LncRNAs HOTAIR in BC therapy

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Contributor: Monica Cantile , Maurizio Di Bonito , Margherita Cerrone , Francesca Collina , Michelino De Laurentiis , Gerardo Botti

Breast cancer (BC) is the most common cancer type among women, and morbidity and mortality rates are still very high. Despite new innovative therapeutic approaches for all BC molecular subtypes, the discovery of new molecular biomarkers involved in tumor progression has been fundamental for the implementation of personalized treatment strategies and improvement of patient management. Many experimental studies indicate that long non-coding RNAs (lncRNAs) are strongly involved in BC initiation, metastatic progression, and drug resistance. In particular, aberrant expression of HOX transcript antisense intergenic RNA (HOTAIR) lncRNA plays an important role in BC contributing to its progression and represents a predictor of BC metastasis. For its proven prognostic value, HOTAIR could represent a potential therapeutic target in BC.

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1. Introduction

Breast cancer (BC) is the most prevalent cancer type in women and a leading cause of cancer mortality in the world. Breast cancer is a very heterogeneous disease, and its histological classification is mainly based on the expression of hormonal receptors such as estrogen receptor (ER), progesterone receptor (PR), and ERBB2 receptor (HER2) [1]. With respect to gene expression, BC is classified into five molecular subtypes including luminal ER positive (luminal A and luminal B), HER2 enriched, basal-like (also known as triple-negative breast cancer), and normal breast-like subtype [2]. Currently, the choice of routine treatment strategy is based on various factors including tumor size, morphology, grade, metastases, and ER, PR, and HER2 expression [3]. In the last ten years, new innovative therapeutic approaches have been optimized, in particular for triple-negative breast cancer [4]. However, the identification of other prognostic/predictive markers is fundamental for implementing personalized treatment strategies in BC. In this context, our understanding of the mechanisms that regulate gene expression has focused on a class of non-coding RNA molecules (ncRNAs) which have aberrant activity that has largely been described in BC tumor progression [5].

Long non-coding RNAs (lncRNAs) represent a class of ncRNAs, longer than 200 nucleotides, involved in various aspects of cellular homeostasis, such as proliferation, apoptosis, mobility, gene transcription, and post-transcriptional processing [6][7][8]. They can be classified into different categories based on their genomic position, subcellular localization, and function [8]. Regarding their location in the genome, lncRNAs are classified into sense, antisense, bidirectional, and intergenic and intronic lncRNAs, while according to their subcellular location, lncRNAs are classified as nuclear lncRNAs and cytoplasmic lncRNAs. The identification of their precise cellular sub-

localization is fundamental to understanding their cellular activity [9]. Long non-coding RNAs are essential epigenetic regulators of transcription functioning as: i) molecular signals to regulate transcription in response to various stimuli [10]; (ii) decoys, modulating the transcription by sequestering regulatory factors and reducing their availability [11]; (iii) scaffolds, playing a structural role as platforms for the assembly of multiple-component complexes such as ribonucleoprotein (RNP) complexes [12]; (iv) enhancer RNAs, influencing the three-dimensional (3D) organization of DNA (chromatin interactions) [13]; (v) short peptides coders which may also interfere with transcription [14].

Long non-coding RNA's role in cancer has been widely described, highlighting their capability to influence cell cycle regulation, cell proliferation, trans-differentiation, survival, immune response, metastatic progression, and therapeutic response [15]. Moreover, many lncRNAs are transcriptionally regulated by key tumor suppressors or oncogenes [16][17]. In cancer, lncRNAs are mainly involved in chromatin remodeling [18]. They can directly interact with many histone and DNA-modifying enzymes to participate in covalent modifications of histones or DNA. Furthermore, several lncRNAs have recently been found to be capable of modulating the non-covalent, ATP-dependent chromatin remodeling process, indicating an extensive role of lncRNAs in chromatin regulation.

Being LncRNAs expressed in a specific manner in a type of cancer and regulating fundamental processes during tumor progression, they could represent not only exceptional diagnostic, prognostic, and predictive markers but also potential therapeutic targets. Many lncRNAs have been associated with BC, and most of them interfere with crucial processes during BC carcinogenesis [19][20].

2. LncRNAs in Breast Cancer

Long non-coding RNAs play a main role in BC tumor progression (Table 1). They are able of inducing the metastatic process by modulating cell proliferation, invasion, migration, epithelial–mesenchymal transition (EMT), and self-renewal capacity. Clinically, many lncRNAs are involved in therapeutic sensitivity, and they are becoming important circulating biomarkers [21][22].

Among the lncRNAs involved in BC evolution, *H19* is one of the most studied. Its aberrant expression is associated with an increased risk of BC, both in human and cell models [23]. Moreover, its detection in plasma of BC patients also suggests its use as a circulating marker [24]. The expression level of *H19* is associated with tumor size, lymph nodes status, and poor prognosis, especially in triple-negative BC (TNBC) [25]. Furthermore, the overexpression of *H19* is able to induce chemotherapy resistance in BC cells and its silencing sensitizes BC endocrine therapy resistance (ETR) cells to tamoxifen and fulvestran treatment [26][27]. Long non-coding RNA *XIST* (X inactive specific transcript) is strongly associated with BC evolution, and it is able to suppress BC cell growth, migration, and invasion via the miR-155/CDX1 axis [28]. Aberrant expression of *BCAR4* (breast cancer anti-estrogen resistance 4) is mainly involved in acquiring BC tamoxifen resistance [29] in an independent manner of estrogen receptor I (ESRI) [30]. In addition, *BCAR4* is able to promote metastasis through the interaction with chemokine CCL21 and its receptor CXCR7 in BC cell models [31]. Colon cancer-associated transcript 2 (*CCAT2*) is overexpressed, in particular, in TNBC cells, in which it is able to promote cell proliferation, migration, and invasion. In addition,

aberrant expression of *CCAT2* significantly induces stem-like characteristics in TNBC cells [32]. Urothelial carcinoma associated 1 (*UCA1*) is upregulated in tamoxifen-resistant BC cells [33], and its knockdown reduces cell survival and migration ability and promotes apoptosis of tamoxifen-resistant BC cells [34]. The role of lncRNA *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1) in BC has been widely discussed. Many studies suggested its role as a metastasis-promoting marker [35], but other in vitro and xenograft studies have highlighted contradictory effects on BC tumor cells [36]. A recent genetic study has showed that *MALAT1* is able to bind and inactive *TEAD* (*TEA* domain transcription factor 1), a pro-metastatic transcription factor, and consequently suppresses BC metastasis [37]. Nuclear enriched abundant transcript 1 (*NEAT1*) is another lncRNA involved in breast gland development, and it has been associated with BC evolution. It is able to promote proliferation and progression in BC cells [38]. Nuclear enriched abundant transcript overexpression is associated with tumor size, histological grade, metastasis, and poor survival [39]. Most of the other lncRNAs described in the literature are mainly associated with therapeutic resistance in BC. The upregulation of lncRNA-*ATB* (long non-coding RNA activated by TGF-Beta) [40], *TINCR* (Tissue differentiation-inducing non-protein coding RNA) [41], *UCA1* [42], *AGAP2-ASI* (Arf GAP with GTP-binding protein-like domain, Ankyrin repeat, and PH domain 2) [43], and the downregulation of *GAS5* (growth arrest-specific 5) [44] are strongly involved in acquiring trastuzumab resistance in BC patients. The upregulation of *BCAR4*, *UCA1*, and *CCAT2*, as previously indicated, together with the aberrant expression of lncRNA-*ROR* (regulator of reprogramming) [45], lncRNA uc.57 [46], *LINP1* (LncRNA in non-homologous end-joining pathway 1) [47], *DSCAM-ASI* (Down syndrome cell adhesion molecule-antisense RNA 1) [48], *ADAMTS9-AS2* (*ADAM* metallopeptidase with thrombospondin Type 1 motif 9-antisense RNA 2) [49], *CyTOR* (cytoskeleton regulator RNA) [50], and the downregulation of *GAS5* [51] are involved in the promotion resistance mechanisms of tamoxifen and chemotherapy.

Table 1. Main lncRNAs (long non-coding RNAs) involved in BC (breast cancer) progression.

LncRNA	Expression	Activity	Drug Resistance	References
H19	Upregulated	Promoting tumor growth, metastasis, poor prognosis	Endocrine therapy and chemotherapy resistance	[23][24][25][26][27]
XIST	Downregulated	Suppressing cell growth, migration, and invasion	Chemotherapy resistance	[28]
BCAR4	Upregulated	Promoting tumor growth, metastasis, poor prognosis	Endocrine therapy resistance	[30][31][32]

CCAT2	Upregulated	Promoting cell proliferation, migration, invasion, stem-like phenotype	Endocrine therapy resistance	[33]
UCA1	Upregulated	Promoting cell proliferation, migration, invasion	Endocrine therapy and trastuzumab resistance	[34][35]
MALAT 1	Upregulated	Promoting cell proliferation, migration, invasion, stem-like phenotype	-	[36][37][38]
NEAT1	Upregulated	Promoting tumor growth, metastasis, poor prognosis	Chemotherapy resistance	[39][40]
LncRNA-ATB	Upregulated	Promoting cell proliferation, migration, metastasis	Trastuzumab resistance	[41]
GAS5	Downregulated	Promoting apoptosis	Endocrine therapy and chemotherapy resistance	[45]
AGAP2-ASI	Upregulated	Promoting cell proliferation, migration, invasion	Trastuzumab and chemotherapy resistance	[44]
TINCR	Upregulated	Promoting cell proliferation, migration, invasion, suppressing apoptosis	Trastuzumab resistance	[48]
LncRNA-ROR	Upregulated	Promoting cell proliferation, migration, invasion	Chemotherapy resistance	[46]
CyTOR	Upregulated	Promoting tumor growth, metastasis, poor prognosis	Endocrine therapy resistance	[51]

LINP1	Upregulated	Promoting tumor growth, metastasis, poor prognosis, involved in DNA repair mechanisms	Endocrine therapy and chemotherapy resistance	[52]

3. LncRNA HOTAIR and Its Role in Cancer

HOX transcript antisense RNA (*HOTAIR*) is an lncRNA 2158 bp long, consisting of 6 exones, located on chromosome 12q13.13 between *HOXC11* and *HOXC12* genes [52]. Its promoter contains binding sites for many transcription factors, such as AP1, Sp1, ERE elements, HRE elements, and NF-kB [53]. HOX transcript antisense RNA (*HOTAIR)* is a key regulator of chromatin status and a mediator of transcriptional silencing [53]. Early studies showed that *HOTAIR* is capable to bind the *PRC2* (Polycomb repressive complex) at the 5' end [52]. The formation of the molecular complex is able to maintain cell stemness and suppress cell differentiation by trimethylation of the H3K27 histone complex and subsequent transcriptional repression of differentiation genes [53]. HOX transcript antisense RNA *(HOTAIR)* is also able to interact at the 3' end with the lysine-specific histone demethylase 1A (*LSD1*), another chromatin modifier which is critical for gene silencing [54]. Lysine-specific histone demethylase 1A *(LSD1)* can form a multiprotein complex via activation of RE1-silencing transcription factor (REST) and CoREST which are critical players in gene silencing [54]. HOX transcript antisense RNA (*HOTAIR)* acts as a molecular scaffold for the conjunction of the two complexes. The HOTAIR-PRC2-LSD1 complex leads epigenetic changes contributing to the targeted gene silencing and represses their transcription via H3K27 trimethylation (PRC2 activity) and H3K4 demethylation (LSD1 activity). For example, the HOTAIR-PRC2-LSD1 complex can be redirected towards the 5' end of the HOXD locus on chromosome 2 where the genes, implicated in metastatic suppression are silenced by methylation and demethylation of H3K27 and H3K4, respectively [55].

HOX transcript antisense RNA *(HOTAIR)* can also alter gene expression both at the post-transcriptional level, either by base pairing with translation factors or ribosomes to control translation or by binding to splicing factors to modulate splicing, and at the post-translational level. For this last function, it is reported that *HOTAIR* could serve as a ubiquitination protein and subsequent degradation platform [56].

Most lncRNAs possess miRNA recognition elements (MREs), suggesting that the transcription of some miRNAs is regulated by lncRNAs and some lncRNAs are involved in synthesis, maturation, and degradation of miRNAs [57]. Many studies reported the interaction between *HOTAIR* and microRNAs highlighting that these interactions are able to modulate different cellular processes [58][59].

During embryogenesis, *HOTAIR* is involved in the development of the lumbosacral region, and its activity is closely linked to the recruitment of PRC2 to its targeted HOX D genes for their repression.

Several studies have pointed out the role of *HOTAIR* as a cell cycle-associated gene. HOX transcript antisense RNA *(HOTAIR)* promotes the cell cycle passing through the restriction point during the G1 phase by regulating CDK4/6-cyclin D and the Rb-E2F pathway [60].

In the last ten years, the aberrant *HOTAIR* expression in the majority of solid cancers has been reported, underlining its main role in modulating tumor initiation, growth, angiogenesis, progression, recurrence, drug resistance, and poor prognosis [61][62]. In urological cancers, *HOTAIR* overexpression is able to increase prostate cancer cells growth and invasion by binding androgen receptor (*AR*) protein and blocking its degradation [63]. In bladder cancer patients, *HOTAIR* is an independent prognostic factor of tumor recurrence [64]. It is also involved in chemo sensitivity to doxorubicin [65] and can be detected in the urine of bladder cancer patients [66]. In gynecological tumors, *HOTAIR* is overexpressed in epithelial ovarian cancer tissues and correlates with International Federation of Gynecology and Obstetrics (FIGO) stage, histological grade of the tumor, lymph node metastases, and poor survival [67]. In cervical cancer tissues, *HOTAIR* is associated with clinical-pathological features, lymph node metastases, and prognosis [68]. HOX transcript antisense RNA *(HOTAIR)* is also able to interact with different mRNAs in cervical cancer cells modulating cell growth and proliferation [69]. Moreover, the detection of circulating levels of *HOTAIR* is strongly associated with advanced tumor disease, lymph nodes metastases, and poor survival in cervical cancer patients [70]. Aberrant *HOTAIR* expression in endometrial carcinoma correlates with grade, lymph nodes metastases, and poor prognosis [71], and it is associated with cisplatin resistance acquisition [72]. In gastrointestinal tract tumors, *HOTAIR* upregulation appears as an important marker in colorectal cancer [73] and gastric cancer [74], showing a strong relation with stage, lymph nodes, distant metastases, and worse survival. In gastric cancer, *HOTAIR* has been detected in patients' plasma, and its circulating level is able to predict which patient can benefit from fluorouracil and platinum combination therapy [74]. In liver cancer, *HOTAIR* is overexpressed and strongly correlates with clinical-pathological features, and tumor progression [75]. In addition, *HOTAIR* silencing increases chemotherapy sensitivity to cisplatin and doxorubicin hepatocellular carcinoma patients [76]. In oral cancers, *HOTAIR* overexpression has been described in laryngeal squamous cell carcinoma (LSCC) and is associated with histopathological grade and stage [77]. Also, in LSCC cells, *HOTAIR* is involved in the modulation of sensitivity to cisplatin [78]. In lung cancer, aberrant expression of *HOTAIR* correlates with advanced stage, lymph nodes metastases, and poor prognosis [79]. A higher *HOTAIR* expression is also strongly associated with cisplatin resistance in non-small cell lung cancer (NSCLC) patients [80]. Circulating *HOTAIR* has been detected in lung cancer plasma, and it appears to be associated with clinical-pathological features of the patients [81].

Many studies have highlighted the role of *HOTAIR* also in tumor microenvironment (TME) intracellular signaling. In TME, *HOTAIR* is able to modulate different molecular pathways involved in tumor phenotype modifications during metastatic progression [82].

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