


# Long Non-Coding RNA and Breast Cancer

Tianzhu Zhang, MD<sup>1,2</sup>, Hui Hu, MD<sup>1</sup>, Ge Yan, MD<sup>1,2</sup>, Tangwei Wu, MD<sup>1</sup>, Shuiyi Liu, MD<sup>1,3</sup>, Weiqun Chen, MD<sup>1,3,4</sup>, Yong Ning, PhD<sup>2</sup>, and Zhongxin Lu, PhD<sup>1,2,3,4</sup> 

Technology in Cancer Research & Treatment  
Volume 18: 1-10  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1533033819843889  
journals.sagepub.com/home/tct



## Abstract

Breast cancer, one of the most common diseases among women, is regarded as a heterogeneous and complicated disease that remains a major public health concern. Recently, owing to the development of next-generation sequencing technologies, long non-coding RNAs have received extensive attention. Numerous studies reveal that long non-coding RNAs are playing important roles in tumor development. Although the biological function and molecular mechanisms of long non-coding RNAs remain enigmatic, recent researchers have demonstrated that an array of long non-coding RNAs express abnormally in cancers, including breast cancer. Herein, we summarized the latest literature about long non-coding RNAs in breast cancer, with a particular focus on the multiple molecular roles of regulatory long non-coding RNAs that regulate cell proliferation, invasion, metastasis, and apoptosis.

## Keywords

long non-coding RNA, breast cancer, molecular mechanisms, cell proliferation, invasion, metastasis, apoptosis

## Abbreviations

ANCR, anti-differentiation noncoding RNA; Caspases, cysteine aspartate specific proteases; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; HOTAIR, HOX transcript antisense; lncRNAs, long non-coding RNAs; LSD1, lysine-specific demethylase 1; MAPK, Mitogen-activated protein kinase; miRNAs, microRNAs; mRNA, messenger RNA; mTOR, mammalian target of rapamycin; ncRNAs, non-coding RNAs; NFκB, nuclear factor-κB; ORF, open reading frame; PRC2, polycomb repressive complex 2; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TUG1, taurine-upregulated gene 1.

Received: September 14, 2018; Revised: January 7, 2019; Accepted: March 21, 2019.

## Introduction

The American Cancer Society estimated that, in 2018, there were 1 735 350 new cancer cases and 609 640 cancer deaths in the United States.<sup>1</sup> Breast cancer is the most prevalent cancer diagnosed in women in the United States and worldwide, and it is the second leading cause of cancer death among women after lung cancer.<sup>2</sup> Although great advances have been made in early detection and therapeutics of breast cancer over the last 20 years, breast cancer remains a major public health problem.

The advances in next-generation sequencing technologies reveal that at least 75% of the human genome are actively transcribed into RNAs, although less than 2% of these transcripts are translated into proteins.<sup>3</sup> Based on their length, non-coding RNAs (ncRNAs) are divided into 2 major groups: short ncRNAs and long ncRNAs (lncRNAs). Short ncRNAs are generally less than 200 nucleotides, which include small-

<sup>1</sup> Department of Medical Laboratory, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

<sup>2</sup> School of Laboratory Medicine, Hubei University of Chinese Medicine, Wuhan, China

<sup>3</sup> Cancer Research Institute of Wuhan, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

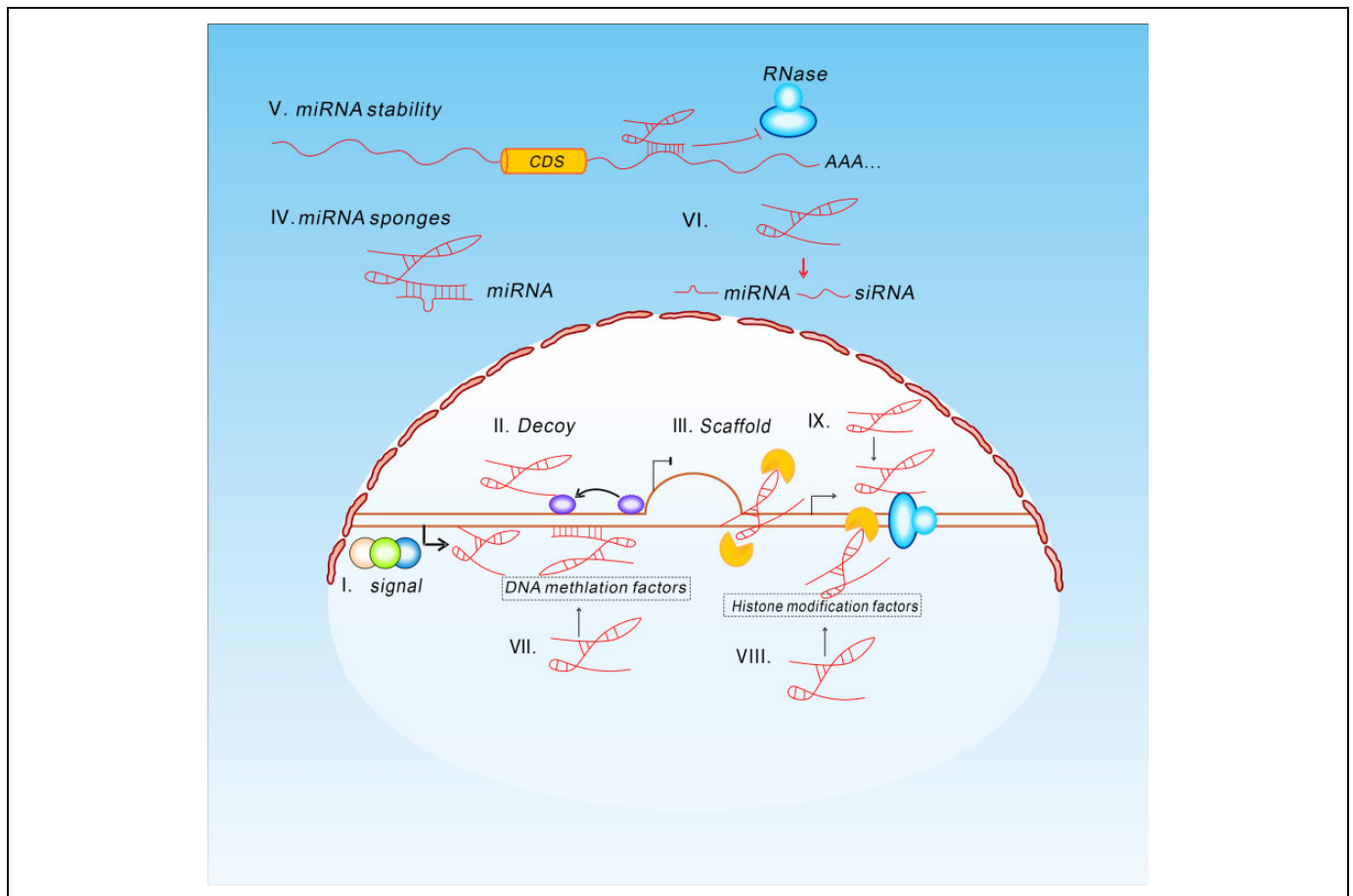
<sup>4</sup> Key Laboratory for Molecular Diagnosis of Hubei Province, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

## Corresponding Authors:

Zhongxin Lu, PhD, Department of Medical Laboratory, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, No 26, Shengli St, Jiangan District, Wuhan 430014, China.  
Email: lzx71@yahoo.com

Yong Ning, PhD, School of Laboratory Medicine, Hubei University of Chinese Medicine, No 1, Huangjia Lake West Road, Wuhan 430065, China.  
Email: ningyong128@163.com





**Figure 1.** Function of long noncoding RNAs (lncRNAs). (A) lncRNAs act as signal; (B) lncRNAs act as decoy; (C) lncRNAs act as scaffold; (D) lncRNAs act as microRNA (miRNA) sponges; (E) lncRNAs protect messenger RNA (mRNA) from degradation; (F) lncRNAs function as a precursor for miRNA; (G) lncRNAs regulate DNA methylation; (H) lncRNAs regulate histone modification; (I) lncRNAs regulate chromatin remodeling and structure.

interfering RNAs, piwi-related RNAs, transfer RNAs, and microRNAs (miRNAs). The lncRNAs are greater than 200 nucleotides and sometimes as long as 100 kb.<sup>4</sup> Over the past 20 years, short ncRNAs, especially miRNAs, have been extensively studied. The biological function of many miRNAs has been elucidated<sup>5</sup>; however, our knowledge about the functional role of lncRNAs is rather limited, as these lncRNAs were often considered to be products of evolutionary waste or transcription noises. In this work, we will review the biological role of lncRNAs in human cancer, particularly in breast cancer.<sup>6-10</sup>

## Definition and Classification of lncRNAs

Long ncRNAs are endogenous RNA molecules with a length that ranges from 200 nt to 100 kb that lack open reading frames (ORFs). Based on their gene loci, characteristics, and relationship with their neighbor genes, the lncRNAs can be divided into 6 categories: (1) intergenic lncRNAs, also known as large intervening ncRNAs, or lincRNAs, which are defined as autonomously transcribed ncRNAs that do not overlap annotated coding genes,<sup>11</sup> such as lncRNA MALAT1,<sup>12,13</sup> LINK-A,<sup>14</sup> lncRNA ALIEN,<sup>15</sup> lncRAM,<sup>16</sup> and lncRNA UCC<sup>17</sup>; (2)

intronic lncRNAs, which are produced internally by an intron without any epitope of an ORF that overlaps at either end, such as lncRNA SPRY4-ITI<sup>18</sup> and lncRNA MEG8-ITI<sup>19</sup>; (3) bidirectional lncRNAs, which start from the divergence direction of the promoter or enhancer region, typically within hundreds of base pairs; these lncRNA are also termed as enhancer-related RNA,<sup>20-22</sup> like lncRNA LEENE<sup>23</sup> and lncRNA HCCLS<sup>24</sup>; (4) overlapping sense lncRNAs, which are transcribed in the same direction as an ORF and overlap with the ORF for at least one exon, such as lncRNA GAS5<sup>25</sup>; (5) antisense lncRNAs, also known as natural antisense transcript, are transcribed from the antisense strand of an ORF, such as lncRNA GATA6-AS,<sup>26</sup> lncRNA ASBEL,<sup>27</sup> lncRNA UCHL1,<sup>28</sup> and lncRNA ANRIL<sup>29</sup>; (6) lncRNAs that are hosted by an miRNA gene or an miRNA cluster, such as lncRNA LOC554202<sup>30</sup> and lncRNA MIR100HG.<sup>31</sup>

## Mechanism of lncRNAs in Cancer Biology

Long ncRNAs, lacking an ORF, participate in biological processes at 3 different levels: transcriptional level, posttranscriptional level, and epigenetic level (Figure 1). At transcriptional

**Table 1.** Functions of lncRNAs in Breast Cancer.

lncRNA	Functions	Reference
<b>Oncogene</b>		
ARNILA	Invasion and metastasis	Fang Yang <i>et al</i> <sup>45</sup>
Lnc015192	Migration, invasion, and EMT	Xiaojia Huang <i>et al</i> <sup>46</sup>
EPIC1	Cell cycle progression	Zehua Wang <i>et al</i> <sup>47</sup>
GACAT3	Proliferation	Hua Zhong <i>et al</i> <sup>48</sup>
ITGB2-AS1	Migration and Invasion	Mengyao Liu <i>et al</i> <sup>49</sup>
MIR100HG	Proliferation	Shaowei Wang <i>et al</i> <sup>50</sup>
CHET1	Proliferation, invasion, and migration	Rui Song <i>et al</i> <sup>51</sup>
NNT-AS1	Progression	Yan Li <i>et al</i> <sup>52</sup>
P10247	Metastasis	Yuxia Yang <i>et al</i> <sup>53</sup>
EZR-AS1	Tumor growth and metastasis	Yu Bai <i>et al</i> <sup>54</sup>
TUG1	Apoptosis, proliferation, and metastasis	Shulin Fan <i>et al</i> <sup>55</sup> ; Teng Li <i>et al</i> <sup>56</sup>
PRLB	Proliferation and metastasis	Yiran Liang <i>et al</i> <sup>57</sup>
PVT1	Proliferation	Jianming Tang <i>et al</i> <sup>37</sup>
LNC00511	Proliferation and invasion	Guanming Lu <sup>58</sup>
ATB	EMT	Ronghui Li <i>et al</i> <sup>59</sup>
NEAT1	Metastasis	Wanjin Li <i>et al</i> <sup>60</sup>
AC026904.1	Metastasis	Guoyin Li <i>et al</i> <sup>61</sup>
UCA1	Metastasis	Guoyin Li <i>et al</i> <sup>61</sup>
<b>Suppressor</b>		
ANCR	Invasion and metastasis	Zhongwei Li <i>et al</i> <sup>62</sup>
MEG3	Proliferation and EMT	Wei Zhang <i>et al</i> <sup>63</sup>
PTENP1	Proliferation and migration	Xianbiao Shi <i>et al</i> <sup>64</sup>
MAGI2-AS3	Cell growth	Yong Yang <i>et al</i> <sup>65</sup>
XIST	Brain metastasis and cell growth	Fei Xing <i>et al</i> <sup>66</sup> ; Ruinian Zheng <i>et al</i> <sup>67</sup>
PDCD4-AS1	Progression	Mahdieh Jadhaliha <i>et al</i> <sup>44</sup>
NKILA	EMT	Wei Wu <i>et al</i> <sup>68</sup>

Abbreviations: EMT, epithelial–mesenchymal transition; lncRNA, long noncoding RNA.

level, (1) lncRNAs act as a signal or decoy to promote or suppress gene expression (Figure 1A and B)<sup>32</sup>; (2) lncRNAs function as scaffold molecules to regulate gene expression via assembling chromatin-modifying complexes at special loci (Figure 1C)<sup>33</sup>; (3) lncRNAs act as a miRNA sponge (also called competitive endogenous RNA) to reverse miRNA suppression of its target genes (Figure 1D).<sup>34</sup> Similarly, lncRNAs may also function as competing endogenous RNAs (ceRNAs) to sponge miRNAs in malignant breast tumors. Feng<sup>35</sup> *et al* demonstrated that lncRNA KCNQ1OT1 enhances tumor growth as a sponge of miR-145 to regulate the expression of CCNE2. At posttranscriptional level, lncRNAs regulate the translation of messenger RNAs (mRNAs) and control their stability via forming double-stranded RNA with mRNAs<sup>36</sup> or regulate protein stability by binding<sup>37</sup> (Figure 1E). In hepatocellular carcinoma, lncRNA-ATB upregulated ZEB1 and ZEB2 by competitively binding the miR-200 family and then induced epithelial–mesenchymal transition (EMT) and invasion. In addition, lncRNA-ATB promoted organ colonization of disseminated tumor cells by binding interleukin 11 mRNA and stimulated signal transducer and activator of transcription 3 (STAT3) signaling. In triple-negative breast cancer, lncRNA PVT1 binds with the KLF5 protein and increases its stability.<sup>37</sup> lncRNA H19 is reported to function as the precursor harboring an miRNA (miR-675; Figure 1F).<sup>38</sup> At epigenetic level, (1) lncRNAs regulate DNA methylation in the promoter region of a downstream

gene to silence it (Figure 1G)<sup>39</sup>; (2) lncRNAs alter methylation, acetylation, or ubiquitination of histones by coacting with histone modification factors (Figure 1H)<sup>40</sup>; (3) lncRNAs directly bind to chromatin modification complexes to reconstruct a chromatin or alter its conformation for regulating the target gene transcription (Figure 1I).<sup>41</sup>

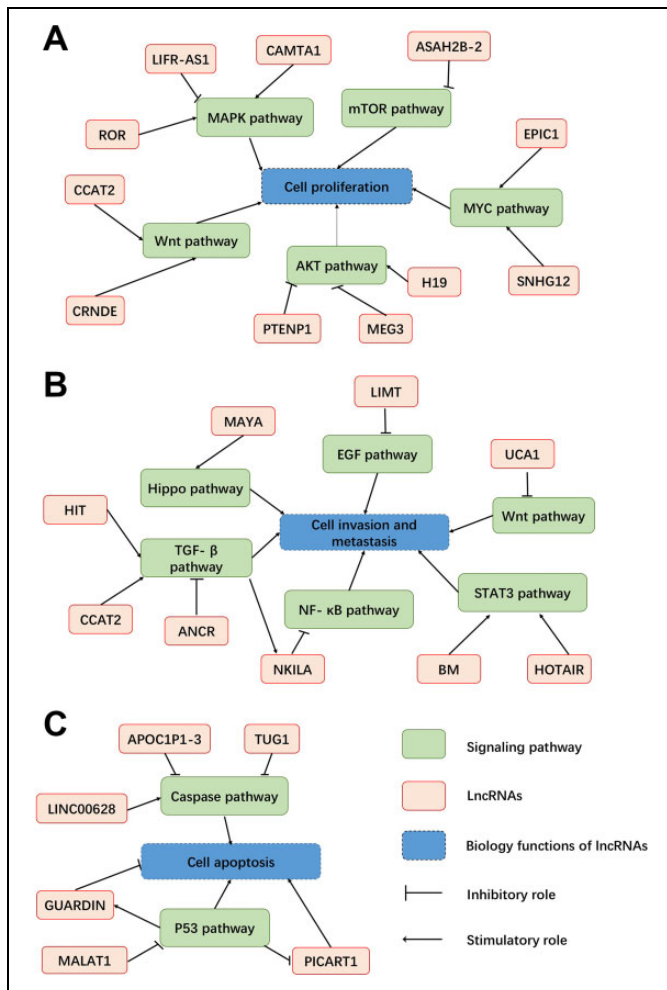
## Functions of lncRNAs in Breast Cancer

Long ncRNAs play a pivotal role in various cancer types including breast cancer. Abnormal expression of lncRNAs contribute significantly to cancer initiation and progression in breast cancer. These lncRNAs include lncRNA MALAT1,<sup>42</sup> lncRNA DANCR,<sup>43</sup> lncRNA PDCD4-AS1,<sup>44</sup> and so on. The functions of lncRNAs in breast cancer are summarized in Table 1.

### Long ncRNAs in Cell Proliferation

Cancer cell proliferation is induced by multiple signaling pathways.<sup>69</sup> Recent research shows that multiple lncRNAs mediate cell proliferation through activating or restraining specific signaling pathways in breast cancer (Figure 2A).<sup>70,71</sup>

**Akt signaling pathway.** The Akt signaling pathway is involved in various biological responses, such as inhibition of apoptosis and stimulation of cell proliferation.<sup>72</sup> H19, a 2.3-kb lncRNA,



**Figure 2.** Regulatory long noncoding RNAs (lncRNAs) in the pathogenesis of breast cancer. (A) lncRNAs in cell proliferation; (B) lncRNAs in cell invasion and metastasis; (C) lncRNAs in apoptosis.

is encoded by the maternal allele and is considered as an oncogene in many cancers.<sup>73,74</sup> A new lncRNA at the H19/IGF2 locus is transcribed in H19 antisense orientation and named 91H. In breast cancer, 91H lncRNA prevents histone and DNA methylation on the maternal allele at the H19/IGF2 locus and thereby is responsible for maintaining the H19/IGF2 genomic imprinting.<sup>75</sup> H19 is activated by E2F1 and promotes the G1-S transition in breast cancer cells.<sup>76</sup> The H19-derived miR-675 downregulates c-Cbl and Cbl-b proteins and activates EGFR and c-Met to promote cell proliferation through Akt activation.<sup>70</sup> Zhang<sup>77</sup> *et al* found that overexpression of lncRNA MEG3 not only causes cell cycle arrest in G0/G1 phase but also suppresses tumor growth in a mouse model of breast cancer through Akt signaling. Chen<sup>78</sup> *et al* showed that lncRNA PTENP1 inhibits the proliferation of breast cancer cells through downregulating mitogen-activated protein kinase (MAPK) and AKT signaling pathways.

**Mitogen-activated protein kinase signaling pathway.** Mitogen-activated protein kinase, a part of the serine-threonine kinase

family, is widely associated with cell proliferation, differentiation, migration, senescence, and apoptosis.<sup>79</sup> Long ncRNA CAMTA1 was first reported to be upregulated in liver cancer cells.<sup>80</sup> In breast cancer, CAMTA1 promotes proliferation of human breast cancer cells via binding miR-20b, which suppresses the expression of vascular endothelial growth factor, an activator of MAPK.<sup>81</sup> Wang *et al*<sup>82</sup> identified 12 to 44 cross-talking pathway pairs mediated by lncRNAs in 4 breast cancer subtypes. They found that lncRNA LIFR-AS1 is a tumor suppressor regulating the expression of IL1R and TGFBR, which in turn activate MAPK and augment breast cancer cell proliferation. Peng *et al*<sup>83</sup> employed CRISPR/Cas9 to knockout linc-ROR in MCF-7 cells and found that linc-ROR promotes estrogen-independent growth and activates the MAPK pathway in breast cancer cells.

**Wnt signaling pathway.** The Wnt signaling pathway is a highly conserved and can be activated via the canonical or noncanonical route. The former plays a vital role in breast cancer initiation and progression.<sup>84,85</sup> Long ncRNAs interact with critical molecules in the canonical pathway, including MYC and  $\beta$ -catenin. LncRNA CCAT2, a novel lncRNA mapping to 8q24, is significantly upregulated in both breast cancer tissues and breast cancer cell lines. CCAT2 promotes breast tumor growth by upregulating  $\beta$ -catenin, a key downstream effector of Wnt signaling.<sup>71</sup> Long ncRNA CRNDE is upregulated in breast cancer and acts as a molecular sponge for different miRNAs such as miR-136 to activate Wnt  $\beta$ -catenin signaling and promote tumor cell proliferation.<sup>86</sup>

**MYC signaling pathways.** The proto-oncogene MYC is amplified in many types of cancer, and MYC activates various downstream genes involved in cell cycle, cell growth, and angiogenesis.<sup>87</sup> Wang *et al* characterized the epigenetic landscape of lncRNA genes across a large number of human tumors including breast cancer. They observed that lncRNA EPIC1 promotes cell cycle progression and proliferation by interacting with MYC and enhances its binding to several target genes. Long ncRNA SNHG12 is upregulated in triple-negative breast cancer and is significantly correlated with tumor size and lymph node metastasis. Moreover, SNHG12 is a direct target gene of MYC, an important member of MYC; silencing SNHG12 expression inhibits breast cancer cells proliferation.<sup>88</sup>

**Other signaling pathways.** Mammalian Target of Rapamycin (mTOR), a 289-kDa serine/threonine protein kinase, is a downstream effector of many frequently activated oncogenic pathways, including Akt and MAPK.<sup>89</sup> Li *et al*<sup>90</sup> identified that silencing lncRNA-ASA2B-2 inhibits breast cancer cell growth via inhibiting mTOR signaling. Bcl-2 family member bcl-w promotes cell proliferation, migration, and invasion in cancers.<sup>91</sup> Long ncRNA HOX transcript antisense RNA (HOTAIR), located in the HOX gene locus,<sup>92</sup> modulates miR-206-mediated bcl-w signaling to facilitate cell proliferation in breast cancer<sup>93</sup> and other cancers.<sup>94,95</sup>

### Long ncRNAs in Cell Invasion and Metastasis

Cancer invasion and metastasis are a multistep process that is responsible for more than 90% of cancer death.<sup>96</sup> Metastasis is a process in which the primary tumor cells disseminate to bloodstream or lymphocytic routes, reach distant secondary organs, and then proliferate.<sup>97</sup> Here, we list the following pathways in which lncRNAs are involved (Figure 2B).

**Signal Transducer and Activator of Transcription 3 signaling pathway.** The activation of STAT3 plays a vital role in the metastasis of many cancers.<sup>98</sup> Long ncRNA-FEZF1-AS1 promotes colorectal cancer proliferation and metastasis by targeting pyruvate kinase 2 (PKM2) to activate STAT3.<sup>99</sup> HOX transcript antisense RNA is upregulated in multiple cancers, especially breast cancer.<sup>100</sup> The 5' end of HOTAIR is recruited to the polycomb repressive complex 2 (PRC2), whereas its 3' end binds lysine-specific demethylase 1 (LSD1) and acts as a scaffold for PRC2 and LSD1 to regulate target gene expression.<sup>101</sup> Expression of HOTAIR and EZH2 is highly correlated in breast cancer tissues, and both lncRNAs are enriched in metastatic lesions compared to the paired primary breast tumors.<sup>102</sup> miR-7, which is inhibited indirectly by HOTAIR, is a negative regulator of STAT3 and breast cancer cell EMT.<sup>103</sup> Besides, lncRNA increases JAK2 kinase activity to mediate oncostatin M- and IL-6-triggered STAT3 phosphorylation. In breast cancer cells, lnc-BM promotes STAT3-dependent expression of ICAM1 and CCL2 to promote brain metastasis.<sup>104</sup>

**Nuclear factor  $\kappa$ B signaling pathway.** Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a critical link between inflammation and cancer that underlies the tumor microenvironment. Nuclear factor  $\kappa$ B is constitutively activated in some breast cancers.<sup>105</sup> Liu et al<sup>106</sup> identified an NF- $\kappa$ B interacting lncRNA NKILA, as a tumor suppressor; NKILA is associated with breast cancer metastasis through binding to NF- $\kappa$ B-I $\kappa$ B complex and repressing NF- $\kappa$ B signaling. In another report, lncRNA NKILA is activated by transforming growth factor  $\beta$  (TGF- $\beta$ ) and suppresses TGF- $\beta$ -induced EMT via blocking NF- $\kappa$ B signaling in breast cancer.<sup>68</sup>

**Transforming growth factor- $\beta$  signaling pathway.** Transforming growth factor- $\beta$  is a multifunctional cytokine belonging to the TGF superfamily. The TGF- $\beta$  signaling pathway is instrumental in regulating cellular activities such as proliferation, differentiation, apoptosis, motility, invasion, extracellular matrix production, angiogenesis, and immune response.<sup>107</sup> There are 2 facets of TGF- $\beta$  in breast cancer: In early stages, it inhibits epithelial cell cycle progression and promotes apoptosis; however, in late stages, it acts as an oncogene and promotes tumor progression and metastasis.<sup>108</sup> Anti-differentiation noncoding RNA (ANCR), an 855-nucleotide lncRNA, is downregulated during differentiation.<sup>109</sup> In breast cancer, ANCR is a potential tumor suppressor and inhibits breast cancer cell migration and metastasis by decreasing RUNX2 expression *in vitro* and *in vivo*.<sup>110</sup> Cheng et al<sup>111</sup> demonstrated that lncRNA HIT, a novel breast cancer-associated lncRNA, promotes TGF- $\beta$ -induced

migration, invasion, and EMT. Wang et al<sup>112</sup> observed that lncRNA CCAT2 also promotes breast cancer growth and metastasis by upregulating the protein expression levels of TGF- $\beta$ , Smad2, and  $\alpha$  smooth muscle actin, all key components of TGF- $\beta$  signaling.

**Other signaling pathways.** The Hippo signaling pathway is first discovered in *Drosophila melanogaster* and is a highly conserved pathway regulating cell proliferation, apoptosis, and metastasis.<sup>113,114</sup> YAP and TAZ are 2 key downstream effectors of the Hippo signaling pathway.<sup>115</sup> Yang et al<sup>116</sup> identified an ROR1-HER3-lncRNA signaling axis modulating the Hippo-YAP pathway to regulate bone metastasis; this lncRNA (MAYA) is part of an RNA-protein complex that activates YAP and elicits osteoclast differentiation and bone metastasis. The epidermal growth factor (EGF) is a small 53 amino acid residue protein involved in normal cell growth, oncogenesis, and metastasis. Yarden et al<sup>117</sup> found that knockdown of EGF-regulated lncRNA LIMT enhances cellular migration and invasion *in vitro* as well as metastasis in breast cancer. Hu et al discovered that knockdown of lncRNA UCA1 significantly increases expression of E-cadherin but downregulates N-cadherin, Vimentin, and Snail and suppresses the protein expression of  $\beta$ -catenin, a key protein of Wnt signaling pathway in breast cancer.<sup>118</sup>

### Long ncRNAs in Apoptosis

Apoptosis is the programmed cell death that is essential to normal tissue development. Dysregulation of apoptosis promotes tumorigenesis.<sup>119</sup> Many lncRNAs participate in cellular apoptosis (Figure 2C).

**p53 signaling pathway.** p53 is a tumor-suppressor protein that regulates the expression of a wide variety of genes involved in apoptosis, growth arrest, and inhibition of cell cycle progression and differentiation.<sup>120</sup> Long ncRNAs are key components of the p53 pathway.<sup>121</sup> Wu et al<sup>122</sup> demonstrated that the p53-responsive lncRNA GUARDIN sustains breast cancer growth and GUARDIN silencing triggers apoptosis in breast cancer cells. p53-induced tumor suppressive lncRNA PICART1 inhibits breast cancer proliferation and promotes apoptosis through the AKT/GSK3 $\beta$ / $\beta$ -catenin signaling cascade.<sup>123</sup> Long ncRNA MALAT1, located on chromosome 11q13.1, has been reported to regulate the acetylation of p53 by competing with SIRT1 and DBC1 for p53 binding, resulting in reduced cell apoptosis in breast cancer cells.<sup>124</sup>

**Caspase signaling pathway.** Cysteine aspartate specific proteases (Caspases) are a family of cysteine proteases that act in concert in a cascade during apoptosis.<sup>125</sup> Liu et al<sup>126</sup> found that lncRNA LINC00628 is significantly downregulated in breast cancer and that overexpression of LINC00628 causes cell cycle arrested in G0/G1 phase and promotes cell apoptosis by regulating the expression of caspase-3, Bax, and Bcl-2. Taurine-upregulated gene 1 (TUG1) is an lncRNA involved in the progression of several cancers. Li et al<sup>56</sup> found that TUG1

knockdown increases breast cancer cell apoptosis via increases in the activities of caspase 3 and caspase 9. Zhou *et al*<sup>127</sup> discovered that the lincRNA-APOC1P1-3 is overexpressed in breast cancer, and this lincRNA directly binds to tubulin to decrease  $\alpha$ -tubulin acetylation, inactivate caspase,3, and inhibit apoptosis.

## Prospects and Challenges

Initially regarded as transcriptional noises, it is now widely accepted that lincRNAs, like miRNAs, function as important regulators of gene expression and tumorigenesis. The lincRNAs are potential targets for the diagnosis, prognosis, and treatment of human cancers. As we discussed in the review, aberrant lincRNA expression is associated with breast cancer. Unlike protein-coding mRNAs and miRNAs, our understanding of lincRNAs is still in the preliminary stage. There are many gaps in our knowledge of lincRNAs. First, only a small fraction of lincRNAs have been experimentally studied. Whether abnormal lincRNA expression is a cause or consequence of tumorigenesis remains elusive. Second, with an increasing number of lincRNAs detected, their biological functions and mechanisms of action in cancer require further exploration. Third, many lincRNAs are present in the circulation. Several studies have demonstrated that circulating lincRNAs are potential biomarkers in multitype cancers, including cholangiocarcinoma,<sup>128</sup> non-small-cell lung cancer,<sup>129</sup> hepatocellular carcinoma,<sup>130,131</sup> gastric cancer,<sup>132</sup> and so on. However, studies on circulating lincRNAs in cancer are still in early stage. For circulating lincRNAs to be deployed as diagnostic, prognostic, or treatment biomarkers, extensive research is needed.

In conclusion, the discovery of lincRNAs has opened a new door in cancer research. The lincRNAs could become a significant player in cancer diagnosis, prognosis, and therapeutic development, benefiting patients with breast cancer and beyond.

## Authors' Note

Tianzhu Zhang, Cold Spring Harb Perspect Biol Hui Hu, and Ge Yan contributed equally to this work. Our study did not require an ethical board approval because it did not contain human or animal trials.


## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by grants from the Key project of Natural Sciences Foundation of Hubei Province (2015CFA078), Science and technology support program (foreign scientific and technological cooperation) of Hubei Province (2015BHE022), the National Natural Sciences Foundation of China (No. 81372931), the Yellow Crane Talent Plan Foundation, Research Fund of Wuhan Public Health Bureau (WX14C13 and WX14B10) and Youth Foundation of Wuhan Central Hospital (YQ14A01 and YQ15A03).

## ORCID iD

Zhongxin Lu, PhD  <https://orcid.org/0000-0002-3365-0881>

## References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7-30.
2. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin.* 2017;67(6):439-448.
3. Djebali S, Davis CA, Merkel A, et al. Landscape of transcription in human cells. *Nature.* 2012;489(7414):101-108.
4. Kapranov P, Cheng J, Dike S, et al. RNA maps reveal new RNA classes and a possible function for pervasive transcription. *Science.* 2007;316(5830):1484-1488.
5. Ha M, Kim VN. Regulation of microRNA biogenesis. *Nat Rev Mol Cell Biol.* 2014;15(8):509-524.
6. Tan DSW, Chong FT, Leong HS, et al. Long noncoding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma. *Nat Med.* 2017;23(10):1167-1175.
7. Hosono Y, Niknafs YS, Prensner JR, et al. Oncogenic role of THOR, a conserved cancer/testis long non-coding RNA. *Cell.* 2017;171(7):1559-1572 e1520.
8. Sanchez Calle A, Kawamura Y, Yamamoto Y, Takeshita F, Ochiya T. Emerging roles of long non-coding RNA in cancer. *Cancer Sci.* 2018;109(7):2093-2100.
9. Hu X, Sood AK, Dang CV, Zhang L. The role of long noncoding RNAs in cancer: the dark matter matters. *Curr Opin Genet Dev.* 2018;48:8-15.
10. Hao S, Yao L, Huang J, et al. Genome-wide analysis identified a number of dysregulated long noncoding RNA (lincRNA) in human pancreatic ductal adenocarcinoma. *Technol Cancer Res Treat.* 2018;17. doi: 10.1177/1533034617748429.
11. Ransohoff JD, Wei Y, Khavari PA. The functions and unique features of long intergenic non-coding RNA. *Nat Rev Mol Cell Biol.* 2018;19(3):143-157.
12. Kandath C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. *Nature.* 2013; 502(7471):333-339.
13. Khurana E, Fu Y, Chakravarty D, Demichelis F, Rubin MA, Gerstein M. Role of non-coding sequence variants in cancer. *Nat Rev Genet.* 2016;17(2):93-108.
14. Lin A, Hu Q, Li C, et al. The LINK-A lincRNA interacts with PtdIns(3,4,5)P3 to hyperactivate AKT and confer resistance to AKT inhibitors. *Nat Cell Biol.* 2017;19(3):238-251.
15. Lorenzen JM, Thum T. Long noncoding RNAs in kidney and cardiovascular diseases. *Nat Rev Nephrol.* 2016;12(6):360-373.
16. Yu X, Zhang Y, Li T, et al. Long non-coding RNA Linc-RAM enhances myogenic differentiation by interacting with MyoD. *Nat Commun.* 2017;8:14016.
17. Huang FT, Chen WY, Gu ZQ, et al. The novel long intergenic noncoding RNA UCC promotes colorectal cancer progression by sponging miR-143. *Cell Death Dis.* 2017;8(5):e2778.
18. Yu J, Han Q, Cui Y. Decreased long non-coding RNA SPRY4-IT1 contributes to ovarian cancer cell metastasis partly via

- affecting epithelial-mesenchymal transition. *Tumour Biol.* 2017; 39(7). doi: 10.1177/1010428317709129.
19. Yang W, Li D, Wang G, et al. Three intronic lncRNAs with monoallelic expression derived from the MEG8 gene in cattle. *Anim Genet.* 2017;48(3):272-277.
  20. Wang D, Garcia-Bassets I, Benner C, et al. Reprogramming transcription by distinct classes of enhancers functionally defined by eRNA. *Nature.* 2011;474(7351):390-394.
  21. Kim TK, Hemberg M, Gray JM, et al. Widespread transcription at neuronal activity-regulated enhancers. *Nature.* 2010;465(7295):182-187.
  22. Kim TK, Hemberg M, Gray JM. Enhancer RNAs: a class of long noncoding RNAs synthesized at enhancers. *Cold Spring Harb Perspect Biol.* 2015;7(1):a018622.
  23. Miao Y, Ajami NE, Huang TS, et al. Enhancer-associated long non-coding RNA LEENE regulates endothelial nitric oxide synthase and endothelial function. *Nat Commun.* 2018;9(1):292.
  24. Peng L, Jiang B, Yuan X, et al. Super-enhancer-associated long non-coding RNA HCCL5 is activated by ZEB1 and promotes the malignancy of hepatocellular carcinoma. *Cancer Res.* 2019;79(3):572-584.
  25. Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. *Sci Signal.* 2010;3(107):ra8.
  26. Neumann P, Jae N, Knau A, et al. The lncRNA GATA6-AS epigenetically regulates endothelial gene expression via interaction with LOXL2. *Nat Commun.* 2018;9(1):237.
  27. Xia Y, Xiao X, Deng X, et al. Targeting long non-coding RNA ASBEL with oligonucleotide antagonist for breast cancer therapy. *Biochem Biophys Res Commun.* 2017;489(4):386-392.
  28. Schein A, Zucchelli S, Kauppinen S, Gustincich S, Carninci P. Identification of antisense long noncoding RNAs that function as SINEUPs in human cells. *Sci Rep-UK.* 2016;6:33605.
  29. Liu B, Shen ED, Liao MM, et al. Expression and mechanisms of long non-coding RNA genes MEG3 and ANRIL in gallbladder cancer. *Tumour Biol.* 2016;37(7):9875-9886.
  30. Augoff K, McCue B, Plow EF, Sossey-Alaoui K. miR-31 and its host gene lncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer. *Mol Cancer.* 2012; 11:5.
  31. Lu Y, Zhao X, Liu Q, et al. lncRNA MIR100HG-derived miR-100 and miR-125b mediate cetuximab resistance via Wnt/beta-catenin signaling. *Nat Med.* 2017;23(11):1331-1341.
  32. Hung T, Wang Y, Lin MF, et al. Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet.* 2011;43(7):621-629.
  33. Yap KL, Li S, Munoz-Cabello AM, et al. Molecular interplay of the noncoding RNA ANRIL and methylated histone H3 lysine 27 by polycomb CBX7 in transcriptional silencing of INK4a. *Mol Cell.* 2010;38(5):662-674.
  34. Li Y, Chen D, Gao X, Li X, Shi G. lncRNA NEAT1 regulates cell viability and invasion in esophageal squamous cell carcinoma through the miR-129/CTBP2 Axis. *Dis Markers.* 2017;2017:5314649.
  35. Feng W, Wang C, Liang C, et al. The dysregulated expression of KCNQ1OT1 and its interaction with downstream factors miR-145/CCNE2 in breast cancer cells. *Cell Physiol Biochem.* 2018; 49(2):432-446.
  36. Yuan JH, Yang F, Wang F, et al. A long noncoding RNA activated by TGF-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma. *Cancer cell.* 2014;25(5):666-681.
  37. Tang J, Li Y, Sang Y, et al. lncRNA PVT1 regulates triple-negative breast cancer through KLF5/beta-catenin signaling. *Oncogene.* 2018;37(34):4723-4734.
  38. Steck E, Boeuf S, Gabler J, et al. Regulation of H19 and its encoded microRNA-675 in osteoarthritis and under anabolic and catabolic in vitro conditions. *J Mol Med.* 2012;90(10):1185-1195.
  39. Berghoff EG, Clark MF, Chen S, Cajigas I, Leib DE, Kohtz JD. Evf2 (Dlx6as) lncRNA regulates ultraconserved enhancer methylation and the differential transcriptional control of adjacent genes. *Development.* 2013;140(21):4407-4416.
  40. Liu X, Duan X, Holmes JA, et al. A novel lncRNA regulates HCV infection through IFI6. *Hepatology.* 2018;69(3):1004-1019.
  41. Bohmdorfer G, Wierzbicki AT. Control of chromatin structure by long noncoding RNA. *Trends Cell Biol.* 2015;25(10):623-632.
  42. Kim J, Piao HL, Kim BJ, et al. Long noncoding RNA MALAT1 suppresses breast cancer metastasis. *Nat Genet.* 2018;50(12):1705-1715.
  43. Tang J, Zhong G, Zhang H, et al. lncRNA DANCR upregulates PI3K/AKT signaling through activating serine phosphorylation of RXRA. *Cell Death Dis.* 2018;9(12):1167.
  44. Jadalih M, Gholamalamdari O, Tang W, et al. A natural antisense lncRNA controls breast cancer progression by promoting tumor suppressor gene mRNA stability. *PLoS Genet.* 2018; 14(11):e1007802.
  45. Yang F, Shen Y, Zhang W, et al. An androgen receptor negatively induced long non-coding RNA ARNILA binding to miR-204 promotes the invasion and metastasis of triple-negative breast cancer. *Cell Death Differ.* 2018;25(12):2209-2220.
  46. Huang X, Xie X, Liu P, et al. Adam12 and lnc015192 act as ceRNAs in breast cancer by regulating miR-34a. *Oncogene.* 2018;37(49):6316-6326.
  47. Wang Z, Yang B, Zhang M, et al. lncRNA epigenetic landscape analysis identifies EPIC1 as an oncogenic lncRNA that interacts with MYC and promotes cell-cycle progression in cancer. *Cancer Cell.* 2018;33(4):706-720 e709.
  48. Zhong H, Yang J, Zhang B, et al. lncRNA GACAT3 predicts poor prognosis and promotes cell proliferation in breast cancer through regulation of miR-497/CCND2. *Cancer Biomark.* 2018; 22(4):787-797.
  49. Liu M, Gou L, Xia J, et al. lncRNA ITGB2-AS1 could promote the migration and invasion of breast cancer cells through up-regulating ITGB2. *Int J Mol Sci.* 2018;19(7):pii: E1866.
  50. Wang S, Ke H, Zhang H, et al. lncRNA MIR100HG promotes cell proliferation in triple-negative breast cancer through triplex formation with p27 loci. *Cell Death Dis.* 2018;9(8):805.
  51. Song R, Zhang J, Huang J, Hai T. Long non-coding RNA GHET1 promotes human breast cancer cell proliferation, invasion and migration via affecting epithelial mesenchymal transition. *Cancer Biomark.* 2018;22(3):565-573.
  52. Li Y, Lv M, Song Z, Lou Z, Wang R, Zhuang M. Long non-coding RNA NNT-AS1 affects progression of breast cancer

- through miR-142-3p/ZEB1 axis. *Biomed Pharmacother.* 2018; 103:939-946.
53. Yang YX, Wei L, Zhang YJ, et al. Long non-coding RNA p10247, high expressed in breast cancer (lncRNA-BCHE), is correlated with metastasis. *Clin Exp Metastasis.* 2018;35(3): 109-121.
54. Bai Y, Zhou X, Huang L, Wan Y, Li X, Wang Y. Long noncoding RNA EZR-AS1 promotes tumor growth and metastasis by modulating Wnt/beta-catenin pathway in breast cancer. *Exp Ther Med.* 2018;16(3):2235-2242.
55. Fan S, Yang Z, Ke Z, et al. Downregulation of the long non-coding RNA TUG1 is associated with cell proliferation, migration, and invasion in breast cancer. *Biomed Pharmacother.* 2017; 95:1636-1643.
56. Li T, Liu Y, Xiao H, Xu G. Long non-coding RNA TUG1 promotes cell proliferation and metastasis in human breast cancer. *Breast Cancer.* 2017;24(4):535-543.
57. Liang Y, Song X, Li Y, et al. A novel long non-coding RNA-PRLB acts as a tumor promoter through regulating miR-4766-5p/SIRT1 axis in breast cancer. *Cell Death Dis.* 2018;9(5):563.
58. Lu G, Li Y, Ma Y, et al. Long noncoding RNA LINC00511 contributes to breast cancer tumorigenesis and stemness by inducing the miR-185-3p/E2F1/Nanog axis. *J Exp Clin Cancer Res.* 2018;37(1):289.
59. Li RH, Chen M, Liu J, et al. Long noncoding RNA ATB promotes the epithelial-mesenchymal transition by upregulating the miR-200c/ Twist1 axis and predicts poor prognosis in breast cancer. *Cell Death Dis.* 2018;9(12):1171.
60. Li W, Zhang Z, Liu X, et al. The FOXN3-NEAT1-SIN3A repressor complex promotes progression of hormonally responsive breast cancer. *J Clin Invest.* 2017;127(9):3421-3440.
61. Li GY, Wang W, Sun JY, et al. Long non-coding RNAs AC026904.1 and UCA1: a "one-two punch" for TGF-beta-induced SNAIL2 activation and epithelial-mesenchymal transition in breast cancer. *Theranostics.* 2018;8(10):2846-2861.
62. Li Z, Hou P, Fan D, et al. The degradation of EZH2 mediated by lncRNA ANCR attenuated the invasion and metastasis of breast cancer. *Cell Death Differ.* 2017;24(1):59-71.
63. Zhang W, Shi S, Jiang J, Li X, Lu H, Ren F. LncRNA MEG3 inhibits cell epithelial-mesenchymal transition by sponging miR-421 targeting E-cadherin in breast cancer. *Biomed Pharmacother.* 2017;91:312-319.
64. Shi X, Tang X, Su L. Over-expression of long non-coding RNA PTENP1 inhibits cell proliferation and migration via suppression of miR-19b in breast cancer cells. *Oncol Res.* 2018;26(6): 869-878.
65. Yang Y, Yang H, Xu M, et al. Long non-coding RNA (lncRNA) MAGI2-AS3 inhibits breast cancer cell growth by targeting the Fas/FasL signalling pathway. *Hum Cell.* 2018;31(3):232-241.
66. Xing F, Liu Y, Wu SY, 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(15): 4316-4330.
67. Zheng R, Lin S, Guan L, et al. Long non-coding RNA XIST inhibited breast cancer cell growth, migration, and invasion via miR-155/CDX1 axis. *Biochem Biophys Res Commun.* 2018; 498(4):1002-1008.
68. Wu W, Chen F, Cui X, et al. LncRNA NKILA suppresses TGF-beta-induced epithelial-mesenchymal transition by blocking NF-kappaB signaling in breast cancer. *Int J Cancer.* 2018;143(9): 2213-2224.
69. Chen J, Liu S, Hu X. Long non-coding RNAs: crucial regulators of gastrointestinal cancer cell proliferation. *Cell Death Discov.* 2018;4:50.
70. Vennin C, Spruyt N, Dahmani F, et al. H19 non coding RNA-derived miR-675 enhances tumorigenesis and metastasis of breast cancer cells by downregulating c-Cbl and Cbl-b. *Oncotarget.* 2015;6(30):29209-29223.
71. Cai Y, He J, Zhang D. Long noncoding RNA CCAT2 promotes breast tumor growth by regulating the Wnt signaling pathway. *Onco Targets Ther.* 2015;8:2657-2664.
72. Yang SX, Polley E, Lipkowitz S. New insights on PI3K/AKT pathway alterations and clinical outcomes in breast cancer. *Cancer Treat Rev.* 2016;45:87-96.
73. Hu Q, Yin J, Zeng A, et al. H19 functions as a competing endogenous RNA to regulate EMT by sponging miR-130a-3p in glioma. *Cell Physiol Biochem.* 2018;50(1):233-245.
74. Wang M, Han D, Yuan Z, et al. Long non-coding RNA H19 confers 5-Fu resistance in colorectal cancer by promoting SIRT1-mediated autophagy. *Cell death & dis.* 2018;9(12):1149.
75. Vennin C, Spruyt N, Robin YM, Chassat T, Le Bourhis X, Adriaenssens E. The long non-coding RNA 91 H increases aggressive phenotype of breast cancer cells and up-regulates H19/IGF2 expression through epigenetic modifications. *Cancer Lett.* 2017;385:198-206.
76. Berteaux N, Lottin S, Monte D, et al. H19 mRNA-like noncoding RNA promotes breast cancer cell proliferation through positive control by E2F1. *J Biol Chem.* 2005;280(33):29625-29636.
77. Zhang CY, Yu MS, Li X, Zhang Z, Han CR, Yan B. Overexpression of long non-coding RNA MEG3 suppresses breast cancer cell proliferation, invasion, and angiogenesis through AKT pathway. *Tumour Biol.* 2017;39(6). doi: 10.1177/1010428317701311.
78. Chen S, Wang Y, Zhang JH, et al. Long non-coding RNA PTENP1 inhibits proliferation and migration of breast cancer cells via AKT and MAPK signaling pathways. *Oncol Lett.* 2017;14(4):4659-4662.
79. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. *Oncogene.* 2007;26(22):3279-3290.
80. Ding LJ, Li Y, Wang SD, et al. Long noncoding RNA lncCAMTA1 promotes proliferation and cancer stem cell-like properties of liver cancer by inhibiting CAMTA1. *Int J Mol Sci.* 2016;17(10):pii: E1617.
81. Lu P, Gu Y, Li L, Wang F, Yang X, Yang Y. Long noncoding RNA CAMTA1 promotes proliferation and mobility of human breast cancer cell line MDA-MB-231 via targeting miR-20b. *Oncol Res.* 2018;26(4):625-635.
82. Wang L, Li J, Zhao H, et al. Identifying the crosstalk of dysfunctional pathways mediated by lncRNAs in breast cancer subtypes. *Mol Biosyst.* 2016;12(3):711-720.
83. Peng WX, Huang JG, Yang L, Gong AH, Mo YY. Linc-RoR promotes MAPK/ERK signaling and confers estrogen-



- independent growth of breast cancer. *Mol cancer*. 2017;16(1):161.
84. Polakis P. Wnt signaling in cancer. *Cold Spring Harb Perspect Biol*. 2012;4(5):a008052.
85. Zhan T, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene*. 2017;36(11):1461-1473.
86. Huan J, Xing L, Lin Q, Xui H, Qin X. Long noncoding RNA CRNDE activates Wnt/beta-catenin signaling pathway through acting as a molecular sponge of microRNA-136 in human breast cancer. *Am J Transl Res*. 2017;9(4):1977-1989.
87. Hsieh AL, Walton ZE, Altman BJ, Stine ZE, Dang CV. MYC and metabolism on the path to cancer. *Semin Cell Dev Biol*. 2015;43:11-21.
88. 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(2):533-545.
89. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell*. 2017;169(2):361-371.
90. Li J, Zhang J, Jin L, Deng H, Wu J. Silencing lnc-ASA2B-2 inhibits breast cancer cell growth via the mTOR pathway. *Anticancer Res*. 2018;38(6):3427-3434.
91. Chen XN, Wang KF, Xu ZQ, et al. MiR-133b regulates bladder cancer cell proliferation and apoptosis by targeting Bcl-w and Akt1. *Cancer cell int*. 2014;14:70.
92. Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. *Cell*. 2007;129(7):1311-1323.
93. Ding W, Ren J, Ren H, Wang D. Long noncoding RNA HOTAIR modulates MiR-206-mediated Bcl-w signaling to facilitate cell proliferation in breast cancer. *Sci Rep*. 2017;7(1):17261.
94. Zhang Y, Zhou Y, Xu T, et al. Clinical value of long noncoding RNA HOTAIR as a novel biomarker in digestive cancers: a meta-analysis. *Technol Cancer Res Treat*. 2018;17. doi: 10.1177/1533034618756783.
95. Li N, Wang Y, Liu X, et al. Identification of circulating long noncoding RNA HOTAIR as a novel biomarker for diagnosis and monitoring of non-small cell lung cancer. *Technol Cancer Res Treat*. 2017. doi: 10.1177/1533034617723754.
96. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. *Nat rev Cancer*. 2003;3(6):453-458.
97. Sethi N, Kang Y. Unravelling the complexity of metastasis - molecular understanding and targeted therapies. *Nat rev Cancer*. 2011;11(10):735-748.
98. Mali SB. Review of STAT3 (Signal Transducers and Activators of Transcription) in head and neck cancer. *Oral Oncol*. 2015; 51(6):565-569.
99. Bian Z, Zhang J, Li M, et al. LncRNA-FEZ1-AS1 promotes tumor proliferation and metastasis in colorectal cancer by regulating PKM2 signaling. *Clin Cancer Res*. 2018;24(19):4808-4819.
100. Gupta RA, Shah N, Wang KC, et al. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature*. 2010;464(7291):1071-1076.
101. Tsai MC, Manor O, Wan Y, et al. Long noncoding RNA as modular scaffold of histone modification complexes. *Science*. 2010;329(5992):689-693.
102. Chisholm KM, Wan Y, Li R, Montgomery KD, Chang HY, West RB. Detection of long non-coding RNA in archival tissue: correlation with polycomb protein expression in primary and metastatic breast carcinoma. *PLoS One*. 2012;7(10):e47998.
103. Zhang H, Cai K, Wang J, et al. MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway. *Stem Cells*. 2014;32(11):2858-2868.
104. Wang S, Liang K, Hu Q, et al. JAK2-binding long noncoding RNA promotes breast cancer brain metastasis. *J clin invest*. 2017;127(12):4498-4515.
105. Ruland J. Return to homeostasis: downregulation of NF-kappaB responses. *Nat immunol*. 2011;12(8):709-714.
106. Liu B, Sun L, Liu Q, et al. A cytoplasmic NF-kappaB interacting long noncoding RNA blocks IkappaB phosphorylation and suppresses breast cancer metastasis. *Cancer Cell*. 2015;27(3):370-381.
107. Syed V. TGF-beta signaling in cancer. *J Cell Biochem*. 2016; 117(6):1279-1287.
108. Zarzynska JM. Two faces of TGF-beta1 in breast cancer. *Mediators Inflamm*. 2014;2014:141747.
109. Kretz M, Webster DE, Flockhart RJ, et al. Suppression of progenitor differentiation requires the long noncoding RNA ANCR. *Genes Dev*. 2012;26(4):338-343.
110. Li Z, Dong M, Fan D, et al. LncRNA ANCR down-regulation promotes TGF-beta-induced EMT and metastasis in breast cancer. *Oncotarget*. 2017;8(40):67329-67343.
111. Richards EJ, Zhang G, Li ZP, et al. Long non-coding RNAs (LncRNA) regulated by transforming growth factor (TGF) beta: LncRNA-hit-mediated TGFbeta-induced epithelial to mesenchymal transition in mammary epithelia. *J Biol Chem*. 2015; 290(11):6857-6867.
112. Wu ZJ, Li Y, Wu YZ, et al. Long non-coding RNA CCAT2 promotes the breast cancer growth and metastasis by regulating TGF-beta signaling pathway. *Eur rev med pharmaco*. 2017; 21(4):706-714.
113. Badouel C, McNeill H. SnapShot: the hippo signaling pathway. *Cell*. 2011;145(3):484-484.e481.
114. Meignin C, Alvarez-Garcia I, Davis I, Palacios IM. The salvador-warts-hippo pathway is required for epithelial proliferation and axis specification in Drosophila. *Curr Biol*. 2007; 17(21):1871-1878.
115. Zanconato F, Cordenonsi M, Piccolo S. YAP/TAZ at the roots of cancer. *Cancer Cell*. 2016;29(6):783-803.
116. Li C, Wang S, Xing Z, et al. A ROR1-HER3-lncRNA signalling axis modulates the Hippo-YAP pathway to regulate bone metastasis. *Nat Cell Biol*. 2017;19(2):106-119.
117. Sas-Chen A, Aure MR, Leibovich L, et al. LIMT is a novel metastasis inhibiting lncRNA suppressed by EGF and downregulated in aggressive breast cancer. *EMBO Mol Med*. 2016;8(9):1052-1064.
118. Xiao C, Wu CH, Hu HZ. LncRNA UCA1 promotes epithelial-mesenchymal transition (EMT) of breast cancer cells via enhancing Wnt/beta-catenin signaling pathway. *Eur rev med pharmaco*. 2016;20(13):2819-2824.

119. Plati J, Bucur O, Khosravi-Far R. Dysregulation of apoptotic signaling in cancer: molecular mechanisms and therapeutic opportunities. *J Cell Biochem.* 2008;104(4):1124-1149.
120. Zhang S, Zhou L, Hong B, et al. Small-molecule NSC59984 Restores p53 pathway signaling and antitumor effects against colorectal cancer via p73 activation and degradation of mutant p53. *Cancer Res.* 2015;75(18):3842-3852.
121. Zhang A, Xu M, Mo YY. Role of the lncRNA-p53 regulatory network in cancer. *J Mol Cell Biol.* 2014;6(3):181-191.
122. Hu WL, Jin L, Xu A, et al. GUARDIN is a p53-responsive long non-coding RNA that is essential for genomic stability. *Nat Cell Biol.* 2018;20(4):492-502.
123. Cao Y, Lin M, Bu Y, et al. p53-inducible long non-coding RNA PICART1 mediates cancer cell proliferation and migration. *Int J Oncol.* 2017;50(5):1671-1682.
124. Chen R, Liu Y, Zhuang H, et al. Quantitative proteomics reveals that long non-coding RNA MALAT1 interacts with DBC1 to regulate p53 acetylation. *Nucleic Acids Res.* 2017;45(17):9947-9959.
125. Crawford ED, Seaman JE, Barber AE, 2nd, et al. Conservation of caspase substrates across metazoans suggests hierarchical importance of signaling pathways over specific targets and cleavage site motifs in apoptosis. *Cell Death Differ.* 2012;19(12):2040-2048.
126. Chen DQ, Zheng XD, Cao Y, et al. Long non-coding RNA LINC00628 suppresses the growth and metastasis and promotes cell apoptosis in breast cancer. *Eur rev med pharmaco.* 2017; 21(2):275-283.
127. Liao XH, Wang JG, Li LY, et al. Long intergenic non-coding RNA APOC1P1-3 inhibits apoptosis by decreasing alpha-tubulin acetylation in breast cancer. *Cell Death Dis.* 2016;7(5):e2236.
128. Shi J, Li X, Zhang F, et al. The plasma lncRNA acting as fingerprint in hilar cholangiocarcinoma. *Cell Physiol Biochem.* 2018;49(5):1694-1702.
129. Peng W, Wang J, Shan B, et al. Diagnostic and prognostic potential of circulating long non-coding RNAs in non small cell lung cancer. *Cell Physiol Biochem.* 2018;49(2):816-827.
130. Sun L, Su Y, Liu X, et al. Serum and exosome long non coding RNAs as potential biomarkers for hepatocellular carcinoma. *J Cancer.* 2018;9(15):2631-2639.
131. Lee YR, Kim G, Tak WY, et al. Circulating exosomal noncoding RNAs as prognostic biomarkers in human hepatocellular carcinoma. *Int J Cancer.* 2019;144(6):1444-1452.
132. Xian HP, Zhuo ZL, Sun YJ, Liang B, Zhao XT. Circulating long non-coding RNAs HULC and ZNF1-AS1 are potential biomarkers in patients with gastric cancer. *Oncol Lett.* 2018; 16(4):4689-4698.