

The research progression of correlation between long non-coding RNA and breast cancer

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Abstract Long non-coding RNA (lncRNA) is a group of length more than 200 nucleotides, the lack of complete open reading frame and no protein-coding function RNAs, which play an important role during the development of breast cancer and other malignant tumors. With the evolution of molecular biology, gene therapy of tumor has been the most intensively studied recent years. Compared with microRNA, the functional roles of lncRNAs are still being elucidated. Therefore, it is hopeful to provide new thoughts for diagnosis and treatment of tumor gene level by deepening the study of lncRNAs.

Keywords lncRNAs; Mechanisms; Breast cancer; Gene

Introduction

Breast cancer is now the most frequently diagnosed cancer in women worldwide, and also is one of the well explored human cancers with genome-wide technologies (M. Muthuswami, et al., 2013). There are much more influencing factors of breast cancer, and the differences of reproduction, hormone levels and so on lead to different morbidities in various countries or areas. The reproductive factors of adding risk of coming down with breast cancer include long history of menstruation, nullipara and postmenopausal hormone replacing treatment (Zhang X, et al., 2013). Current treatment of breast cancer includes hormonal therapy, cytotoxic chemotherapy, immunotherapy and targeted therapy (Yue Zhao, et al., 2014). Despite survival advantages achieved by using such therapies, many breast tumors are not eradicated completely due to acquiring resistance, significant toxicities, or relapse following an initial response, thus resulting in metastatic disease at later stages that leads to patient death (Yan Zhang, 2013). Therefore, genomic information can be combined with clinic pathological characteristics to create novel diagnostic and therapeutic strategies remains an important component in the current management of this malignancy (J.

Zhou, et al., 2013).

LncRNAs

It is estimated, approximately, that there are only 20,000 protein-coding genes, representing <2% of total genomic sequence, while the rest 98% RNAs are with limited or no protein-coding capacity (Harrow J, et al., 2012). LncRNAs is a kind of length more than 200 nucleotides, the lack of complete open reading frame and no protein-coding function RNAs of which lays in cell nucleus with the function of regulating gene expression in various levels and served as skeleton for modifying chromatin complex (Kim E D, et al., 2012). Recent researches show that lncRNAs play an important role in several biological processes, including X chromosome inactivation, nuclear structure, genomic imprinting, transcriptional interference, and development (JEREMY E W, et al., 2009). Dysfunction of lncRNAs has been strongly associated with cell fate determination and human disease pathogenesis, including cancers (G. Chen, et al., 2013), it is unadvisable to have dismissed lncRNAs as evolutionary junk or transcriptional noise with this clarification. While it is much more difficult to explore the function of lncRNAs due to their lack of open reading frames and poor sequence conservation.

LncRNAs are mainly transcribed by RNA polymerase II, and they are divided into two classes of oncogenes and tumor suppressor genes according to their functions on the occurrence and development of cancer. These two groups of genes, normally, can level off by repairing DNA injuries timely or promoting abnormal cells apoptosis, while the balance including quantity and function could be disequilibrated by oncogenes, and lead to cancerization finally (Jie Lv, et al., 2014).

LncRNAs are expressed in various tissues, and their functions are diversified: interfering the expression of downstream gene and the cutting of mRNA, combining with DNA or proteins directly, thus to affect the transcriptional level of genes and activity of proteins. Thus, lncRNAs also play an important role on epigenetic. In a word, the regulatory mechanisms of lncRNAs are complex.

lncRNAs and breast cancer

Abnormal expression of lncRNAs in breast cancer

One of the main functions of lncRNAs is to influencing expressive levels of downstream or other genes through expressive changes of lncRNAs itself. H19 is derived from a large imprinted locus on human chromosome 11p15.5. This lncRNA is abundantly expressed in the developing embryo, highly expressed in the mammary bud and adjacent tissues and differentially regulated during mammary gland development. H19 is expressed exclusively from the maternal allele where it acts to regulate the expression of IGF-2 (insulin-like growth factor 2, Igf-2), while not expressed in adult tissues (DeBaun M R, et al., 2002). The variation of expression quantity of H19 correlates with the development of tumors such as cell proliferation, migration and preterminal differentiation. These results are in favor of the standpoint that H19 could be regarded as oncogene. We notice that the lack of H19 would accelerate the growth of tumors from studies of some tumor cell lines, this finding may illustrate the opposite function of H19-cancer suppressor gene. Therefore, H19 may play dual roles of promoting and restraining cancers. LncRNA BC200 expression is highly elevated in breast invasive tumors but not in normal breast tissues or benign tumors. In addition,

large scale of genomic studies show that statistical differences exist in the expression of Loc554202, XIST, MALAT-1 and BC1 between breast cancer and normal tissues. Long stress induced non-coding transcript 5 (LSINCT5) is a nuclear localized lncRNA that was discovered in screens to identify lncRNAs upregulated upon treatment with stress inducing chemicals, and expression of LSINCT5 is increased in breast and ovarian cancer (Silva J M, et al., 2011). Because of its high expression in proliferative tissues and cancer, LSINCT5 could potentially function as a regulator of proliferation. Additionally, knockdown of LSINCT5 leads to altered expression of several genes, including suppression of CXCR4, a breast cancer marker associated with metastasis, it is speculated that carcinogenesis of LSINCT5 could be exerted by regulating downstream target gene and promoting cell proliferation.

lncRNAs related to apoptosis of breast cancer

As it is now generally accepted that apoptosis plays an essential role in oncogenesis, especially dysregulation of some lncRNAs controlling apoptosis. We have found that, some lncRNAs participate in the occurrence of breast cancer through affecting apoptosis. Growth arrest-specific 5 (Gas5), a non-protein-coding RNA, have been identified as critical to the control of mammalian apoptosis and cell population growth, and it has been confirmed that any important biological activity of GAS5 must be mediated through the introns. Gas5 can affect activity of glucocorticoid receptors (GR) by combining its binding domain, thus to influence cellular sensibility to apoptosis. Maternally expressed gene 3 (MEG3), is derived from an imprinted locus on human chromosome 14q32, encoding lncRNA (Balik V, et al., 2013). With the ability of tumor suppressor, MEG3 could inhibit proliferation of breast cancer by down-regulating gene transcription and DNA methylation, MEG3 also involved in activities of p53, inducing apoptosis together (Wang Pengjun, et al., 2012). It is expected to providing more effective therapeutic target for breast cancer with intensively studies of these tumor suppressor genes in breast cancer tissue.

lncRNAs related to infiltration and metastasis in breast cancer

More and more studies show that a part of lncRNAs play an important role during process of infiltration and metastasis in breast cancer. HOTAIR, a 2.2Kb carcinogenic lncRNA, located in the HOXC locus, is transcribed in an antisense orientation from the HOXC locus, which could promote metastasis by changing state of chromatin. In breast cancer, HOTAIR expression is upregulated in both primary and metastatic tumors, and its expression in primary tumors is strongly correlated with later metastasis, poor prognosis, and even death. HOTAIR acts in trans as a repressor of the HOXD locus by recruiting PRC2, leading to trimethylation of H3K27 and subsequent transcriptional silencing, and then promotes invasion and metastasis of breast cancer by facilitating a series of target proteins. Recently research shows that the promoter of HOTAIR contains multiple functional estrogen response elements near the transcription start site, and is transcriptionally induced by estrogen, this may contribute to illuminating correlation between development of breast cancer and HOTAIR upregulated (Bhan A, et al., 2013). Steroid receptor RNA activator 1 (SRA 1), a type of 0.87Kb secondary structural lncRNA, was firstly obtained from experiment (Novikova IV, et al., 2012). Several research data show that SRA-1 energetically involves in glucose uptake, signaling transduction, production of T3 and metastasis (Shore A N, et al., 2012). SRA-1 may be involved in carcinogenesis of sexual hormone through regulating steroid receptor and expressive levels of other transcription factor. Metastasis associated lung adenocarcinoma transcript 1 (MALAT-1) is an intergenic lncRNA, which was firstly discovered in non-small cell lung cancer as a prognostic marker of later development or metastasis (Gutschner T, et al., 2013). MALAT-1 expression is typically upregulated in breast cancer and metastasizing tissues and has been associated with invasion and metastasis of breast cancer.

lncRNAs involved in epigenetic regulation of breast cancer

Epigenetics refers to the study of mechanisms that alter gene expression without altering the primary

DNA sequence, and it is mainly composed of DNA methylation, histone deacetylase, genomic imprinting and random inactivation of chromosome. DNA methylation, an important component of epigenetics, is essential to protecting DNA from incising by enzyme. DNA methyltransferase (DNMT) may affect expression of some genes by methylation modification at promoter. Such as in breast cancer tissue, methyltransferase modifies genic promoter of MEG3, thus, leads to downregulation of MEG3. Histone modification is also a crucial way of epigenetics (Wenzhu Lou, et al., 2011). Genomic imprinting results from differential epigenetic modifications (such as DNA methylation and histone modifications) established separately in the maternal and paternal germ lines, respectively, such as H19 performed in breast cancer. Some lncRNAs affect genetic coding by changing expressive levels without altering genetic sequence of them, and such a mechanism is confirmed to regulating characteristics of epigenetics (Orum U A, et al., 2011).

Significance of lncRNAs contributed to diagnosis and therapy of breast cancer

The main purpose of tumor research is to find sensitive and specific markers for carcinoma, thus to provide significant values for early diagnosis and therapy, and assessment of prognosis of malignant. Researchers found, so far, that a part of lncRNAs that expressed in tumors own high sensitivity and specificity, and they have potential value of becoming new markers for cancers. At present, researchers have already found some lncRNAs 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. The expression amount of HOTAIR in a third of primary breast cancer is defined as 125 fold more than that detected in normal breast epithelia, and 2000 fold in metastatic tissues. It is generally accepted that HOTAIR has become an independent clinical risk factors. In addition, BC200、XIST、MALAT-1、BC1 are abnormally expressed in breast cancer, and these lncRNAs will provide new ideas for diagnosis and therapy of breast cancer. lncRNAs research has become a new hotspot in the field of modern molecular biology though our

knowledge about lncRNA molecular mechanism exist limitations and lots of difficulties. As discussed above, several lncRNAs have been implicated in breast cancer, and we are confident in that further studies on these lncRNAs could lead to new therapeutic advances for diagnosis and treatment for breast cancer.

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