sites in the survivin gene promoter in 42 patients with breast cancer.

| Sp1 binding site | Variations | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| A | \ | \ | \ | \ | \ |
| B | -184G/A | \ | \ | \ | \ |
| C | -171G/A | \ | \ | \ | \ |
| D | -150G/A | -151G/A | \ | \ | \ |
| E | -129C/T | -130G/A | -132C/T | -140G/A | -141C/T |
| F | -94C/T | -95C/T | -101G/A | | \ |
| G | -82G/A | -84G/A | -87G/A | \ | \ |

Sp, specificity protein.

Table II. Correlation between Sp1 binding site variation and survivin expression in 42 breast cancer samples.

| Sp1 binding site | Low survivin expression, n (%) | High survivin expression, n (%) | Total n (%) | Value | |
|---|---|---|---|---|---|
| | | | | $\chi^2$ | P-value |
| Mutated | 8 (19.0) | 4 (9.5) | 12 (28.6) | | |
| Not mutated | 6 (14.3) | 24 (57.1) | 30 (71.4) | | |
| Total | 14 (33.3) | 28 (66.7) | 42 (100) | 8.400 | 0.004 |

Sp, specificity protein.

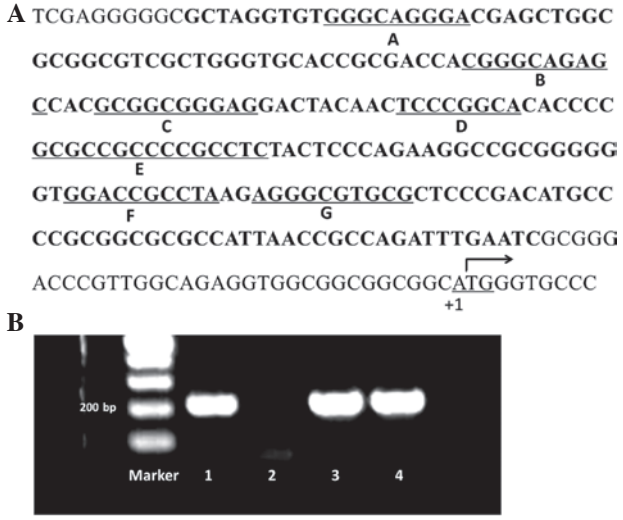


Figure 1. Sequence analysis of the survivin gene promoter. (A) DNA sequence analysis of the 5' flanking region of the human survivin gene. Numbering is from the translation initiation site ATG. The 207 bp PCR sequence is shown in bold and the putative bindings sites for Sp1 are underlined and numbered A-G. (B) Nested PCR of the survivin promoter. PCR products were separated on a 1.5% agarose gel stained with ethidium bromide and were observed under ultraviolet light. 1, 3 and 4 represent three samples which were subsequently sequenced. PCR, polymerase chain reaction; Sp, specificity protein.

site variations in the survivin promoter and had high survivin expression. Case 2 had a -130 G to A homozygous variation and its survivin expression was low. Moreover, case 3 had a -150 G to A heterozygous variation and low expression of survivin (Fig. 2).

## Discussion

Breast cancer is a heterogeneous group of tumors which differ in molecular characteristics, prognosis and response to therapy (25,26). Somatic mutations occurring at any stage of cancer development may affect the properties of the cancer cells. Certain recurrent somatic alterations in breast cancer have been reported, including human epidermal growth factor receptor 2 amplifications, which were the first successful therapeutic targets defined by a genomic aberration (27). Several studies have investigated mutations across different breast cancer subtypes (28-31) and recurrent somatic gene mutations, particularly in coding regions, including core-binding factor, beta subunit (28), TP53 (28) and GATA3 (32), have been identified in breast cancer. Genomic alterations which affect survivin expression in breast cancer cells have been reported and loss of heterozygosity in breast cancer has been associated with survivin expression (19). In addition, the survivin gene is located at 17q25, a hotspot for mutations in breast cancer and other tumors (33-35). Thus, the high mutation rate at the survivin gene promoter may be associated with genomic instability.

In addition to somatic gene mutations, SNPs have been a focus of cancer research. The -31 G/C SNP of the survivin gene promoter has been reported to be associated with gastric (36), colorectal (17), lung (37) and urothelial cancer (38) as well as

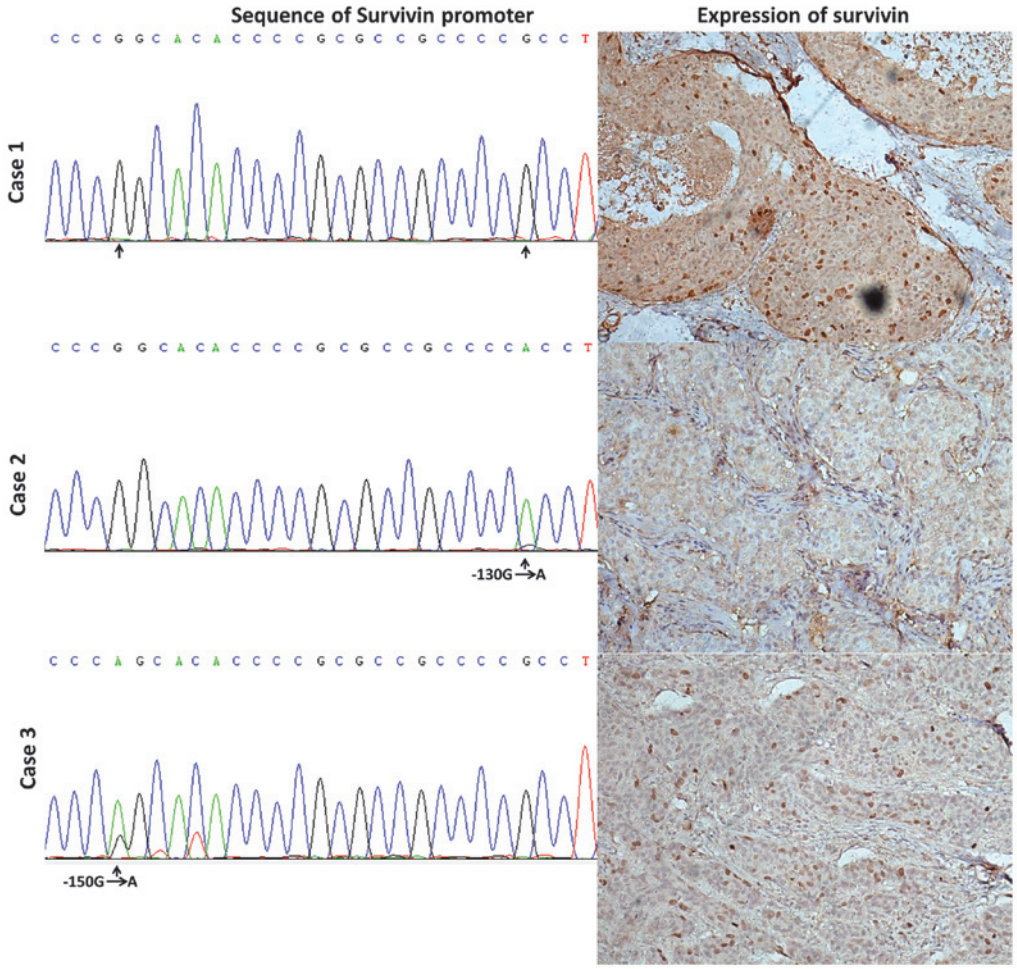


Figure 2. Sp1 binding site mutations in the survivin gene promoter and survivin protein expression in breast cancer tissues. Case 1 represents a case which had no putative Sp1 binding site mutations and high survivin expression. Case 2 represents a case which had a -130 G to A mutation and case 3 represents a case which had a -150 G to A mutation. Cases 2 and 3 had low survivin expression. Sp, specificity protein.

esophageal squamous cell carcinoma (39), and may be a risk factor for cancer development. However, the -31 G/C polymorphism has not been associated with cervical (40) or breast (32) cancer. Based on the central role of survivin in multiple cellular networks, it is important to elucidate the factors regulating and influencing survivin expression (6).

The transcription factor Sp1 is one of the most important regulators of survivin. Sp1 binds to GC-rich motifs in various promoters and is involved in numerous cellular processes, including cell differentiation, growth and apoptosis, as well as immune responses, DNA damage responses and chromatin remodeling (41). Polymorphisms of Sp1 binding sites which affect protein expression have been investigated in several studies (42-45), particularly in patients with cancer. For example, the -216 G/T polymorphism of the Sp1 binding site at the epidermal growth factor receptor promoter region has been reported to be associated with altered promoter activity and gene expression *in vitro* and *in vivo* (43). Furthermore, SNPs of the Sp1 binding site at the mouse double minute 2 homolog promoter have been associated with risk of breast and ovarian cancer, and Sp1 binding site polymorphisms at the matrix metalloproteinase-2 promoter have been correlated with risk of gastric (44) and lung cancer (45). Prior to the identification of Sp1 binding site polymorphisms at the survivin promoter, survivin expression was shown to be regulated by Sp1 through several Sp1 binding sites in the survivin promoter, which were close to the translation initiation site, and mutations in these binding sites were found to decrease survivin expression *in vitro* (20-22,46,47). In the present study, low survivin expression was observed to correlate with Sp1 binding site variation in the survivin promoter *in vivo*. While the mechanism underlying the high mutation rate in the survivin gene promoter region and the functional significance of such mutations in breast cancer remain to be fully elucidated, the phenomenon suggests that survivin promoter genotypes may influence survivin expression, thus influencing individual susceptibility to the initiation and development of certain types of cancer.

## Acknowledgements

The authors would like to thank Lanping Quan and Jinfeng Bai from the Laboratory of Cell and Molecular Biology for their technical assistance, as well as Sangon Biotech (Shanghai) Co., Ltd. (Shanghai, China) for the DNA sequencing. The present study was supported by grants from the National Natural Science Foundation of China (nos. 31171322 and 81021061).

## References


1. Li F and Ling X: Survivin study: an update of 'what is the next wave'? J Cell Physiol 208: 476-486, 2006.
2. Li F: Survivin study: what is the next wave? J Cell Physiol 197: 8-29, 2003.
3. Jha K, Shukla M and Pandey M: Survivin expression and targeting in breast cancer. Surg Oncol 21: 125-131, 2012.
4. Altieri DC: New wirings in the survivin networks. Oncogene 27: 6276-6284, 2008.
5. Altieri DC: Survivin, cancer networks and pathway-directed drug discovery. Nat Rev Cancer 8: 61-70, 2008.
6. Guha M and Altieri DC: Survivin as a global target of intrinsic tumor suppression networks. Cell Cycle 8: 2708-2710, 2009.
7. Waligórska-Stachura J, Jankowska A, Waśko R, *et al*: Survivin - prognostic tumor biomarker in human neoplasms - review. Ginekol Pol 83: 537-540, 2012.
8. Sarti M, Pinton S, Limoni C, *et al*: Differential expression of testin and survivin in breast cancer subtypes. Oncol Rep 30: 824-832, 2013.
9. Dedić Plavetić N, Jakić-Razumović J, Kulić A and Vrbanec D: Prognostic value of proliferation markers expression in breast cancer. Med Oncol 30: 523, 2013.
10. Song J, Su H, Zhou YY and Guo LL: Prognostic value of survivin expression in breast cancer patients: a meta-analysis. Tumour Biol 34: 2053-2062, 2013.
11. Xu C, Yamamoto-Ibusuki M, Yamamoto Y, *et al*: High survivin mRNA expression is a predictor of poor prognosis in breast cancer: a comparative study at the mRNA and protein level. Breast Cancer: Sep 12, 2012 (Epub ahead of print).
12. Li X, Dang X and Sun X: Expression of survivin and VEGF-C in breast cancer tissue and its relation to lymphatic metastasis. Eur J Gynaecol Oncol 33: 178-182, 2012.
13. Adamkov M, Kajo K, Vybohova D, Krajcovic J, Stuller F and Rajcani J: Correlations of survivin expression with clinicomorphological parameters and hormonal receptor status in breast ductal carcinoma. Neoplasma 59: 30-37, 2012.
14. Kapoor S: Beyond pancreatic carcinoma: The close relationship between survivin levels and prognosis in systemic malignancies. World J Clin Oncol 3: 80-81, 2012.
15. Johnson ME and Howerth EW: Survivin: a bifunctional inhibitor of apoptosis protein. Vet Pathol 41: 599-607, 2004.
16. Gazouli M, Tzanakis N, Rallis G, *et al*: Survivin -31G/C promoter polymorphism and sporadic colorectal cancer. Int J Colorectal Dis 24: 145-150, 2009.
17. Li XB, Li SN, Yang ZH, Cao L, Duan FL and Sun XW: Polymorphisms of survivin and its protein expression are associated with colorectal cancer susceptibility in Chinese population. DNA Cell Biol 32: 236-242, 2013.
18. Xu Y, Fang F, Ludewig G, Jones G and Jones D: A mutation found in the promoter region of the human survivin gene is correlated to overexpression of survivin in cancer cells. DNA Cell Biol 23: 419-429, 2004.
19. Boidot R, Vegran F, Jacob D, *et al*: The expression of BIRC5 is correlated with loss of specific chromosomal regions in breast carcinomas. Genes Chromosomes Cancer 47: 299-308, 2008.
20. Li F and Altieri DC: Transcriptional analysis of human survivin gene expression. Biochem J 344: 305-311, 1999.
21. Xu R, Zhang P, Huang J, Ge S, Lu J and Qian G: Sp1 and Sp3 regulate basal transcription of the survivin gene. Biochem Biophys Res Commun 356: 286-292, 2007.
22. Mityaev MV, Kopantzev EP, Buzdin AA, Vinogradova TV and Sverdlov ED: Functional significance of a putative Sp1 transcription factor binding site in the survivin gene promoter. Biochemistry (Mosc) 73: 1183-1191, 2008.
23. Zhang G, Zhu H, Wang Y, *et al*: Krüppel-like factor 4 represses transcription of the survivin gene in esophageal cancer cell lines. Biol Chem 390: 463-469, 2009.
24. Li Y, Xie M, Yang J, *et al*: The expression of antiapoptotic protein survivin is transcriptionally upregulated by DEC1 primarily through multiple Sp1 binding sites in the proximal promoter. Oncogene 25: 3296-3306, 2006.
25. Sørlie T, Perou CM, Tibshirani R, *et al*: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 98: 10869-10874, 2001.
26. Chin K, DeVries S, Fridlyand J, *et al*: Genomic and transcriptional aberrations linked to breast cancer pathophysiologies. Cancer Cell 10: 529-541, 2006.
27. King CR, Kraus MH and Aaronson SA: Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science 229: 974-976, 1985.
28. Banerji S, Cibulskis K, Rangel-Escareno C, *et al*: Sequence analysis of mutations and translocations across breast cancer subtypes. Nature 486: 405-409, 2012.
29. Sjöblom T, Jones S, Wood LD, *et al*: The consensus coding sequences of human breast and colorectal cancers. Science 314: 268-274, 2006.
30. Wood LD, Parsons DW, Jones S, *et al*: The genomic landscapes of human breast and colorectal cancers. Science 318: 1108-1113, 2007.
31. Kan Z, Jaiswal BS, Stinson J, *et al*: Diverse somatic mutation patterns and pathway alterations in human cancers. Nature 466: 869-873, 2010.
32. Usary J, Llaca V, Karaca G, *et al*: Mutation of GATA3 in human breast tumors. Oncogene 23: 7669-7678, 2004.
33. Ly M, Valent A, Diallo G, *et al*: Gene copy number variations in breast cancer of Sub-Saharan African women. Breast 22: 295-300, 2013.
34. Orsetti B, Courjal F, Cuny M, Rodriguez C and Theillet C: 17q21-q25 aberrations in breast cancer: combined allelotyping and CGH analysis reveals 5 regions of allelic imbalance among which two correspond to DNA amplification. Oncogene 18: 6262-6270, 1999.
35. Kalikin LM, Frank TS, Svoboda-Newman SM, Wetzel JC, Cooney KA and Petty EM: A region of interstitial 17q25 allelic loss in ovarian tumors coincides with a defined region of loss in breast tumors. Oncogene 14: 1991-1994, 1997.
36. Cheng ZJ, Hu LH and Huang SJ: Correlation of -31G/C polymorphisms of survivin promoter to tumorigenesis of gastric carcinoma. Ai Zheng 27: 258-263, 2008 (In Chinese).
37. Jang JS, Kim KM, Kang KH, *et al*: Polymorphisms in the survivin gene and the risk of lung cancer. Lung Cancer 60: 31-39, 2008.
38. Wang YH, Chiou HY, Lin CT, *et al*: Association between survivin gene promoter -31 C/G polymorphism and urothelial carcinoma risk in Taiwanese population. Urology 73: 670-674, 2009.
39. Yang X, Xiong G, Chen X, *et al*: Polymorphisms of survivin promoter are associated with risk of esophageal squamous cell carcinoma. J Cancer Res Clin Oncol 135: 1341-1349, 2009.
40. Borbély AA, Murvai M, Szarka K, *et al*: Survivin promoter polymorphism and cervical carcinogenesis. J Clin Pathol 60: 303-306, 2007.
41. Wierstra I: Sp1: emerging roles - beyond constitutive activation of TATA-less housekeeping genes. Biochem Biophys Res Commun 372: 1-13, 2008.
42. Grant SF, Reid DM, Blake G, Herd R, Fogelman I and Ralston SH: Reduced bone density and osteoporosis associated with a polymorphic Sp1 binding site in the collagen type I alpha 1 gene. Nat Genet 14: 203-205, 1996.
43. Liu W, Innocenti F, Wu MH, *et al*: A functional common polymorphism in a Sp1 recognition site of the epidermal growth factor receptor gene promoter. Cancer Res 65: 46-53, 2005.
44. Miao X, Yu C, Tan W, *et al*: A functional polymorphism in the matrix metalloproteinase-2 gene promoter (-1306C/T) is associated with risk of development but not metastasis of gastric cardia adenocarcinoma. Cancer Res 63: 3987-3990, 2003.
45. Yu C, Pan K, Xing D, *et al*: Correlation between a single nucleotide polymorphism in the matrix metalloproteinase-2 promoter and risk of lung cancer. Cancer Res 62: 6430-6433, 2002.
46. Cheng Q, Ling X, Haller A, *et al*: Suppression of survivin promoter activity by YM155 involves disruption of Sp1-DNA interaction in the survivin core promoter. Int J Biochem Mol Biol 3: 179-197, 2012.
47. Estève PO, Chin HG and Pradhan S: Molecular mechanisms of transactivation and doxorubicin-mediated repression of survivin gene in cancer cells. J Biol Chem 282: 2615-2625, 2007.