Roles and expression profiles of long non-coding RNAs in triple-negative breast cancers

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

| Citation       | Kong, Xiangyi, Wenyue Liu, and Yanguo Kong. 2017. "Roles and expression profiles of long non-coding RNAs in triple-negative breast cancers." Journal of Cellular and Molecular Medicine 22 (1): 390-394. doi:10.1111/jcmm.13327. http://dx.doi.org/10.1111/jcmm.13327. |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Published Version | doi:10.1111/jcmm.13327                                                                                                                                                                                                                                           |
| Citable link    | http://nrs.harvard.edu/urn-3:HUL.InstRepos:34868949                                                                                                                                                                                                               |
| Terms of Use    | This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA |
Roles and expression profiles of long non-coding RNAs in triple-negative breast cancers

Xiangyi Kong a, b, #, Wenyue Liu c, d, #, Yanguo Kong a, *

a Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
b Department of Breast Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
c Plastic Surgery Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
d Tissue Engineering and Wound Healing Laboratory, Department of Surgery, Division of Plastic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Received: May 15, 2017; Accepted: July 3, 2017

Abstract

Triple-negative breast cancer (TNBC) refers to the breast cancers that express little human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR) and oestrogen receptor (ER). When compared to other types of breast cancers, TNBC behaves more aggressively with relatively poorer prognosis. Moreover, except chemotherapy, no targeted treatments have been approved yet until now. Although the molecular-biological mechanisms of the initiation and development of TNBC have been explored a lot, the exact details underlying its progressions are still not clear. Long non-coding RNAs (lncRNAs), with the length greater than 200 nucleotides, are non-protein coding transcripts. Previous researches have shown that lncRNAs are significantly involved in a variety of pathophysiological processes such as cell migration, invasion, proliferation, differentiation and development. lncRNAs’ dysregulated expressions have been observed in many types of tumours including TNBCs. This article will review the functional roles and dysregulations of lncRNAs in TNBCs. These lncRNAs are worthy of exploitation regarding their potential application values of TNBC’s diagnosis and treatment.

Keywords: Long non-coding RNAs ● triple-negative breast cancer ● expression

Introduction

TNBCs account for almost 20% of all types of breast cancers across the world (approximately, 0.2 million cases per year). TNBCs tend to be more usually diagnosed in young females (<40-year-old) than hormone-positive breast cancers. According to Trivers et al’s [1] survey data, there were twofold higher attributable risks of TNBCs in ≤40-year-old females than >50-year-old females. Additionally, TNBCs are more common among black women than white women. Histopathologically, TNBCs are more likely to be of high grade (mostly are infiltrating ductal carcinomas, though a rare histologic subtypes, medullary carcinoma, is also generally triple-negative) [2]. TNBC can exhibit geographic necroses, stromal lymphocytic responses and pushing borders of invasion [3]. By definition, TNBCs lack immunohistochemical expressions of HER2, PR and ER. As the three biomarkers are currently the only known approved therapeutic targets of breast cancer, considerable effort has been made to better understand other biological forces driving TNBC [3, 4].

Although the TNBCs mostly consist of the basal-like molecular subtype, considerable heterogeneities within TNBCs still exist. As examples, in one study of utilizing DNA and RNA profiling of TNBCs, four stable subtypes were identified: basal-like immune-activated, basal-like immunosuppressed, mesenchymal and luminal androgen receptor [5]. Other molecular-biological mechanisms underlying TNBC’s development include mutations and dysregulated expressions of many DNA repair genes [e.g. breast cancer susceptibility gene (BRCA)] [6] and tumour-suppression genes such as p53 [7]. These molecular features may have implications for chemotherapy sensitivity to platinum or other directly DNA-damaging agents. The identification of effective biomarkers for early diagnosis of TNBCs and a better understanding of the systems of the neoplastic advancement are consequently keenly awaited.

LncRNA and cancers

LncRNAs, with the length greater than 200 nucleotides, are non-protein coding transcripts. Their roles in cancer initiation and
Long intergenic non-coding RNA for kinase activation (LINK-A)

LINK-A, also called NR_015407 or LOC339535, is a ~1.5 kb intergenic lncRNA [18]. LINK-A is considered to play a significant role in the growth-factor-mediated HIF1α cell signal transduction pathway. According to Lin et al.’s study, LINK-A expression levels were much higher in 2 stage-III TNBC tissues than in their paired adjacent non-cancer breast tissues, ERPR+/HER2+, HER2-/ERPR+ and ERPR-/HER2+ breast cancer tissues, suggesting the close association between TNBC and LINK-A expressions [18]. Consistently, they also found that overexpressed LINK-A in TNBC tissues and cells are associated with poorer prognoses and progression-free survivals [18]. Moreover, different from typical nuclear IncRNAs, they found that LINK-As are mainly located adjacent to cellular membranes or in cytoplasm [18]. LINK-A could promote tumourigenesis in TNBC through LINK-A-dependent signalling pathway activation. Hence, targeting LINK-A, with much promising therapeutic potential, might be able to provide a favourable strategy to block the HIF1α signalling pathway in TNBCs. Whether LINK-As are released into circulation continuously through cell apoptosis or actively secreted from TNBC cells through exosome pathways still needs further research.
The HOX transcript antisense intergenic IncRNA (HOTAIR)

HOTAIR is a 2.3 kb non-coding transcript derived from the intergenic region of the HOXC homeotic gene cluster [12]. HOTAIR plays a critical role in oncogenesis, whose expressions significantly increased in a variety of cancers including hepatocellular carcinoma [19], gastric cancer [20], intestinal cancer [21] and breast cancer [22]. HOTAIR overexpression correlates with more severe tumour distant metastases and poorer prognosis. HOTAIR was the first IncRNA shown to promote tumour progression and be related to poor prognosis in breast cancer [23]. HOTAIR was involved in regulating malignant biological behaviour of TNBC through a variety of ways. HOTAIR expression was significantly up-regulated by oestrogen in TNBC cells MDA-MB-231 and BT549 and increased the migration of them. HOTAIR can also indirectly suppress certain miRNA expressions in TNBC, reverse epithelial-mesenchymal transition (EMT) partially, decrease the breast cancer stem cell population, and attenuate cell metastasis and invasion [24]. Considering the key roles of HOTAIR in TNBC, attenuating HOTAIR functions to gain treatment effects is promising [12]. Yang et al. also found Delphinidin-3-glucoside could down-regulate HOTAIR expressions in TNBC cells in both vitro and vivo. These studies elucidate some unidentified mechanism in TNBC linking signalling with HOTAIR regulation which may be exploited for therapeutic gain [25]. These researches identified several mechanisms underlying TNBC’s genesis and progression. HOTAIR dysregulation is the most important mechanism, which offers a new target and orientation for TNBC therapy.

Rhabdomyosarcoma 2-associated transcript (RMST)

RMST, located on chromosome 12q21 in human beings, was initially reported in rhabdomyosarcomas and was found to be expressed at lower levels in embryonal rhabdomyosarcomas than in alveolar rhabdomyosarcomas [26]. Udeh et al. found that RMST exhibits prominent expressions in regions of the roof plate of the anterior neural tube, the isthmus and the midbrain floor plate. Subsequent studies demonstrated that RMST was closely related to neuronal differentiation [27]. Studies also have shown that together with sex determining region Y-box 2 (SOX2), RMST could co-regulate many downstream genes involved in neurogenesis. In Ng et al.’s RNA interference and genome-wide SOX2-binding studies, RMST was found to be indispensable for SOX2’s combination with promoter regions of neurogenic transcription factors [27].

Yang et al. sequenced eight paired non-cancer samples and TNBC samples, and identified several abnormally expressed IncRNAs, among which, compared to adjacent non-cancer breast tissues, RMST was significantly down-regulated in TNBC [28]. Moreover, low RMST were also associated with poor outcomes and worse prognosis than higher RMST, suggesting the cancer-suppression roles of RMST in breast cancer [28]. However, Yang’s study had some limitations: (i) they did not perform in vivo experiments or ectopic expressions, which could help with confirming core IncRNAs’ roles in TNBCs; (ii) they only conducted the strand-specific and Poly-A-dependent RNA sequencing, which was likely to lead to the loss of IncRNAs without Poly-A.

Small nucleolar RNA host gene 12 (SNHG12)

Small nucleolar RNA host genes (SNHGs) have been reported to contribute to the progression of cancers. SNHG12 (also known as GASS) is a novel IncRNA identified to be up-regulated in several cancer cells, such as human osteosarcoma cell, nasopharyngeal carcinoma cell and human endometrial carcinoma [29, 30]. The original identification of SNHG12 from a subtraction cDNA library depended on its increased abundance in growth-arrested mouse NIH 3T3 fibroblasts [31]. Subsequently, it has been shown that it was the alterations of the biodegradation rate rather than the transcription rate that regulated the expression levels of SNHG12 [32]. Mourtada et al. found that overexpression of certain SNHG12 transcripts induces growth arrest and apoptosis in human breast cancer cell lines. SNHG12 levels were down-regulated significantly in human breast cancer cell lines, suggesting that the decrease in SNHG12 expressions might play important roles in the oncogenesis. According to their study, in breast cancer cell lines, SNHG12 expressions were generally inversely correlated to tumorigenic behaviours [11].

SNHG12 played important roles in cancer cell proliferation and migration. Wang et al. discovered that SNHG12 was up-regulated in colorectal cancer tissues and cells. They also detected the effect of SNHG12 on cell proliferation, cell cycle, apoptosis and the related proteins expression in CRC cells [33]. Subsequently, Wang et al. utilized RNA sequencing (RNA-seq) to explore the IncRNAs expression profiles in TNBC and identified that SNHG12 was remarkably increased in TNBC [34]. Subsequently, they determined that SNHG12 is significantly up-regulated in 102 TNBC tumour tissues compared to 95 non-cancerous breast tissues by qRT-PCR (P < 0.001). The expression levels of SNHG12 were statistically related to the lymph node metastasis (P = 0.041) and the tumour size (P = 0.012) [34]. Patients with higher SNHG12 expression levels were inclined to have larger tumours and metastatic lymph nodes. Mechanistic investigations show that SNHG12 is a direct transcriptional target of c-MYC. The depletion of c-MYC by siRNA in TNBC cell lines BT-549 and MDA-MB-231 significantly reduced SNHG12 transcript levels (P < 0.05) [34]. In addition, SNHG12 levels were markedly increased in BT-549 and MDA-MB-231 cells transfected with c-MYC overexpression plasmid. Silencing SNHG12 expression inhibits TNBC cells proliferation and apoptosis promotion, whereas enforced expression of SNHG12 promoted TNBC cells proliferation and migration. In addition, they reveal that SNHG12 was mainly located in cytoplasm and may regulate MMP13 expression to promote cells migration [34]. However, SNHG12’s biological roles still have not yet been identified in in vivo experiments, and the mechanisms by which SNHG12 mediates the apoptosis or proliferation remains unclear.
SnaR

SnaR, a double-stranded IncRNA of 117 nt, is transcribed by RNA polymerase-III linked with nuclear factor 90 (NF90). SnaR binds important proteins implicated in multiple cellular functions by in vivo cross-linking followed by immune-precipitation, indicating the possibility that it has critical roles in the regulation of cancer’s initiation and progression [35]. Several snaR transcripts have been found to be associated with ribosomes in cytoplasm [36]. What is more, it has been observed that these regulatory roles in cell growth and gene translation are species specific and tissue specific. Lee H et al. reported that in 5-FU-resistant colon cancer cells, snaR was down-regulated. Additionally, after 5-FU treatment, the down-regulation could decrease Annexin V-positive (ANN+) apoptotic cells, indicating that snaR might negatively regulate cell growth and tissue development after 5-FU treatment [37]. In Lee et al.’s study, diverse breast cancer cell lines based on molecular subtype, namely BT20, BT474, T47D, SKBR3, MCF7 and MDA-MB-231, were used to explore the role of IncRNAs [38]. Although various IncRNAs were expressed highly in each cell line, snaR and ANRIL were identified as being predominantly up-regulated in MDA-MB-231 cell line and the hormone receptor-expressing cell line (MCF7). Particularly, snaR was shown to be 16.82 ± 3.44-fold more highly expressed in the TNBC cells than control [38]. The invasion, migration and proliferation of TNBC cells could be significantly inhibited after snaR-knockdown. So, if the knockdown of snaR can be applied clinically to TNBC, it would provide an innovative treatment for such cancer.

Conclusion

TNBC generally behaves more aggressively with a relatively poorer prognosis than other phenotypes of breast cancer. Our understanding of the cellular origin and pathogenic mechanisms of TNBC remains fragmented. In the past several years, the researchers have witnessed a steep rise of interest in the study of IncRNAs in many diseases, including various kinds of cancer. Recent studies have identified a series of dysregulated IncRNAs in TNBC. These IncRNAs may serve as biomarkers and therapeutic targets for TNBC in the future.

Acknowledgements

We would like to thank our colleagues at the Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Funding source: This study was supported by Peking Union Medical College Youth Research Funds (2016) (Project No. 3332016010; Grant recipient: X.K.) and Peking Union Medical College Graduate Student Innovation Fund (2015) (Project No. 2015-1002-02-09; Grant recipient: X.K.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

We have no conflicts of interests.

References

1. Trivers KF, Lund MJ, Porter PL, et al. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control. 2009; 20: 1071–82.
2. Livasay CA, Karaca G, Nanda R, et al. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006; 19: 264–71.
3. Gadi VK, Davidson NE. Practical approach to triple-negative breast cancer. J Oncol Pract. 2017; 13: 293–300.
4. Costa RLB, Gradishar WJ. Triple-negative breast cancer: current practice and future directions. J Oncol Pract. 2017; 13: 301–3.
5. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011; 121: 2750–67.
6. Bayraktar S, Gutierrez-Barrera AM, Liu D, et al. Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. Breast Cancer Res Treat. 2011; 130: 145–53.
7. Turner N, Moretti E, Siciari O, et al. Targeting triple negative breast cancer: is p53 the answer? Cancer Treat Rev. 2013; 39: 541–50.
8. Li Z, Yu X, Shen J. Long non-coding RNAs: emerging players in osteosarcoma. Tumour Biol. 2016; 37: 2811–6.
9. Li Z, Shen J, Chan MT, et al. TUG1: a pivotal oncogenic long non-coding RNA of human cancers. Cell Prolif. 2016; 49: 471–5.
10. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature. 2010; 464: 1071–6.
11. Mourtada-Maarabouni M, Pickard MR, Hedge VL, et al. GASS, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. Oncogene. 2009; 28: 195–208.
12. Wang Q, Gao S, Li H, et al. Long noncoding RNAs (IncRNAs) in triple negative breast cancer. J Cell Physiol. 2017; doi: 10.1002/jcp.25830. [Epub ahead of print].
13. Zhang Y, Xu Y, Feng L, et al. Comprehensive characterization of IncRNA-mRNA related ceRNA network across 12 major cancers. Oncotarget. 2016; 7: 64148–67.
14. Iyer MK, Niknafs YS, Malik R, et al. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 2015; 47: 199–208.
15. Augoff K, McCue B, Plow EF, et al. miR-31 and its host gene IncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer. Mol Cancer. 2012; 11: 5.
16. Liu YR, Jiang YZ, Xu XE, et al. Comprehensive transcriptome analysis identifies novel molecular subtypes and subtype-specific chromatin states in hormone receptor-positive breast cancer. Breast Cancer Res. 2016; 18: 33.
17. Koduru SV, Tiwari AK, Leberfinger A, et al. A comprehensive NGS data analysis of differentially regulated miRNAs, piRNAs, IncRNAs and sn/snoRNAs in triple negative breast cancer. J Cancer. 2017; 8: 578–96.
18. Lin A, Li C, Xing Z, et al. The LINK-A IncRNA activates normoxic HIF1alpha signalling in triple-negative breast cancer. Nat Cell Biol. 2016; 18: 213–24.
19. Su DN, Wu SP, Chen HT, et al. HOTAIR, a long non-coding RNA driver of malignancy whose expression is activated by FOXC1, negatively regulates miRNA-1 in hepatocellular carcinoma. Oncol Lett. 2016; 12: 4061–7.
20. Fagonee S, Durazzo M. HOTAIR and gastric cancer: a lesson from two meta-analyses. Panminerva Med. 2017; 59: 201–2.
21. Lu X, Bai D, Liu X, et al. Sedentary lifestyle related exosomal release of Hotair from gluteal-femoral fat promotes intestinal cell proliferation. Sci Rep. 2017; 7: 45648.

22. Zhou Y, Wang C, Liu X, et al. Long non-coding RNA HOTAIR enhances radioresistance in MDA-MB231 breast cancer cells. Oncol Lett. 2017; 13: 1143–8.

23. Tao S, He H, Chen Q. Estradiol induces HOTAIR levels via GPER-mediated miR-148a inhibition in breast cancer. J Transl Med. 2015; 13: 131.

24. Eades G, Wolftson B, Zhang Y, et al. lincRNA-RoR and miR-145 regulate invasion in triple-negative breast cancer via targeting ARF6. Mol Cancer Res. 2015; 13: 330–8.

25. Yang X, Luo E, Liu X, et al. Delphinidin-3-glucoside suppresses breast carcinogenesis by inactivating the Akt/HOTAIR signaling pathway. BMC Cancer. 2016; 16: 423.

26. Chan AS, Thorner PS, Squire JA, et al. Identification of a novel gene NCRMS on chromosome 12q21 with differential expression between rhabdomyosarcoma subtypes. Oncogene. 2002; 21: 3029–37.

27. Ng SY, Boqu GK, Soh BS, et al. The long noncoding RNA RMST interacts with SOX2 to regulate neurogenesis. Mol Cell. 2013; 51: 349–59.

28. Yang F, Liu YH, Dong SY, et al. Co-expression networks revealed potential core IncRNAs in the triple-negative breast cancer. Gene. 2016; 591: 471–7.

29. Cancer Genome Atlas Research N, Weinstein JN, Collisson EA, et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet. 2013; 45: 1113–20.

30. Wang L, Park HJ, Dasari S, et al. CPAT: Coding-Potential Assessment Tool using an alignment-free logistic regression model. Nucleic Acids Res. 2013; 41: e74.

31. Schneider C, King RM, Philipson L. Genes specifically expressed at growth arrest of mammalian cells. Cell. 1988; 54: 787–93.

32. Smith CM, Steitz JA. Classification of gas5 as a multi-small-nucleolar-RNA (snoRNA) host gene and a member of the 5’-terminal oligopyrimidine gene family reveals common features of snoRNA host genes. Mol Cell Biol. 1998; 18: 6897–909.

33. Wang JZ, Xu CL, Wu H, et al. LncRNA SNHG12 promotes cell growth and inhibits cell apoptosis in colorectal cancer cells. Braz J Med Biol Res. 2017; 50: e6079.

34. Wang O, Yang F, Liu Y, et al. C-MYC-induced upregulation of lncRNA SNHG12 regulates cell proliferation, apoptosis and migration in triple-negative breast cancer. Am J Transl Res. 2017; 9: 533–45.

35. Parrott AM, Mathews MB. Novel rapidly evolving hominid RNAs bind nuclear factor 90 and display tissue-restricted distribution. Nucleic Acids Res. 2007; 35: 6249–58.

36. Parrott AM, Tsai M, Batchu P, et al. The evolution and expression of the snaR family of small non-coding RNAs. Nucleic Acids Res. 2011; 39: 1485–500.

37. Lee H, Kim C, Ku JL, et al. A long non-coding RNA snaR contributes to 5-fluorouracil resistance in human colon cancer cells. Mol Cells. 2014; 37: 540–6.

38. Lee J, Jung JH, Chae YS, et al. Long non-coding RNA snaR regulates proliferation, migration and invasion of triple-negative breast cancer cells. Anticancer Res. 2016; 36: 6289–95.