MINI-REVIEW

Functional Roles of Long Non-coding RNA in Human Breast Cancer

Ni Ye, Bin Wang, Zi-Fang Quan, San-Jie Cao, Xin-Tian Wen, Yong Huang, Xiao-Bo Huang, Rui Wu, Xiao-Ping Ma, Qi-Gui Yan*

Abstract

The discovery of long noncoding RNA (LncRNA) changes our view of transcriptional and posttranscriptional regulation of gene expression. With application of new research techniques such as high-throughput sequencing, the biological functions of LncRNAs are gradually becoming to be understood. Multiple studies have shown that LncRNAs serve as carcinogenic factors or tumor suppressors in breast cancer with abnormal expression, prompts the question of whether they have potential value in predicting the stages and survival rate of breast cancer patients, and also as therapeutic targets. Focusing on the latest research data, this review mainly summarizes the tumorigenic mechanisms of certain LncRNAs in breast cancer, in order to provide a theoretical basis for finding safer, more effective treatment of breast cancer at the LncRNA molecular level.

Keywords: Long non - coding RNAs; biological function; breast cancer; tumorigenic mechanism

Asian Pac J Cancer Prev, **15 (15)**, 5993-5997

Introduction

Breast cancer occurs in mammary gland epithelial tissue, 99 % of breast cancer in women, only 1 % of men. It has become a threat to women's physical and mental health. Although, mammary gland is not the important organs to maintain life and the situ breast cancer is not fatal, but the connection between the breast cancer cells is loose and cells fall off easily, finally, forming cancer metastasis though the blood and lymph which imperil patient's life. With technology advance, such as high-throughput sequencing, microarray, let scientists have a deeper understanding of molecular biology, especially non-coding RNA. Actually, there is < 2% of the total genome sequence as protein-coding genes, however, at least 98% of the genome are transcribed into non-coding RNA (ncRNA), including 53% non-repetitive sequences and 45% middle to highly-repetitive sequences involving in introns, regulatory RNA genes and intergenic regions (Szymanski et al., 2006; Ponting et al., 2010), which suggest that ncRNA play an important regulatory role in organisms growth and metabolism.

RNA and Cancer

So far, the study of ncRNA is mainly concentrated on the miRNA and LncRNA. The length of miRNA is about 22 nucleotides. MiRNA through its seeds region combines with 3'UTR region of target mRNAs to realize inhibition or degradation of the target mRNAs, in turn, regulating the expression of gene. According to the prediction of vertebrate, a miRNA can regulate more than 400 target genes and form a very complicated and precise regulation network (Hutvagner et al., 2002; Lai et al., 2002; Zeng et al., 2003). At present, researchers have found more than 50% of miRNA genes in the chromosome fragile site, and these fragile sites in malignant tumors were often lack, amplification and rearrangement, which prompted unbalanced expression of miRNAs in tumor pathogenesis played an important role (Burk et al., 2008; Yan et al., 2008; Swanton et al., 2009).

The length of LncRNA transcript range from 200 nt to 100 kb. Researchers discovered most of the identified LncRNAs are transcribed by RNA polymerase IIand are polyadenylated. Initially, LncRNAs were considered as "transcription noise", but current researches reveal LncRNA has a crucial biological role in cell differentiation and metabolism (Wapinski et al., 2011). LncRNA with an abnormal expression in multiple tumors show they could act as an important role in corresponding cancer.

LncRNA and Breast Cancer

Recent evidences suggest that LncRNAs have a closely connection with breast cancer occurrence and development. In this review, we summarize mainly biological functions of LncRNA including mediated by miRNAs and functional role of some certain LncRNAs which involved in breast cancer as oncogenes or tumor suppressor genes, so as to provide theoretical basis for

*College of Veterinary Medicine, Sichuan Agricultural University, Yaan, Sichuan, China *For correspondence: yanqigui@126.com*

finding new treatment of human breast cancer at LncRNA molecular level.

Biological functions of long non-coding RNAs

Relative to the small molecule ncRNA, LncRNA have long nucleotide and complex secondary structures, so that LncRNA become a very important regulatory factor in the human genome, including at transcriptional, post-transcriptional and epigenetic levels to regulate DNA methylation, histone modification, chromatin remodeling and gene silencing (Chen et al., 2010; Wang et al., 2011). 1) LncRNA can serve as signal molecule , when cells undergo specific stimuli, LncRNA as potential biomarkers will show corresponding tissue specificity (Clemson et al., 1996). 2) As the decoy to induce and to combine with specific protein, and then impeded the reaction of its downstream sequence, such as P21 associated ncRNA DNA damage activated (PANDA) (Hung et al., 2011). 3) Some LncRNA which play a guiding role can combine with DNA or proteins and then guide the specific complex to the correct position on the chromosome, such as LncRNA HOTTIP (Flynn et al., 2012). 4) LncRNA can act as skeleton for protein complex to put two superficial modification enzyme together, such as Hox transcript antisense RNA (HOTAIR) (Rain et al., 2007). 5) LncRNAs can regulate miRNAs which involved in multiple cancer pathways , so that the LncRNA indirectly regulate the proliferation activity of cells. Some LncRNA, such as LncRNA H19, through the shearing function can form a precursor of miRNAs, processing to mature specific miRNAs, and then regulate the expression of target genes (Fejes et al., 2009; Wilusz et al., 2009). Individual LncRNA can play an endogenous miRNA sponges to inhibit the expression of miRNA, in turn, to affect some malignant biological behavior of tumor cells (Wang et al., 2010). In addition, Cesana has found man and rat skeletal muscle linc-MD1 LncRNA can serve as competing endogenous RNA (ceRNA)to specific bind of miR-133 and miR-135 respectively and indirectly regulate targets of this two miRNAs (Cesana et al., 2011). At present, the study of LncRNA is still in a shallow state that a lot of LncRNAs are undetected or physiological roles are unclear, but the above functions are enough to show, whether direct or indirect, LncRNA is a crucial regulator in life process, including the growth, diseases and even cancer of the organism.

Long non-coding RNAs which involved in breast cancer

Oncogenic long non-coding RNAs: Researchers have found many tumorigenicity LncRNAs involving in multiple signaling pathways have a vital relationship with the occurrence of breast cancer and have confirmed their abnormal expression is not the result of breast cancer appearance, but they act as one of important contributors to breast cancer. So they may have great potential as targets for breast cancer treatment.

H19: The H19 gene is one of the first genes to been identified having a vital role in genomic imprinting during growth and development. It's length is 2.3 kb and it locates on chromosome 11 *p* 15.5 which lies within 200 kb downstream of insulin-like growth factor 2 (IGF-2) gene, but these alleles, the paternal IGF-2 and maternal H19, are selectively expressed (Zemel et al., 1992; Zhang et al., 1992; Giannoukakis et al., 1993; Gabory et al., 2010). H19 involves in multiple cancers, such as esophagus (Hibi et al., 1996), liver (Fellig et al., 2005), breast cancer and so on (Matouk et al., 2007). In breast cancer or breast cancer cells except MDA-MB-231 cells, researchers have found LncRNA H19 is overexpression. The protein of oncogene, c-Myc, is extensive in breast cancer and can directly induces transcription of H19 by allele-specific binding, and H19, a bona fide target gene of E2F controlled by E2F1 factor via binding to H19 promoter, can regulate cell cycle progression, especially the transition of G1 to S (Berrteaux et al., 2005). Research on hepatocellular carcinoma has proclaimed that the expression of E2F1 was induced by most dangerous carcinogen, aflatoxin B1, which up-regulates H19 expression to promote cell growth and invasion directly and indirectly (Lv et al ., 2014), while inhibition of H19 expression by small interfereing RNA (siRNA) will hinder the progress through the S-phase of cell cycle. Further study focused on the isogenic model MCF-7/MCF-7Ras have detected overexpression of H19 strengthen the aggressive phenotype of tumor cells and is a marker for cell proliferation, which elucidate the oncogenic function of H19 in breast cancer (Lottin et al., 2002; Barsyte et al., 2006; Berrteaux et al., 2005). In addition, LncRNA H19 has been confirmed that it is the precursor of miR-675 whose direct target is tumor suppressor retinoblastoma (RB). H19 indirectly affects the regulation of RB in primary human colorectal cancer (CRC) (Tsang et al., 2010). At present, researchers have not discovered miR-675 has corresponding role in breast cancer. With the deepening of the research, more effects of H19 in breast cancer will be revealed. In sum, the high-expression of H19 is not an outcome of breast cancer but a participant to induce breast cancer. So we can use siRNA treatment to inhibit H19 and then to impede differentiation of breast cancer cell.

LSINCT5-Long stress induced non-coding transcripts: LSINCT5 is an intergenic LncRNA about 2.6kb located in Chr 5p somewhere in between IRX2 and IRX4 genes (information taken from UCSC Browser March 2006 version). LncRNA LSINCT5 is potentially transcribed by RNA Polymerase III and polyadenylated from the negative strand. This LncRNA highly express in breast cancer tissue and cell lines. Experiment found that the expression of LSINCT5 in breast cancer cell lines and primary breast tumor tissues compared to corresponding normal cell lines and normal benign breast tissue increased 10 times and 7 times respectively, however knocking down LSINCT5 by antisense oligos (ASOs) could decrease proliferation in breast cancer lines (Silva et al., 2011). Current study reveals the decrease of LSINCT5 expression would change the expression of multiple genes and this LncRNA has an important role in processes of cellular proliferation. Some researchers suppose LSINCT5 is one of the non-coding transcripts forming paraspeckle (Sasaki et al., 2009; Sunwoo et al., 2009). In breast cancer, the molecular mechanisms of LSINCT5 mainly involved

two important genes, LncRNA NEAT1 and the protein-coding gene PSPC1 (paraspeckle component1) which have significant decrease when inhibit LSINCT5 in breast cell lines (Silva et al., 2011). The function of NEAT1 is an essential structural determinant of paraspeckles which comprised by recently transcribed NEAT1 RNA and DBHS (Drosopbila melanogaster behavior, human splicing)protein dimers while this dimers consist of PSPC1 (Fox et al., 2005; Clemson et al., 2009). In anthropogenic of undifferentiated embryonic stem cells, some mRNAs play an important role in maintaining pluripotent of stem cells, due to lack of NEAT1 and paraspeckles, for example Lin28 which can be quickly out of the nucleus after transcription, and then translate stem cells needed Lin28 protein (Chen et al., 2009) but when LSINCT5 overexpress, there are opposite effect, which prompt NEAT1 has a decisive role in anthropogenic embryonic stem cell fate. In addition, study also found other genes CXCR4, a chemokine receptor in the GPCR gene family, which is a crucial breast cancer marker related with invasion and metastasis was significantly affected by knocking down the expression of LSINCT5 (Hassan et al., 2011). Thus it can be seen that LSINCT5 reinforce cellular proliferation and involve in multiple processes, which let LSINCT5 has potential value as a marker to diagnose breast cancer or a target for tumor treatment.

HOTAIR-Hox transcript antisense RNA: HOTAIR, a 2.2 kb carcinogenic LncRNA, is expressed from the Hox C residing in Chr12q13.13 and was initially discovered as a gene repressor for Hox C gene (Rinn et al., 2007; Tsai et al., 2010). Recent study revealed HOTAIR, in both primary and metastatic breast cancer, was overexpression more than hundreds of times comparing with normal breast tissue. In addition, the dysregulated HOTAIR in breast cancer cells results in increasing cell invasion in vitro and metastasis in vivo (Gupta et al., 2010). Furthermore, researcher have confirmed that the function of HOTAIR is to act as a scaffold for PRC2 (Polyconb-repressive complex 2) and LSD1/CoREST complexes. The 3'region of HOTAIR binds LSD1, a histone lysine demethylase which mediates enzymatic demethylation of H3K4Me2 while the 5' region of HOTAIR combine with PRC2 complex responsible for H3K27 methylation, leading to obtain a repressive histone mark and loss of an activating histone mark (Tsai et al., 2010). Interestingly, when deplete PRC2, the metastatic effect and gene regulatory effects brought by HOTAIR overexpression are largely reversed (Wan et al., 2010). Experiment also show that targeting on HOTAIR by specific siRNA can significantly inhibit HOTAIR gene expression, and this interference can suppress cell epithelial mesenchymal transitions (EMT), finally, decreasing cell proliferation and promoting cell apoptosis (Yang et al., 2012). This LncRNA though changing the activity of enzyme belonging to Polycomb group proteins, controls differentiation pathways during breast cancer development, which prompt the interaction between HOTAIR and PRC2 could play an important role in breast cancer invasiveness. Thus HOTAIR whose expression level is a powerful predictor of metastases and survival rate in breast cancer (Gupta et al., 2010). In the aspect of treatment, exclusion of through molecular inhibitors (Hu et al., 2013), there may be other way. the curcumin can significantly inhibit the invasion and migration of multiple cancer cells by triggering epigenetic events (Balasubramanian et al., 2007). There have been study in Renal Cell Carcinoma (RCC) show HOTAIR may be involved in the curcumin-induced inhibition of metastasis (Pei et al., 2014) which provide a basis for finding the curcumin treatment of breast cancer with HOTAIR as a target.

Tumor-suppressor LncRNA

Tumor-suppressor LncRNAs can via tumor-suppressor pathways to prevent oncogenesis, and when they dysfunctional in those ways, cells population will growth and then form cancer. Until now, apoptosis failure is one of obstacles to complete elimination of tumor in resistant cancer cells growth.

GAS5-Growth Arrest-Specific 5: GAS5 was initially isolated from NIH3T3 cells (Schneider et al., 1988) which located in Chr1q25 1.The length of GAS5 is about 0.6-1.8 kb. GAS5 can control mammalian cell's apoptosis and differentiation . It has been observed significant down-regulation in breast cancer and breast cancer cells. The expression levels of GAS5 in breast cancer tissue relative to untransformed breast epithelial tissue from the same patients reduce more than 65%. This diminution was distinguished in both stages IandII breast cancer, which hint the reduction of GAS5 expression is an early event in oncogenesis (Mourtada-Maarabouni et al., 2009). The expression level of it may be a maker to predict stages in cancer.GAS5 acts as a molecular decoy to regulate the activity of glucocorticoids in response to nutrient starvation by interacting directly with the DNA-binding sites of the glucocorticoid receptor (GR), a especial kind of nuclear receptors , and then preventing GR interaction with cognate glucocorticoid response elements to decrease cell metabolism , So in breast cancer , decrease of GAS5 maybe maintain activity of tumor cells under low-nutrient condition (Coccia et al., 1992; Mourtada-Maarabouni et al., 2009; Kino et al., 2010). Furthermore, researchers have also proved GAS5 is associated with RCC genesis and overexpression of GAS5 in the RCC cell line A498 can arrest cell cycling, induce cell apoptosis, also suppress cell migration and invasion (Qiao et al., 2013), which is more proof of GAS5 playing an important role in cancer occurrence and development. So finding an effective way or designing a vector to induce the expression of GAS5 may have potential value to become therapeutic approach for breast cancer.

Conclusions

LncRNA play an important role in life process. It is no longer the "noise" in the process of transcription but the change of its expression relates to diseases. Thus, LncRNA became one of hot topics in the study of cancer. Though, the study of LncRNA is still in early stages, but with research on LncRNA, its mechanism in tumor will be gradually understood and more LncRNA will be

discovered. At present, researchers have already found some LncRNA play an important role in breast cancer, for example serving as a biological marker, to predict stages, metastasis and survival rate of breast cancer patient, and it even provide new way for the treatment of breast cancer. For example the RNAi treatment has applied to various diseases. It also has a good application to silence tumorigenicity LncRNA. Using a plasid-based system to knockdown human H19 has made significant progress in the treatment of bladder cancer (Smaldone et al., 2010). In breast cancer, through small molecular inhibitors of PRC2 or/and endogenous HOTAIR to prevent the interactions between HOTAIR and PCR2 or LSD1 complex can limit the metastatic potential of breast cancer (Tsai et al., 2011). Although, our knowledge about LncRNA molecular mechanism exist limitations, but LncRNA involved in multiple biological processes show that it can be used as a candidate for tumor diagnosis, treatment and prognosis, which may help human to conquer breast cancer totally someday.

References

Balasubramanian S, Eckert RL (2007). Keratinocyte proliferation, differentiation, and apoptosis-differential mechanisms of regulation by curcumin, EGCG and apigenin. *Toxicol Appl Pharmacol*, **224**, 214-9.

Barsyte-Lovejoy D, Lau SK, Boutros PC, et al (2006). The c-Myc oncogene directly induces the H19 noncoding RNA by allele-specific binding to potentiate tumorigenesis. *Cancer Res*, **66**, 5330-7.

Berteaux N, Lottin S, Monté D, et al (2005). H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. *J Biol Chem*, **280**, 29625-36.

Burk U, Schubert J, Wellner U, et al (2008). A reciprocal repression between ZEB1 and members of the miR-200 family promotes EMT and invasion in cancer cells. *EMBO Rep*, **9**, 582-9.

Cesana M, Cacchiarelli D, Legnini I, et al (2011). A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. *Cell*, **147**, 358-69.

Chen L-L, Carmichael GG (2009). Altered nuclear retention of mRNAs containing inverted repeats in human embryonic stem cells: Functional role of a nuclear noncoding RNA. *Mol Cell*, **35**, 467-78.

Chen L-L, Carmichael GG (2010). Decoding the function of nuclear long non-coding RNAs. *Curr Opin Cell Biol*, **22**, 357-64.

Chen W, Böcker W, Brosius J, et al (1997). Expression of neural BC200 RNA in human tumours. *J Pathol*, **183**, 345-51.

Clemson CM, Hutchinson JN, Sara SA, et al (2009). An Architectural Role for a Nuclear Noncoding RNA: NEAT1 RNA Is Essential for the Structure of Paraspeckles. *Mol cell*, **33**, 717-26.

Clemson CM, McNeil JA, Willard HF, et al (1996). XIST RNA paints the inactive X chromosome at interphase: evidence for a novel RNA involved in nuclear/chromosome structure. *J Cell Biol*, **132**, 259-75.

Coccia EM, Cicala C, Charlesworth A, et al (1992). Regulation and expression of a growth arrest-specific gene (gas5) during growth, differentiation and development. *Mol Cell Biol*, **12**, 3514-21.

Fejes-Toth K, Sotirova V, Sachidanandam R, et al (2009). Post-transcriptional processing generates a diversity of 5' -modified long and short RNAs. *Nature*, **457**, 1028-32.

Fellig Y, Ariel I, Ohana P, et al (2005). H19 expression in hepatic metastases from a range of human carcinomas. *J Clin Pathol*, **58**, 1064-8.

Flynn RA , Chang HY (2012). Active chromatin and noncoding RNAs: an intimate relationship. *Curr Opin Gene Dev*, **22**, 172-8.

Fox AH, Bond CS, Lamond AI (2005). P54nrb forms a heterodimer with PSP1 that localizes to paraspeckles in an RNA-dependent manner. *Mol Biol Cell*, **16**, 5304-15.

Gabory A, Jammes H, Dandolo L (2010). The H19 locus: Role of an imprinted non-coding RNA in growth and development. *Bioessays*, **32**, 473-80.

Giannoukakis N, Deal C, Paquette J, et al (1993). Parental genomic imprinting of the human IGF2 gene. *Nat Genet*, **4**, 98-101.

Gupta RA, Shah N, Wang KC, et al (2010). Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature*, **464**, 1071-6.

Hassan S, Buchanan M, Jahan K, et al (2011). CXCR4 peptide antagonist inhibits primary breast tumor growth, metastasis and enhances the efficacy of anti-VEGF treatment or docetaxel in a transgenic mouse model. *Int J Cancer*, **129**, 225-32.

Hibi K, Nakamura H, Hirai A, et al (1996). Loss of H19 imprinting in esophageal cancer. *Cancer Res*, **56**, 480-2.

Hu Q, Chen WX, Zhong SL, et al (2013). Current progress in the treatment of metaplastic breast carcinoma. *Asian Pac J Cancer P*, **14**, 6221-5.

Hung T, Wang Y, Lin MF, et al (2011). Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet*, **43**, 621-9.

Hutvágner G, Zamore PD (2002). A microRNA in a multiple-turnover RNAi enzyme complex. *Science*, **297**, 2056-60.

Kino T, Hurt DE, Ichijo T, et al (2010). Noncoding RNA gas5 is a growth arrest-and starvation-associated repressor of the glucocorticoid receptor. *Sci Signal*, **3**, ra8.

Lai EC (2002). MicroRNAs are complementary to 3' UTR sequence motifs that mediate negative post-transcriptional regulation. *Nat Genet*, **30**, 363.2.

Lottin S, Adriaenssens E, Dupressoir T, et al (2002). Over-expression of an ectopic H19 gene enhances the tumorigenic properties of breast cancer cells. *Carcinogenesis*, **23**, 1885-95.

Lv J, Yu YQ, Li SQ, et al (2014). Aflatoxin B1 promotes cell growth and invasion in hepatocellular carcinoma HepG2 cells through H19 and E2F1. *Asian Pac J Cancer Prev*, **15**, 2565-70.

Matouk IJ, DeGroot N, Mezan S, et al (2007). The H19 non-coding RNA is essential for human tumor growth. *PLoS One*, **2**, e845.

Mourtada-Maarabouni M, Pickard M, Hedge V, et al (2009). GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. *Oncogene*, **28**, 195-208.

Olson P, Lu J, Zhang H, et al (2009). MicroRNA dynamics in the stages of tumorigenesis correlate with hallmark capabilities of cancer. *Gene Dev*, **23**, 2152-65.

Pei CH, Wu HY, Fan FT, et al (2014). Influence of curcumin on HOTAIR-mediated migration of human renal cell carcinoma cell. *Asian Pac J Cancer Prev*, **15**, 4239-43.

Ponting CP, Belgard TG (2010). Transcribed dark matter: meaning or myth? *Hum Mol Genet*, **19**, R162-8.

Qiao HP, Gao WH, Huo JX, et al (2013). Long non-coding RNA GAS5 functions as a tumor suppressor in renal cell carcinoma. *Asian Pac J Cancer Prev*, **14**, 1077-82.

Rinn JL, Kertesz M, Wang JK, et al (2007). Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell*, **129**, 1311-23.
Sasaki Y, Hiro se T, et al (2009), How to build a paraspeckle. *Genome Biol*, **10**, 227.
Schneider C, King RM, Philipson L et al (1988). Genes specifically expressed at growth arrest of mammalian cells. *Cell*, **54**, 787-93.
Silva JM, Boczek NJ, Berres MW et al(2011).LSINCT 5 is overexpressed in breast and ovarian cancer and affects cellular proliferation. *Rna Bilo*, **8**, 496-505.
Smaldone MC, Davies BJ, et al (2010). BC-819 a plasmid comprising the H19 gene regulatory sequences and diphtheria toxin A, for the potential targeted therapy of cancers. *Curr Opin Mol Ther*, **12**, 607-16.
Sunwoo H, Dinger ME, Wilusz JE, et al (2009). MEN ε/β nuclear-retained non-coding RNAs are up-regulated upon muscle differentiation and are essential components of paraspeckles. *Genome Res*, **19**, 347-59.
Swanton C, Caldas C (2009). Molecular classification of solid tumours: towards pathway-driven therapeutics. *Brit J Cancer*, **100**, 1517-22.
Szymanski M, Barciszewski J (2006). RNA regulation in mammals. *Ann NY Acad Sci*, **1067**, 461-8.
Tsai M-C, Manor O, Wan Y, et al (2010). Long noncoding RNA as modular scaffold of histone modification complexes. *Science*, **329**, 689-93.
Tsai M-C, Spitale RC, Chang HY (2011). Long intergenic noncoding RNAs: new links in cancer progression. *Cancer Res*, **71**, 3-7.
Tsang WP, Ng EK, Ng SS, et al (2010). Oncofetal H19-derived miR-675 regulates tumor suppressor RB in human colorectal cancer. *Carcinogenesis*, **31**, 350-8.
Wan Yue, Howar Y (2010). Flight of noncoding RNAs in cancer metastasis. *Cell Cycle*, **9**, 3391-2.
Wang J, Liu X, Wu H, et al (2010). CREB up-regulates long non-coding RNA, HULC expression through interaction with microRNA-372 in liver cancer. *Nucleic Acids Res*, **38**, 5366-83.
Wang KC, Chang HY (2011). Molecular mechanisms of long noncoding RNAs. *Mol Cell*, **43**, 904-14.
Wapinski O, Chang HY (2011). Long noncoding RNAs and human disease. *Trends Cell Biol*, **21**, 354-61.
Wilusz JE, Sunwoo H, Spector DL (2009). Long noncoding RNAs: functional surprises from the RNA world. *Gene Dev*, **23**, 1494-504.
Yang tao, Li jun tang, Wang li juan, et al (2012). The influence of interference IncRNAs HOTAIR in human breast cancer cells MDA-MB-231. *Chin J Cell Mol Immunol*, **28**, 97-8.
Yan L-X, Huang X-F, Shao Q, et al (2008). MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. *RNA*, **14**, 2348-60.
Zemel S, Bartolomei MS, Tilghman SM (1992). Physical linkage of two mammalian imprinted genes, H19 and insulin-like growth factor 2. *Nat Genet*, **2**, 61-5.
Zeng Y, Yi R, Cullen BR (2003). MicroRNAs and small interfering RNAs can inhibit mRNA expression by similar mechanisms. *Proc Natl Acad Sci USA*, **100**, 9779-84.
Zhang Y, Tycko B (1992). Monoallelic expression of the human H19 gene. *Nat Genet*, **1**, 40-44.