# lncRNAs and Breast Cancer Development

**Randa H. Mohamed [a,*], Mohamed M. Alkilany [b], Hoda K. El-feky [a], Bassel T. Abdelmoeim [c], Amal F Abd-Elmageed [a]**

[a] Medical Biochemistry Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[b] General Surgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

[c] Faculty of Medicine, Ain Shams University, Cairo, Egypt

**Corresponding author:** Randa H. Mohamed

**E-mail:** randahussiny@yahoo.com

**Conflict of interest:** None declared.

**Funding:** No funding sources

**Abstract**

Breast cancers are highly heterogenous between and within tumors. Genomic instability is postulated to contribute to this process, also facilitating a high degree of plasticity, as the capability to adapt and survive in hostile microenvironments. Mechanisms leading to genomic instability include microsatellite and chromosomal instability, which by contrast participate respectively to the acquisition of point mutations and accumulations of chromosomal aberrations. While models of cancer evolution have been postulated, the increasing evidence that lncRNAs can have a causative role in cancer raises the question regarding the relevance and the biological consequences of the mutations in noncoding genes and regions at the different stages of the process of tumorigeneses. Though metastasis occurrence represents the overwhelming cause of mortality in breast cancer patients, the molecular mechanisms that drive tumor cells to acquire metastatic traits are still largely unknown. In this respect, the identification of metastatic mediators would be of certain prognostic and therapeutic benefit. Dysregulation of lncRNA expression has been found to contribute to breast cancer metastatic progression through aberrant regulation of tumor-suppressive or oncogenic pathways. The great majority of lncRNAs implicated in the metastatic process act as oncogenic factors

**Keywords:** lncRNAs, breast cancer

*Tob Regul Sci.™ 2022 ;8(2):* 708 - 717

*DOI: doi.org/10.18001/TRS.8.2.49*

## Introduction

Breast cancers are highly heterogenous between and within tumors. Genomic instability is postulated to contribute to this process, also facilitating a high degree of plasticity, as the capability to adapt and survive in hostile microenvironments. Mechanisms leading to genomic instability include microsatellite and chromosomal instability, which by contrast participate respectively to the acquisition of point mutations and accumulations of chromosomal aberrations. While models of cancer evolution have been postulated, the increasing evidence that

lncRNAs can have a causative role in cancer raises the question regarding the relevance and the biological consequences of the mutations in noncoding genes and regions at the different stages of the process of tumorigeneses [1].

lncRNAs in breast cancer progression and metastasis

Though metastasis occurrence represents the overwhelming cause of mortality in breast cancer patients, the molecular mechanisms that drive tumor cells to acquire metastatic traits are still largely unknown. In this respect, the identification of metastatic mediators would be of certain prognostic and therapeutic benefit. Dysregulation of lncRNA expression has been found to contribute to breast cancer metastatic progression through aberrant regulation of tumor-suppressive or oncogenic pathways. The great majority of lncRNAs implicated in the metastatic process act as oncogenic factors [2].

HOX transcript antisense intergenic lncRNA (HOTAIR)

HOTAIR is a trans-acting lncRNA, transcribed from the HOXC locus on chromosome 12q13.13, which guides silencing complexes to specific sites genome-wide. The expression of HOTAIR is low in normal mammary epithelia and progressively increases in breast cancer primary tumors and metastases. High HOTAIR expression in primary tumors correlates with decreased metastasis-free survival and overall survival [2].

Protein phosphatase 1 (PP1) nuclear-targeting subunit (PNUTS)

The human PNUTS gene encodes two variants, the PNUTS mRNA and the lncRNA-PNUTS (also known as PPP1R10), which are generated as a result of alternative splicing site utilization. Differential processing of the PNUTS preRNA leads to up-regulation of lncRNA-PNUTS expression in human breast tumors compared with their non-tumor counterpart, and increased expression of lncRNA-PNUTS correlates with that of mesenchymal markers [3].

MST1/2-Antagonizing for YAP Activation (MAYA)

MAYA expression is upregulated in tumor samples compared to healthy breast tissues and is associated with advanced-stage and unfavorable patient outcomes [4].

MAYA was identified as a prognostic biomarker to predict bone metastasis in breast cancer and suggests a promising therapeutic strategy for metastatic patients [5].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)

MALAT1 is an oncogenic lncRNA that exhibits its tumor promoting effects in several cancers including BC. Its chromosomal location is 11q13. MALAT1 is a nuclear lncRNA that is highly conserved among mammals. it has been repeatedly reported that MALAT1 promotes proliferation, tumor development, and metastasis of BC. In addition, the expression level of MALAT1 was reported to have a high prognostic value as it was negatively correlated to the survival of ER-negative, lymph node-negative patients of the HER-2 and TNBC molecular subtypes. Collectively, these studies highly propose MALAT1 as a core signaling molecule promoting BC development and progression and consequently a potential therapeutic target for several BC subtypes [6].

Long intergenic non-protein coding RNA (Linc-ZNF469-3)

Linc-ZNF469-3 upregulation was negatively correlated to the overall survival and the disease-free survival in the TNBC cohort, while there was no evident association for patients with non-TNBC. Linc-ZNF469-3 upregulation increases the self-renewal properties of breast cancer stem cells (CSCs), promotes migration and invasion in breast cancer cell lines, and enhances lung metastasis of TNBC in mice [7].

Long intergenic non-protein coding RNA 1638 (LINC01638)

LINC01638 is an additional lncRNA implicated in maintaining the mesenchymal characteristics of TNBC cells and was found overexpressed in HER2-positive breast cancer tissues relative to their matched normal tissues, also strongly correlated with disease progression and poor outcome of TNBC patients [8].

Nuclear factor-κB interacting long noncoding RNA (NKILA)

NKILA encoded by a gene at chromosome 20q13, acts as a tumor suppressor in breast cancer. NKILA indeed reduces the invasiveness capability of breast cancer cell lines [9].

Likewise, ectopic expression of NKILA in breast cancer cell line xenografts inhibits cancer metastasis to the lungs, liver, and lymph nodes and prolongs mouse survival. NKILA expression is reduced in invasive breast carcinomas with no distal or regional lymph node metastasis compared to benign mammary tissues and is further down-regulated in metastatic lesions. Overall, reduction of NKILA expression correlates with poor patient survival [10].

long noncoding RNA Lnc-BM

It has been reported that elevated expression of the lncRNA Lnc-BM (long noncoding for brain metastasis) in primary breast cancer correlates with higher rates of recurrence in the brain rather than other distant organs [11].

lncRNA X-inactive specific transcript (XIST)

The expression of the XIST is significantly down-regulated in brain metastatic tumors and its levels inversely correlate with tumor dissemination to the central nervous system [12].

NCT02915744 III, NCT0200088 lncRNAs and linc-ZNF469-3

In addition, the expression of NCT02915744 III and NCT0200088 lncRNAs correlates with brain metastasis of breast cancer patients. Regarding other sites of metastasis, Wang et al. reported that high linc-ZNF469-3 expression is significantly correlated to lung metastasis in TNBC patients [7].

Tumor-associated macrophages (TAMs) have been implicated in the promotion of breast cancer growth and metastasis, and multiple TAM-secreted cytokines have been identified as associated with poor clinical outcomes. However, the therapeutic targets existing in the loop between TAMs and cancer cells are still required for further investigation. Herein, the cytokine array validated that C-X-C motif chemokine ligand 1 (CXCL1) is the most abundant chemokine

secreted by TAMs, and CXCL1 can promote breast cancer migration and invasion ability, as well as epithelial-mesenchymal transition (EMT) in both mouse and human breast cancer cells [13].

In vivo breast cancer xenografts demonstrated that CXCL1 silencing in TAMs results in a significant reduction in breast cancer growth and metastatic burden. CXCL1-based therapy might become a novel strategy for breast cancer metastasis prevention [7].

lncRNA in the interaction with breast cancer microenvironment and immune response

The dynamic nature of the tumor microenvironment contributes to determining the progression of breast cancer, influencing metastasis, resistance to therapy, and tumor growth. Within the tumor microenvironment, hypoxia is a common factor of advanced cancer, at the stage when tumor growth overcomes the ability of neo-vascularization to provide sufficient blood supply to the developing malignant tissue. Activation of the cellular oxygen-sensing mechanism promotes activation of hypoxia-inducible factor-1 (HIF-1), which, promoting adaptation to hypoxia, also enhances aerobic glycolysis. [14].

Interaction between HIF-1 and the lncRNA network appears to be equally important for the regulation of the HIF-1 signaling. The lncRNA LINK-A (long intergenic non-coding RNA for kinase activation) has been shown upregulated in human TNBC and has a significant prognostic value, as high expression level is associated with poor survival expectancy [15].

Thus, lncRNAs can represent alternative oncogenic pathways to promote oxygen-independent HIF-1 hyperactivation in cancer. The oncogenic role of LINK-A has been expanded beyond the control of HIF-1 signaling. Expression of LINK-A in TNBC is associated with reduced CD8+ T cells and antigen-presenting cells (APC) infiltration75, indicating that LINK-A is correlated with an immunosuppressive microenvironment [16].

This would data open to designing protocol for patient stratification for immunotherapy response or immunotherapy combinations, it remains to be determined whether and how LINK-A dependent regulation of HIF-1 and the hypoxic microenvironment has a role in the immunosuppressive mechanism. The importance of the reciprocal interaction between cancer immune infiltration and microenvironmental hypoxia has been shown at different levels and with more recent evidence implicating also lncRNAs [17].

Reduction of lncRNA X-inactive–specific transcript (XIST) correlates with brain metastasis in breast cancer patients. Loss of XIST facilitates the release of miRNA-503 containing exosomes, upregulating immune suppressive cytokines, and suppressing infiltration and proliferation of T-cells [12].

LncRNAs can be determinant of tumor-mediated T cell response. Pro-apoptotic microenvironment (i.e. FasL, TRAIL, and TNF) can contribute to immune evasion by promoting activation-induced cell death (AICD) of T cells. In this context, NKILA, which can function as a tumor-suppressive lncRNA, can promote AICD by inhibiting NF-κB in activated T cells. Modulation of lncRNAs is therefore a potential strategy to engineer adoptively transferred T cells to achieve antitumoral immunotherapeutic effects [18].

NF-κB Interacting LncRNA

NKILA (NF-kB interacting long noncoding RNA), encoded by a gene at chromosome 20q13, acts as a tumor suppressor in breast cancer. NKILA indeed reduces the invasiveness capability of breast cancer cell lines [9].

NKILA was found to be a 2,570 nucleotide (nt) intronless transcript that is identical to AK056098 in GeneBank or uc002xyu in the UCSC database. Apart from a few short potential open reading frames (ORF) that have a limited chance (<1%) of encoding short ORF encoded polypeptides. NKILA does not have a typical protein-coding ORF that is longer than 300 nt. Confocal microscopy for fluorescent in situ hybridization (FISH) showed that NKILA located primarily in the cytoplasm, which was confirmed by nuclear/cytoplasm fractionation, suggesting that NKILA may exert its biological function in the cytoplasm [19].

NF-κB Interacting LncRNA (NKILA) has inhibitory roles on NF-κB. NF-κB regulates expression of several molecules participating in various crucial physiological reaction including immune responses, cell proliferation and differentiation, as well as cell death. Therefore, NKILA can be involved in the pathogenesis of a wide spectrum of human disorders. Numerous studies in hepatocellular carcinoma, breast cancer, melanoma, glioma and other types of neoplasms have indicated the role of NKILA in blockage of tumor growth and inhibition of metastasis [20].

NKILA is an lncRNA Upregulated by Inflammatory Cytokines via NF-κB Signaling:

It was found that TNF-α treatment upregulated NKILA copy number by 5.8-folds. Using 5′- and 3′- rapid amplification of cDNA ends, [19]. NKILA Is a Negative Regulator of NF-κB Signaling because elevated NF-κB activity is associated with enhanced invasiveness of tumor cells [21].

Liu et al. [9] showed that NKILA acts as a negative regulator to suppress both the basal and cytokine-stimulated NF-κB activities in breast cancer cells by Inhibits IκB Phosphorylation by Interacting with the NF-κB:IκB Complex.

The cytoplasmic localization of NKILA implies that the lncRNA may function by interacting with cytoplasmic NF-κB:IκBcomplex. Indeed, confocal microscopy for NKILA FISH and p65 immunostaining showed ~80% co-localization of NKILA [22].

Further in vitro and in vivo assays including apoptosis assays, knock-down and knock-in experiments have verified such roles. In addition to its roles in neoplastic conditions, NKILA is involved in the pathogenesis of immune-related disorders. Dysregulation of expression of NKILA has been reported in patients with diverse conditions such as epilepsy, osteoarthritis, periodontitis and coronary artery disease [23].

Role of NKILA in non-neoplastic conditions:

NKILA can affect several physiological processes through modulation of expression of NF- κB. As NF-κB has as essential role in regulation of immune responses and production of cytokines [24],

NKILA can modulate tissue hemostasis, immune response balance and normal functions of several tissues. Accordingly, abnormal expression of this lncRNA can affect function of these

tissues. Liu et al. have assessed the role NKILA in a hypoxia/reoxygenation (H/R) cell model as well as an animal model of ischemia-reperfusion (I/R) injury [25].

• In refractory and non-refractory epilepsy:

NKILA expression has been reported to be elevated in both refractory and non-refractory epileptic patients [26].

• In osteoarthritis:

Moreover, expressions of NKILA and specificity protein 1 (SP1) have been decreased, while miR-145 has been elevated in cartilage samples of patients with osteoarthritis. Forced over-expression of NKILA in chondrocytes has enhanced proliferation and suppressed their apoptosis. miR-145 has been identified as target of NKILA in these cells. Besides, SP1 is a target of miR-145 [27].

• In coronary artery disease:

NKILA has also been among down-regulated transcripts in patients with coronary artery disease [28]. A long term follow up of patients with diabetes mellitus has shown elevated plasma levels of NKILA in those who developed diabetic cardiomyopathy but not in those with other comorbidities. Plasma concentration of NKILA at 6 months before diagnosis could differentiate patients with diabetic cardiomyopathy from others. Over-expression of NKILA has enhanced apoptosis of cardiomyocytes [29].

Role of lncRNA NKILA in different malignencies:

In previous studies, lncRNA NKILA acts as a tumor suppressor gene in some malignancies and involves in the pathological processes of cancer initiation and progression.

• In breast cancer:

Liu and collaborators [9] reported that NKILA prevents breast cancer metastasis by suppressing the activation of the NF-kB signaling pathway. Constitutive activation of NF-kB in human cancers is a crucial determinant of tumor progression. NKILA acts as a negative feedback regulator of NF-kB through its interaction with NF- •B/IkB• to form a stable ternary complex. In this complex, IKK-induced phosphorylation of IkB••, an inhibitor of NF-kB, is prevented because NKILA binding masks the IKK phosphorylating sites. NFkB mediates TGF-•-induced EMT in breast cancer. Notably, during TGF-•-induced EMT, TGF-• induces NKILA expression, to provide a negative feedback mechanism that ultimately prevent excessive activation of the NF-kB signaling pathway [10].

• In melanoma:

In the study of malignant melanoma, Bian et al. [30] reported that NKILA could inhibit the development of tumor by regulating NF-κB signaling transduction pathway, indicating that NKILA may serve as a potential therapeutic target for the melanoma.

• In nasopharyngeal carcinoma:

NKILA represses nasopharyngeal carcinoma carcinogenesis and metastasis by NF-κB pathway inhibition [31].

• In non-small cell lung cancer

NKILA was proved to inhibit the invasion and migration of tumor cells through interactions with NF-κB/Snail pathway and plays a role as tumor suppressor gene in non-small cell lung cancer [32].

• In tongue squamous cell carcinoma:

NKILA was reported to play as role as tumor suppressor in the development of tongue squamous cell carcinoma by inhibiting epithelial- mesenchymal transition [33].

• In colon cancer:

Recent advances in the pathogenesis of colon cancer also revealed the involvement of different lncRNAs. Liang et al. [34] have shown that lncRNA H19 plays a role as oncogene to promote the epithelial to mesenchymal transition during the development of colon cancer by sequestering miRNAs.

• In colorectal cancer:

lncRNA HOTAIR was found to be upregulated during the progression of colorectal cancer, and the increased expression level of this lncRNA was found to be closely correlated with the poor prognosis [35].

• In cervical squamous cell carcinoma:

Wang et al. [36] reported that lncRNA NKILA may serve as a tumor suppressor in cervical squamous cell carcinoma (CSCC). NKILA could inhibit proliferation and promote apoptosis of CSCC cells via regulating miRNA-21 expression. They also observed that the serum level of NKILA in both patients with HPV-positive and HPV-negative CSCC was lower significantly than in healthy controls. In fact, the different serum levels of NKILA can help us to differentiate patients with CSCC from healthy controls effectively, so NKILA may become a diagnostic biomarker for patients with early stage CSCC. However, the expression pattern of NKILA in other human diseases remained to investigate and test the diagnostic specificity.

**No Conflict of interest.**

**References:**

1. Standaer, L., Adriaens, C., Radaelli, E., Van Keymeulen, A., Blanpain, C., Hirose, T., et al. The long noncoding RNA Neat1 is required for mammary gland development and lactation. RNA. 2014;20: 1844-1849.
2. Sorensen, K. P., Thomassen, M., Tan, Q., Bak, M., Cold, S., Burton, M., et al. Long non-coding RNA HOTAIR is an independent prognostic marker of metastasis in estrogen receptor-positive primary breast cancer. Breast Cancer Res Treat. 2013;142: 529-536.

3. Grelet, S., Link, L. A., Howley, B., Obellianne, C., Palanisamy, V., Gangaraju, V. K., et al. A regulated PNUTS mRNA to lncRNA splice switch mediates EMT and tumour progression. Nat Cell Biol. 2017;19: 1105-1115.
4. Amelio I, Bernassola F, Candi E. Emerging roles of long non-coding RNAs in breast cancer biology and management. In Seminars in cancer biology 2021 Jul 1 (Vol. 72, pp. 36-45). Academic Press.
5. Arun, G., Diermeier, S., Akerman, M., Chang, K. C., Wilkinson, J. E., Hearn, S., et al. Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. Genes Dev. 2016;30: 34-51.
6. Youness RA, Gad MZ. Long non-coding RNAs: functional regulatory players in breast cancer. Non-coding RNA research. 2019 Mar 1;4(1):36-44.
7. Wang, P. S., Chou, C. H., Lin, C. H., Yao, Y. C., Cheng, H. C., Li, H. Y., et al. A novel long non-coding RNA linc-ZNF469-3 promotes lung metastasis through miR-574-5p-ZEB1 axis in triple negative breast cancer. Oncogene. 2018;37: 4662-4678.
8. Liu, P., Tang, H., Wu, J., Qiu, X., Kong, Y., Zhang, L., et al. Linc01638 Promotes Tumorigenesis in HER2+ Breast Cancer. Curr Cancer Drug Targets. 2019;19: 74-80.
9. Liu, B., Sun, L., Liu, Q., Gong, C., Yao, Y., Lv, X., et al. A cytoplasmic NF-κB interacting long noncoding RNA blocks IκB phosphorylation and suppresses breast cancer metastasis. Cancer Cell, 2015. 27(3), 370– 381.
10. Wu, W., Chen, F., Cui, X., Yang, L., Chen, J., Zhao, J., et al. LncRNA NKILA suppresses TGF-beta-induced epithelialmesenchymal transition by blocking NF-kappaB signaling in breast cancer. Int J Cancer. 2018;143: 2213-2224.
11. Wang, S., Liang, K., Hu, Q., Li, P., Song, J., Yang, Y., et al. JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. J Clin Invest. 2017;127: 4498-4515.
12. Xing, F., Liu, Y., Wu, S. Y., Wu, K., Sharma, S., Mo, Y. Y., et al. Loss of XIST in Breast Cancer Activates MSN-c-Met and Reprograms Microglia via Exosomal miRNA to Promote Brain Metastasis. Cancer Res. 2018;78: 4316-4330. Journal Pre-proof 18.
13. Nie, G., Cao, X., Mao, Y., Lv, Z., Lv, M., Wang, Y., ... & Liu, C. Tumor-associated macrophages-mediated CXCL8 infiltration enhances breast cancer metastasis: Suppression by Danirixin. International Immunopharmacology,2021. 95, 107153.
14. Gómez-Maldonado, L., Tiana, M., Roche, O., Prado-Cabrero, A., Jensen, L., Fernandez-Barral, A., et al. EFNA3 long noncoding RNAs induced by hypoxia promote metastatic dissemination. Oncogene. 2015;34: 2609-2620.
15. Lin, A., Li, C., Xing, Z., Hu, Q., Liang, K., Han, L., et al. The LINK-A lncRNA activates normoxic HIF1alpha signalling in triple-negative breast cancer. Nat Cell Biol. 2016;18: 213-224.
16. Hu, Q., Ye, Y., Chan, L. C., Li, Y., Liang, K., Lin, A., et al. Oncogenic lncRNA downregulates cancer cell antigen presentation and intrinsic tumor suppression. Nat Immunol. 2019;20: 835-851.
17. Chen, F., Chen, J., Yang, L., Liu, J., Zhang, X., Zhang, Y., et al. Extracellular vesicle-packaged HIF-1alpha-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol. 2019;21: 498-510.
18. Huang, D., Chen, J., Yang, L., Ouyang, Q., Li, J., Lao, L., et al. LncRNA NKILA promotes tumor immune evasion by sensitizing T cells to activation-induced cell death. Nat Immunol. 2018;19: 1112-1125

19. Slavoff, S. A., Mitchell, A. J., Schwaid, A. G., Cabili, M. N., Ma, J., Levin, J. Z., et al. Peptidomic discovery of short open reading frame–encoded peptides in human cells. Nature chemical biology, 2013.9(1), 59-64.
20. Hussen, B. M., Azimi, T., Hidayat, H. J., Taheri, M., & Ghafouri-Fard, S. NF-KappaB interacting LncRNA: Review of its roles in neoplastic and non-neoplastic conditions. Biomedicine & Pharmacotherapy,2021: 139, 111604.
21. Ahmmed, B., Kampo, S., Khan, M., Faqeer, A., Kumar, S. P., Yulin, L., et al. Rg3 inhibits gemcitabine-induced lung cancer cell invasiveness through ROS-dependent, NF-κB-and HIF-1α-mediated downregulation of PTX3. Journal of Cellular Physiology,2019. 234(7), 10680-10697.
22. Huber, M. A., Azoitei, N., Baumann, B., Grünert, S., Sommer, A., Pehamberger, H., et al. NF-κB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression. The Journal of clinical investigation, 2004.114(4), 569-581.
23. Ghafouri-Fard, S., Abak, A., Fattahi, F., Hussen, B. M., Bahroudi, Z., Shoorei, H., & Taheri, M. The interaction between miRNAs/lncRNAs and nuclear factor-κB (NF-κB) in human disorders. Biomedicine & Pharmacotherapy,2021: 138, 111519.
24. Park, M. H., & Hong, J. T. Roles of NF-κB in cancer and inflammatory diseases and their therapeutic approaches. Cells,2016. 5(2), 15.
25. Liu, Q., Liu, Z., Zhou, L. J., Cui, Y. L., & Xu, J. M. The long noncoding RNA NKILA protects against myocardial ischaemic injury by enhancing myocardin expression via suppressing the NF-κB signalling pathway. Experimental Cell Research, 2020.387(2), 111774.
26. Mirzajani, S., Ghafouri-Fard, S., Habibabadi, J. M., Arsang-Jang, S., Omrani, M. D., Fesharaki, S. S. H., et al. Expression analysis of lncRNAs in refractory and non-refractory epileptic patients. Journal of Molecular Neuroscience,2020. 70(5), 689-698.
27. Xue, H., Yu, P., Wang, W. Z., Niu, Y. Y., & Li, X. The reduced lncRNA NKILA inhibited proliferation and promoted apoptosis of chondrocytes via miR-145/SP1/NF-κB signaling in human osteoarthritis. Eur Rev Med Pharmacol Sci,2020. 24(2), 535-548.
28. Ebadi, S. Ghafouri-Fard, M. Taheri, S. Arsang-Jang, M.D. Omrani. Expression analysis of inflammatory response-associated genes in coronary artery disease, Arch. Physiol. Biochem. 2020. 1–7.
29. Li, P. Li, J. Su, S. Liu, X. Yang, Y. Yang, S. Niu, LncRNA NKILA was upregulated in diabetic cardiomyopathy with early prediction values, Exp. Ther. Med. 18 (2) (2019) 1221–1225.
30. Bian, D., Gao, C., Bao, K., & Song, G. The long non-coding RNA NKILA inhibits the invasion metastasis cascade of malignant melanoma via the regulation of NF-κB. American Journal of Cancer Research, 2017.7(1), 28– 40.
31. Zhang, Y., Chen, L., Hu, G. Q., Zhang, N., Zhu, X. D., Yang, K. Y., et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. New England Journal of Medicine, 2019.381(12), 1124-1135.
32. Lu, Z., Li, Y., Wang, J., Che, Y., Sun, S., Huang, J., et al. Long non-coding RNA NKILA inhibits migration and invasion of non-small cell lung cancer via NF-κB/Snail pathway. J Exp Clin Cancer Res 2017;36:54.
33. Huang, W., Cui, X., Chen, J., Feng, Y., Song, E., Li, J., et al. Long non-coding RNA NKILA inhibits migration and invasion of tongue squamous cell carcinoma cells via suppressing epithelial- mesenchymal transition. Oncotarget 2016;7:62520-32.

34. Liang, W. C., Fu, W. M., Wong, C. W., Wang, Y., Wang, W. M., Hu, G. X., et al. The lncRNA H19 promotes epithelial to mesenchymal transition by functioning as miRNA sponges in colorectal cancer. Oncotarget 2015;6:22513-25.
35. Kogo, R., Shimamura, T., Mimori, K., Kawahara, K., Imoto, S., Sudo, T., et al. Long noncoding RNA HOTAIR regulates polycomb- dependent chromatin modification and is associated with poor prognosis in colorectal cancers. Cancer Res 2011;7.
36. Wang, S., Liang, K., Hu, Q., Li, P., Song, J., Yang, Y., et al. JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. J Clin Invest. 2017;127: 4498-4515.