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Review Article

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Introduction of Long non-coding RNA and Their Potential Role as a Biomarker in Breast Cancer

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ABSTRACT

Breast cancer (BC), also known as breast tumor, is major life-threatening diseases for women worldwide representing about 30% of all cancers affecting women. In order to cure and prevent the progression of such malignancy, the use of sensitive and specific biomarker is essential to aid the detection of breast cancer at an early stage. Furthermore, it has to be precise enough to monitor progression of the disease, and could predict the individual patient's response to treatment. Unfortunately, markers with such characteristics have not been introduced and implemented in clinical level. Recent Bioinformatics studies have revealed a broad spectrum of noncoding RNAs called lncRNAs that are involved in breast cancer. They have a role in cell growth, apoptosis2, cell migration and invasiveness as well as cancer cell stemness. Although, their exact mechanisms and potential to serve as a biomarkers are yet to be clarified, they could be utilized for diagnostic purposes and therapeutic targets. This review is to summarize the to date information about lncRNAs that are particularly involved in breast cancer and could possibly named as a biomarker in foreseeable future.

Keywords: Long non-coding RNA, Breast Cancer, Biomarker, Metastasis

Introduction

Breast cancer is one of the most frequently diagnosed malignant tumors for women worldwide. Recent studies have provided evidence that the pathogenesis [3]of BC is complicated and environmental and genetic factors (as well as their potential interactions) contribute to the occurrence and development of BC (Sliwinska- Kowalska et al., 2013). [1] Breast cancer is a heterogeneous disease with a large number of genetic alterations. The treatment for different subtypes of breast cancer is often different. However, the molecular pathogenesis of breast cancer remains poorly defined due to its heterogeneity. [2] In addition, in mammary gland, malignant tumors not only continuously grow and spread locally but also disseminate to other tissues through the lymphatic and circulatory systems as well as the body cavity via a process referred to tumor metastasis. Despite survival advantages achieved by using several 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 (Szymanski et al., 2005). Therefore, genomic information can be combined with clinicopathological characteristics to create novel diagnostic and therapeutic strategies remains an important component in the current management of this malignancy (Zhou et al., 2013). [3] Biomarkers that could function as an adjunct to mammography to detect breast cancer at an early stage, to identify aggressive disease or predict metastasis, could have a major impact on the management and outcome of this disease. [4]

Long non-coding RNAs (lncRNAs) are a category of non-coding RNAs, generally longer than 200 bp, which are transcribed from the genome with various regulatory or unknown functions. Lacking an open reading frame, lncRNAs have no protein-coding capability (Bertone et al., 2004). [1] Since lncRNA research is still at an early stage, the function for the

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vast majority of lncRNAs remains to be determined yet. In particular, little is known whether lncRNAs can serve as biomarkers for cancer diagnosis and prognosis. [2] However, lncRNAs are demonstrated to involve in numerous cellular and carcinogenesis [4] processes, including cell growth (Chiyomaru et al., 2013), tumorigenesis (Zhang et al., 2013) and transcriptional regulation (Sheik Mohamed et al., 2010). [1] And many of these transcripts are associated with a variety of human diseases. [5] Hence, they may reveal novel mechanisms of transformation, tumor growth, and metastasis, as well as present new targets for cancer therapy. [6] Due to their key roles in almost every developmental and cellular process, there for the possibility they could function as biomarkers in (breast) cancer is not unthinkable. [4] In the current study, several identified lncRNAs are summarized based on their function in order to emphasize the vital role they can pose in future breast cancer therapy, progression in addition to tumorigenesis.

Cancer Stemness

SOX2OT

SOX2 overlapping transcript (SOX2OT) is an lncRNA located in SOX2 gene, one of key genes in maintaining pluriopotency. Ectopic expression of SOX2OT leads to dramatic increase in SOX2 expression and subsequent increase in breast cancer anchorage-independent 5 growth (Askarian-Amiri et al., 2014). [5] A total of 1106 Chinese individuals with breast cancer, were testified in a survey in order to observe tissues' SOX2OT expression. Results: SOX2OT were overexpressed in BC tissues. [1] These results indicate the potential oncogenic role of SOX2OT in breast cancer by inducing or maintaining the expression of SOX2. [5]

FAL1

FAL1 expression is associated with BMI1 which is a well-known stemness associated factor of cancer cells (Godlewski et al., 2008). [5] FAL1 was also found to regulate the transcription of a large set of genes that are important for cellular proliferation, death and survival as well as cellular movement and protein degradation. [5]. Several functional experiments were conducted to characterize the oncogenic 6properties of FAL1. Knocking down FAL1 in cancer cell lines from different tumor types retarded their proliferation rates and led to cellular senescence. [7

Oncogenic lncRNAs in breast cancer Proliferation and Apoptosis

H19

H19 is a paternally imprinted gene that was widely studied in cancer biology even before lncRNAs had gained the attention of cancer researchers. [6] Expression of H19 is repressed after birth except a basal expression in several adult organs including mammary gland, adrenal gland and uterus (Dugimont et al., 1995; Liu et al., 1995). [8] The mechanism of H19 action is thought to be translational regulation; however, this needs further verification. [5]

In one study, in order to validate the expression of H19 in BC tissues, 24 pairs of BC and control tissues were analyzed, and it has been found that H19 increased in tumor tissues compared with control tissues. To evaluate the clinical significance of circulating lncRNA H19, they examined the association of plasma H19 level with clinicopathological characteristics in these BC patients. It showed that plasma H19 level was significantly associated with lymph node metastasis. Moreover, to evaluate the tumor monitoring values of plasma H19 in BC patients, the expression levels of H19 in 24 paired pre- and postoperative plasma samples from BC patients were measured. The H19 expression levels were found significantly reduced in postoperative plasma compared to that in preoperative plasma. [8]

Also, a research has proclaimed that the expression of E2F1 (an oncogene and tumor suppressor gene) 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. In addition, LncRNA H19 has been confirmed that it is the precursor of miR-675 whose direct target is tumor suppressor retinoblastoma [7](RB). [9]

Although the exact function of H19 in tumor cells is still unclear, it appears to play a pivotal role in the tumorigenic phenotype in breast cancer.

SRA

Steroid Receptor RNA (SRA) was first reported in 1999 as a functional ncRNA able to co-activate steroid nuclear receptors, a receptor that initiates some processes leading to changes in gene expression. In addition to functioning as co-regulators for steroid and non-steroid nuclear receptors, SRAs also contribute to the action of several other transcription factors; (Kelly et al., 2010) plus, the SRA1 locus codes for protein-coding transcripts as well (Lanz et al., 2002). [10]

In a research about iranian population with breast cancer, in order to investigate possible age-dependent variations in expression profiles of lncRNAs, the expression levels of four lncRNAs, including SRA, in breast cancer (BC) samples obtained from younger (<45 years) and older (>45 years) women were examined. Compared to normal tissues, BC tissues

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from both age groups (women under 45 years of age and women above 45 years of age) showed upregulation of SRA. Additionally, their analysis showed significant and direct correlation between the age and the expression levels of three of the four lncRNAs studied in this work. [10]

LOC554202

To address the question of whether lncRNAs–Loc554202 has a role in breast cancer or not, in an investigation, the expression level of lncRNAs–Loc554202 in breast cancer tissues was assayed. Results showed that Loc554202 is significantly increased compared with normal control, and associated with advanced pathologic stage and tumor size. Moreover, knockdown of Loc554202 decreased breast cancer cell proliferation, induced apoptosis and inhibits migration/invasion in vitro and impeded tumorigenesis in vivo. These data suggest an important role of Loc554202 in breast tumorigenesis. [3]

SNHG12

In the first study about SNHG12, Ouchen et al., determined that SNHG12 is upregulated in triple-negative breast cancer8, and its high expression is significantly correlated with tumor size and lymph node metastasis. Silencing SNHG12 expression inhibits TNBC cells proliferation and apoptosis promotion, whereas, SNHG12 overexpression has the opposite effect. In addition, they reveal that SNHG12 may promote cells migration. Taken together, their findings suggest that SNHG12 contributes to the oncogenic potential of TNBC and may be a promising therapeutic target. [11]

LncRNA-Smad7

Transforming growth factor (TGF)-b exhibits both pro-apoptotic and anti-apoptotic effects on epithelial cells in a context-dependent manner. The anti-apoptotic function of TGF-b is mediated by several downstream regulatory mechanisms, and has been implicated in the tumor-progressive phenotype of breast cancer cells. In a survey, RNA sequencing of mouse mammary gland epithelial cells was conducted and a long non-coding RNA, termed lncRNA-Smad7, which has anti-apoptotic functions, was identified as a target of TGF-b. Suppression of lncRNA-Smad7 expression cancelled the anti-apoptotic function of TGF-b. In contrast, forced expression of lncRNASmad7 rescued apoptosis induced by a TGF-b type I receptor kinase inhibitor in the mouse breast cancer cell line. [12]

LSINCT5

In breast cancer, the molecular mechanisms of LSINCT5 mainly involved two important genes, LncRNA NEAT1 and the protein-coding gene PSPC1 (paraspeckle component_ an irregularly shaped compartment of the cell) 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. 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, but when LSINCT5 overexpress, there are opposite effect, which prompt NEAT1 has a decisive role in anthropogenic embryonic stem cell fate. [9]
Experiments 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). This 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. 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. [9]

UCA1

miRNAs play important roles in breast tumorigenesis, as such, miR-143 is generally considered as a tumor suppressor in breast cancer (Jiang et al., 2012; Yan et al., 2014). [13] In an experiment, TUO1 et al., examined whether there are direct interactions between the UCA1 and miR-143 and how they are involved in breast cancer growth and apoptosis. After confirming the interaction between these two, it was observed that the cells with UCA1 knockdown had significantly increased miR-143 expression. In contrast, the cells with UCA1 overexpression had significantly decreased miR-143 expression. [13]

Invasion and metastasis

HOTAIR

HOX transcript antisense RNA (HOTAIR) is considered to be an epigenetic regulator and its function and mechanism are relatively well studied. [5] The HOTAIR lncRNA acts as a scaffold for histone modification complexes, allowing them to coordinately

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interact with the histone modifiers. In turn, HOTAIR guides these proteins to specific genomic regions and regulates gene expression. [6] The HOX genes contain both tumor suppressive genes and oncogenic genes in breast cancer (Cantile et al., 2003). [5]

Recent study revealed HOTAIR, in both primary and metastatic breast cancer, was overexpressed 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). Experiment also show that targeting on HOTAIR by specific siRNA can significantly inhibit HOTAIR gene expression, finally, decreasing cell proliferation and promoting cell apoptosis (Yang et al., 2012). [9]

In one study, 26 datasets with 4140 breast cancer patients were used to identify breast cancer prognosis-associated lncRNAs (BCPALs). Among these lncRNAs, HOTAIR, and five others were confirmed to be BCPALs. Among the six BCPALs, only the increased expression of HOTAIR was associated with a worse prognosis. [14] In another survey, HOTAIR , was increased in primary tumors and metastases and its expression level in primary tumors was a predictor of eventual metastasis and death. [4] Thus, the expression of HOTAIR in primary breast cancer is a powerful predictor of metastasis and survival (Gupta et al., 2010; Sorensen et al., 2013). [5]

Bcr4 (progressive)

LncRNA BCAR4 regulates a number of developmental and tumorigenic processes by activating transcriptional program that promotes cell migration. Increased BCAR4 level was correlated with progressive mammary cancer, and targeting BCAR4 based on knockout of specific gene intensively suppressed breast cancer spread in an animal model (Xing et al., 2014). [6]

Tumor suppressive lncRNAs in breast cancer

GAS5

The growth arrest-specific 5(GAS5) is a non-coding RNA which plays a critical role in controlling mammalian cell apoptosis as well as proliferation (Kino et al., 2010). [5] GAS5 acts as a molecular decoy to regulate the activity of glucocorticoids 9in response to nutrient starvation by interacting directly with the DNA- binding sites of the glucocorticoid receptor (GR), and then preventing GR interaction with cognate glucocorticoid response elements to decrease cell metabolism, therefore, 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). Significant down-regulation of GAS has been observed in breast cancer and breast cancer cells. [9] GAS5 was also found to be regulated by miR21 which is a well-studied oncogenic micro RNA (Zhang et al., 2013). MiR21 regulates numerous genes involved in cell growth and apoptosis (Meng et al., 2007). GAS5 was significantly reduced in cancer cells with miR21 knockdown compared to the control cells. GAS5 expression was also found to be negatively correlated with miR21 expression in clinical specimens of breast cancer (Zhang et al., 2013). Interestingly, when GAS5 was knocked-down, the miR21 expression elevated and ectopic expression of GAS5 decreased miR21 expression (Zhang et al., 2013), suggesting reciprocal suppression of miR21 by GAS5. [5]

In a study, the expression levels of four lncRNAs, including GAS5 in BC samples from women under and above 45 years of age, was evaluated. It was observed that all of four lncRNAs, (MALAT1, SRA, and NEAT1) except GAS5 were overexpressed in cancer cell lines compared to control cell line. [10]

Zfas1

ZFAS1 (zinc finger antisense 1) is a newly identified lncRNA that regulates alveolar development and epithelial cell differentiation in the mouse mammary gland (Askarian-Amiri et al., 2011). Shulin et al., found that ZFAS1 expression was downregulated in different human breast cancer cell lines, and additional experiments further demonstrated that overexpression of ZFAS1 inhibited breast cancer cell proliferation, migration, and invasion in vitro. They found that ZFAS1 overexpression significantly inhibited cell viability both in cancer cells compared to that found in control cells. Overexpression of ZFAS1 promotes cell cycle arrest and induces apoptosis in breast cancer cells, and markedly suppressed cell migratory and invasion capacity compared to that observed in the control group. [15]

XIST

XIST is critical for the X chromosome inactivation in embryogenic development. The long lncRNA spreads along the X chromosome and maintains silencing of the X chromosome (Penny et al., 1996). The role of XIST in breast cancer has been intensively studied but remains controversial and unclear. Most breast tumor cell lines lost the inactive X chromosome and gained one more active X chromosome, whether loss of XIST is leading to the loss of inactivated X chromosome or

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loss of XIST leads to the loss of inactive X chromosome is not clear (Sirchia et al., 2009). In one study the XIST, which was expressed from the inactive X chromosome, was regulated by BRCA1, a breast tumor suppressor (Sirchia et al., 2005). However, XIST can also be abnormally expressed from an active X chromosome (Sirchia et al., 2009). These results indicate that the mechanism of XIST expression in breast cancer cells may be different from that of the normal cells, and further investigation are in need to elucidate about the exact role of XIST. [5]

A total of 40 breast cancer patients were enrolled in a study to determine the role of XIST in breast cancer. The results showed that XIST was remarkably decreased in breast cancer tissues compared to in adjacent non-tumour tissues. Furthermore, they compared the expression level of lncRNA XIST between patients with different clinical stages of breast cancer and results indicated that the level of XIST was significantly lower in stage III-IV patients than in stage I-II patients. The expression level of XIST was also remarkably lower in patients with lymph node metastasis than in those without metastasis. Additionally, experiments revealed that overexpression of XIST significantly inhibited the migration and invasive capacity of breast cancer cell lines. These results indicate that XIST is significantly downregulated in breast cancer and up-regulation of XIST suppressed the growth, migration, and invasion of breast cancer cells. [16]

Future direction

Due to rapid development of techniques and advances in genome monitoring alongside with Bioinformatics tools, several Long non coding RNAs has been monitored in breast cancer. Most of the surveys were to determine first the function and second the possible role of them in Breast Cancer. LncRNAs represent a novel and rarely characterized components of the cancer cells, and therefore, there is a great potential to develop biomarkers using these RNAs for clinical use. However, there are a few shortcomings to use lncRNAs as biomarkers. The most controversial issue is the stability of lncRNA in human bodily fluids since RNAs are considered to be unstable. But lncRNAs are often packed into micro-vesicular particles such as exosomes which may protect them from degradation. Eventually, as lncRNAs play an important role in breast cancer progression, they are potential novel therapeutic targets. RNAs are not considered to be a good target with current technology in clinical level; However, the future advances hold a great promise for targeting lncRNAs for cancer treatment.

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