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Research Article

lncRNAs: As novel biomarkers in diagnosis, prognosis and therapy of non-small cell lung cancer (NSCLC).

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Abstract

Non-small cell lung cancer (NSCLC) is a subtype of lung cancer that behaves similarly to squamous cell carcinoma and adenocarcinoma. Non-small cell lung cancer (NSCLC) is the most common histopathological type, accounting for about 85% of all lung cancers, and is usually diagnosed at advanced stages. Symptoms include persistent cough, shortness of breath, weight loss, or hemoptysis. Surgery combined with chemotherapy improved the long-term survival of patients with NSCLC, but the emergence of drug resistance made chemotherapy less effective. Many lncRNAs are functionally associated with human diseases, especially cancer. Long non-coding RNAs (lncRNAs)- dysregulation has been reported to be involved in breast cancer, colorectal cancer, liver cancer, lung cancer, and leukemia. Commonly, lncRNAs dysregulation exerts impacts on cellular functions such as cell proliferation, resistance to apoptosis, induction of angiogenesis, the advancement of metastasis, and evasion of tumor suppressors. This review provides insight into (lncRNAs) covering a wide range of topics, such as biogenesis, effects on gene expression and regulation, and potential use for biomarkers in the diagnosis, prognosis, and treatment of non-small cell lung cancer (NSCLC).

Keywords: Non-Small Cell Lung Cancer, Long non-Coding RNA, Biomarkers

Introduction

Lung cancer is one of the most devastating malignancies and the leading cause of cancer-related death worldwide [1]. Non-small cell lung carcinoma (NSCLC) is the most common histopathological type accounting for approximately 85% of all lung cancer cases and generally diagnosed at advanced stages [2]. Based on the pathological types, NSCLC is divided into squamous cell carcinoma, adenocarcinoma and large cell carcinoma [3, 4]. It is believed that the low 5-year survival rate (about 15%) is largely attributable to advanced local invasion and/or distant metastasis, and recurrence of NSCLC [5, 6]. It was reported that over 50% of NSCLC patients experienced micro- metastasis before radical surgery, which was the direct cause of postoperative metastasis and recurrence [3,4,7,8]. Even-though surgery combined with chemotherapy increased the long-term survival rate of patients with NSCLC [9], the occurrence of drug resistance limit the efficacy of chemotherapy [10]. Moreover, chemotherapy resistance was the major cause of chemotherapy failure, remarkably limiting its clinical application. [7,8]. Genetic factors, diet, unhealthy lifestyles, and precancerous lesions were all closely associated with the development of NSCLC. In-depth research on NSCLC showed that NSCLC was the result from both genetic and environmental factors. Changes in some oncogenes and tumor suppressor genes ultimately led to impaired cell proliferation, apoptosis, and differentiation. [11,12].

Long non-coding RNAs (lncRNAs) are most commonly defined as non-coding RNAs (ncRNAs) that are over 200 nucleotides in length and are lack of protein-coding capacity, but are able to regulate gene expression at transcriptional, posttranscriptional and epigenetic levels [13]. It is well known that lncRNAs

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play functional roles in various biological processes, such as Cell differentiation, proliferation, invasion and migration. [14]. Accumulating evidence suggested the important role of unregulated or dysregulated lncRNAs in tumorigenesis and development of various cancers, including NSCLC [15,16]. Thus, this review provided our points of view on (lncRNAs), covering a range of issues such as, their biogenesis, effects on gene expression and regulation, and their potential use af biomarkers in the diagnosis, prognosis and therapy of non-small cell lung cancer (NSCLC).

Biogenesis of lncRNAs

LncRNAs are the type of nucleic acid molecules with a length of over 200 nucleotides, which do not have a complete specific open reading frame therefore are not translated to proteins. [17]. In general, lncRNA strictly refers to lncRNA except for rRNA, which can be transcribed in more than 200,000 ways [18]. Although there are many kinds of lncRNAs, most of them are relatively low in copy numbers inside cells; some, even have one copy only in few cells [19]. The greater part of the annotated lncRNAs is expressed in specified cell types, and generally at lower levels than the protein-coding mRNAs [20]. IncRNA can be transcribed from many different parts of a gene including the antisense strand, the promoter region, the intron region, and the mRNA intergenic region. [21-23]. This means lncRNA can be transcribed from anywhere in the genome. Based on the position of lncRNA in the genome, lncRNA can be divided into three categories, namely: long intergenic non-coding RNAs (lincRNAs), natural antisense transcript (NATs), and intron lncRNAs [24-26]. Apart from lncRNA, which lies between the two protein-coding genes, most lncRNA and the associated genes that code for proteins have some degree of overlap in the gene sequence [22, 27,28]. Take, for example, intron lncRNAs are transcribed from the intron of the protein-coding gene, whereas NATs are transcribed from the opposite (complementary) chain of the protein-coding gene [29]. Antisense lncRNA is especially common in mice [30]. Up to 72% of the genomic sites, showed that differential transcription led to the production of antisense lncRNA [31]. Majority of the lncRNAs were transcribed by RNA polymerase II, which were spliced and matured [32]. Like mRNAs, most lncRNAs were hindered or blocked, polyadenylated, and spliced [33]. lncRNAs primary structures were poorly conserved, however their secondary structures and splicing patterns were functionally conserved with tissue or cell specificity [34].

The lncRNAs classification is based on the idea that RNAs with base numbers of over 200 nucleotides can form complex structures at a high level which are distinguishable from miRNA (miRNA). [35]. However, when the base number of an RNA is 50–70 nucleotides, some complex structures can be formed [36]. Notwithstanding the linear structure, lncRNAs likewise have circular RNAs, which may be influenced by the structure. Circular RNAs have a half-life that is longer and more stable than that of linear lncRNAs [37]. In addition, they also have tissue-specific expression in a specific period. This affects the growth and development process, and is related to diseases such as tumors [38].

lncRNAs in Gene Expression and Regulation

lncRNAs have the ability to impact gene functions through RNA-protein, RNA-RNA, or RNA-DNA interactions (Figure 1). They can target all levels of gene regulation, including transcription, mRNA stability, and translation. It is known that lncRNAs interact with RNA or protein in the cytosol to achieve its molecular function. With some lncRNAs and mRNAs base pairs, this interaction leads to changes in these mRNA levels. One kind of lncRNA, lncRNA lnc-MD1 acted as a competitive endogenous lncRNA to inhibit miR-133 [28]. Another type of lncRNA, antisense lncRNA UCHL1 promoted the translation of UCHL1 mRNA by increasing the binding of UCHL1 mRNA to the polymer [39].

Conversely, some lncRNAs, such as lncRNA-p21, paired with the target mRNA to inhibit their translation. In any case, a more general pattern of lncRNA interactions involves interaction with one or more specific proteins. lncRNAs are involved in regulating gene expression through various mechanisms in the cell's nucleus. lncRNAs, serving as modular guidance and scaffolds for proteins, can recruit proteins or RNAs [40]. Sequentially, these complexes accumulate or assemble high-order protein/RNA complexes in cells. These proteins coordinate with each other to secrete inhibitory histone markers and to suppress gene expression of target gene sites. Since lncRNA directs proteins to specific genomic sites or acts as a molecular scaffold to stabilize complex proteins, lncRNA can also contribute to the functional diversity of DNA- binding proteins.

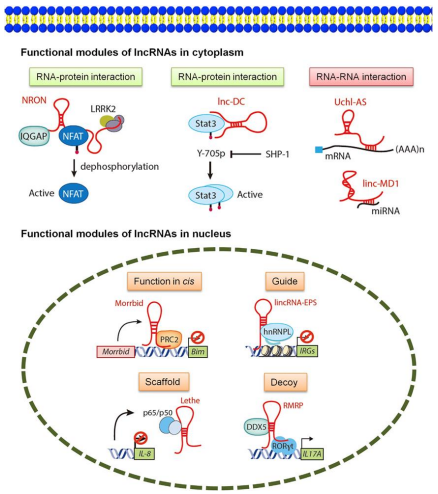

Figure 1. Number of patients per age with breast cancer from 2016 and 2018 in HCM

lncRNAs as Biomarkers

The significance of understanding the mechanisms of lncRNA goes beyond describing gene regulation because lncRNA can be used as a diagnostic marker or drug target, as well as a prognostic marker. One potential diagnostic marker is the prostate cancer-associated transcript 1 (PCAT-1), which can be identified in the urine of prostate cancer patients [41]. Still on prognosis, lncRNAs defined as CAT104, LINC01234 and STXBP5-AS1 are clinically

important for predicting breast cancer survival [42]. Moreover, B.-B. Gao et al. 2019, proposed that lncRNA BC200 regulates cell proliferation and cisplatin resistance in non-small cell lung cancer (NSCLC) via PI3K/AKT pathway. lncRNAs have been suggested as therapeutic targets, but there are difficulties in fully understanding their mechanism of action [43, 44].

Many cancer models have been shown to release extracellular vesicles (Evs)- containing different ncRNAs sets, such as: miRNAs and lncRNAs. There were some specific transcripts abundant in EVs, showing that they might play a role in nearby cells. This was demonstrated in a colorectal cancer model in which miRNA [45], lncRNA [46] and circRNA [47] were selectively exported to EV and were shown to be not simply correlated with cytosolic RNA pool levels. During hypoxia, hepatocellular cancer cells produced Lnc-RoR (regulator of reprogramming), which reduced miR-145 and hypoxia-induced factor 1 alpha (HIF-1_) in recipient cells. [48]. This feature demonstrated the potential for lncRNAs as biomarkers, as shown in liver cancer [49].

lncRNAs as Diagnostic and Prognostic Markers in NSCLC

Non-small cell lung cancer (NSCLC) remains the most common human malignancy and a major public health challenge. Recently, targeted therapy has been developed, and as a result of that, some patients with NSCLC accomplished a favorable clinical outcome [50]. Yet still, a huge number of NSCLC patients displayed unfavorable responses to the emerging targeted therapy. This was largely due to the difference of genetic mutation [51]. Therefore, identifying sensitive cancer biomarkers is very important for the improvement of the overall survival and quality of life [52]. Furthermore, some functional biomarkers can also be used as potential prognostic and diagnostic biomarkers for NSCLC patients. Recently, the critical effect of lncRNA on tumor development is gaining attention and a growing number of lncRNAs have been identified as potential new biomarkers for cancer [53]. Yun-xia et al. conducted a study in which they identified a new NSCLC-associated lncRNA, LINC00668, which was confirmed to be significantly regulated in NSCLC tissue and cell lines. Then, they performed clinical assays which confirmed that high LINC00668 expression was clearly associated with advanced TNM, histological grade, lymph node metastases, and shorter overall survival. More importantly, the results of the univariate and multivariate analyses confirmed that LINC00668 was an independent prognostic marker of overall survival in patients with NSCLC (Table 1).

Ling et al. conducted a study in which they showed that ANRIL lncRNA expression levels were increased in the NSCLC tissue compared to the surrounding non-tumor tissue. In addition, they analyzed existing associations with clinicopathologic features and prognosis to determine whether ANRIL-lncRNA could be considered a potential prognostic factor for predicting clinical outcome in patients with NSCLC (Table 2). According to their findings, increased expression of ANRIL lncRNA was associated with a poor prognosis for overall survival, probably due to the ability of ANRIL lncRNA to stimulate cell growth and metastasis of lung cancer cells. Li et al. conducted a meta-analysis examining the prognostic potential of MALAT1. Although sensitivity to MALAT1 was low for individual diagnostic tests, it was found that MALAT1 could be used as an independent prognostic factor for overall survival in NSCLC with statistical significance [54]. Zhang et al. investigated the clinical potential of several lncRNAs in patients with NSCLC and found a poor prognosis with high intergenic expression of H19, MALAT1 and Hox antisense RNA (HOTAIR) and low expression of taurine upregulation gene 1 (TUG1) and the p21-associated ncRNA DNA damage activated (PANDA) [55]. The above results or findings were indications that individual lncRNAs, as well as combinations, may be important in the diagnosis and prognosis of NSCLC.

Table 1. Univariate and multivariate analyses for overall survival by Cox regression model

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	1.732	0.667–2.315	0.167	–	–	–
Sex	1.559	0.784–2.531	0.132	–	–	–
History of smoking	1.995	0.892–2.654	0.231	–	–	–
Tumor size	1.667	0.732–2.542	0.126	–	–	–
TNM stage	3.554	1.436–5.742	0.001	2.893	1.216–4.146	0.026
Histological grade	3.136	1.377–4.733	0.006	2.769	1.126–4.442	0.021
Lymph node metastasis	3.798	1.338–5.237	0.003	3.218	1.188–4.576	0.011
LINC006 expression	3.569	1.498–5.128	0.001	2.995	1.287–4.674	0.005

Table 2. Correlation between lncRNA ANRIL expression and clinicopathological features in NSCLC patients

Parameters	Group	Total	lncRNA	ANRIL	P Value
			Low	High	
	Male	51	23	28	0.952
	Female	36	16	20	
Age (years)	<60	42	18	24	0.721
	≥60	45	21	24	
Tumor size (cm)		39	16	23	0.520
	≥3 cm	48	23	25	<3
Histology	Adenocarcinoma	38	20	18	0.197
	Squamous cell carcinoma	49	19	30	
TNM Stage	I	26	19	7	0.001
	II-III	61	20	41	
Lymph mode mestasis	Absence	40	32	8	0.000
	Presence	47	7	40	

DMSO (Sigma) and plates were agitated at room temperature for 10 min. The absorbance was measured at 490 nm using an enzyme-labeled analyzer.

lncRNAs in the Therapy of NSCLC

The dominant choice of treatments for NSCLC is curative surgery; However, for most of the patients who are usually in the late stages of the disease, surgery is palliative leaving platinum-based chemotherapy as the last resort. [56]. However, due to increased resistance to chemotherapies and targeted treatments, novel

approaches need to be explored [57]. The function of lncRNAs in all areas of tumorigenesis of NSCLC and in the regulation of signaling pathways, makes lncRNA promising therapeutic targets. Additionally, multiple lncRNAs were reported to be associated increased chemoresistance, which was why targeted treatments could also restore cancer cell sensitivity to chemotherapy agents [57].

There are several approaches to targeting lncRNA in cancer, including genetic attenuation based on interference RNA (RNAi), antisense oligonucleotide (ASO) treatment, small molecule modulator of protein-lncRNA interactions, and delivery of tumor suppressors to lncRNA [57-65]. For example, HOTAIR siRNA intervention or interference reduces migration and invasion of NSCLC cells in vitro and reduces metastasis in a mouse model HOTAIR siRNA xenograft. [66]. Furthermore, HOTAIR siRNA-mediated knockdown also increased the susceptibility of NSCLC cells to cisplatin treatment (Table 3) [67]. However, RNAi could have non-target effects and be problematic for nuclear RNAs, with many lncRNAs functioning at the nucleus of NSCLC. On the contrary, ASOs are useful because of their high affinity and reduced toxicity related to their relatively low targeting effect [68]. In the MALAT1 knockout mouse model, mice injected with MALAT1 ASOs had reduced nodules and lung tumor volume compared with untreated mice (Table 3). Therefore, ASO inhibition of MALAT1 inhibited NSCLC metastases. That approach might be a promising therapeutic future in NSCLC [69]. It was shown that MEG3 decreased in NSCLC which resulted in inhibition of NSCLC apoptosis, invasion, migration and metastasis, and increase of cisplatin sensitivity. [70,71,72]. Overexpression of MEG3 inhibited tumorigenesis in vivo and reduced NSCLC cell proliferation, as well as induced apoptosis in vitro, suggesting that application of tumor suppressor lncRNAs such as MEG3 might be an alternative therapeutic option in NSCLC (Table 3) [73]. However, further research is needed to assess the effectiveness of tumor suppressor lncRNA delivery as a therapeutic measure in the clinical sitting.

Table 3. Therapeutic targeting approaches in NSCLC

LncRNA	Targeting Approach	Effect in NSCLC	Ref.
HOTAIR	siRNA	Reduced migration and invasion in vitro and reduced metastases in vivo	[66]
	siRNA	Increased sensitivity to cisplatin	[67]
MALAT1	ASO	Reduced tumor burden and metastases in vivo	[69]
MEG3	Overexpression of tumor suppressor lncRNA.	Inhibited tumorigenesis in vivo and reduced cell proliferation and apoptosis in vitro	[73]

Conclusion

LncRNA has been shown to function in many important cellular processes, and its role in cancer is attracting more attention [74]. Localization of lncRNAs to a great extent reflects their function and they interact with chromatin, protein and RNA to regulate all stages of gene expression and to influence important signaling cascades. [74]. Although usually tightly regulated, large-scale analyses have showed that lncRNAs were often dysregulated in NSCLC [75]. Many lncRNAs are upregulated and function as oncogenes to enhance NSCLC proliferation, survival, invasion, migration, EMT, and metastasis. Since the poor prognosis for NSCLC was largely due to late diagnosis and a lack of effective treatment for late stage cancer, an alternative approach to the treatment of NSCLC is needed [76]. Individual lncRNAs as well as the combinations of multiple lncRNAs showed promise as diagnostic biomarkers and as well as prognostic and therapeutic indicators in non-small cell lung cancer (NSCLC). However, further study is required to bring lncRNAs to the clinical perspective as diagnostic, prognostic, and therapeutic tools in non-small cell lung cancer (NSCLC).

REFERENCES

1. Torre L.A, Bray F, Siegel R.L, Ferlay J. Lortet-Tieulent, Jemal A.(2012) Global cancer statistics, CA Cancer J. Clin. 65 2015; 87–108, https://doi.org/10.3322/ caac.21262.

2. Miller K.D, Siegel R.L, Lin C.C, Mariotto A.B, Kramer J.L, Rowland J.H, Stein K.D, Alteri R, Jemal A.(2016) Cancer treatment and survivorship statistics, CA Cancer J. Clin. 66; 271–289, https://doi.org/10.3322/caac.21349.

3. Li Y, Tian J, Guo ZJ, Zhang ZB, Xiao CY, Wang XC.(2018) Expression of microRNAs-106b in nonsmall cell lung cancer. J Cancer Res Ther; 14: S295-S298.

4. Maiuthed A, Chantarawong W, Chanvorachote P.(2018) Lung cancer stem cells and cancer stem cell-targeting natural compounds. Anticancer Res; 38: 3797-3809.

5. Torre L.A, Siegel R.L, Jemal A.(2016) Lung Cancer statistics, Adv. Exp. Med. Biol. 893; 1–19, https://doi.org/10.1007/978-3-319-24223-1_1.

6. Deng X.F, Jiang L, Liu Q.X, Zhou D, Hou B, K. Cui, J.X. Min, J.G. Dai,(2016) Lymph node micrometastases are associated with disease recurrence and poor survival for early-stage non-small cell lung cancer patients: a meta-analysis, J. Cardiothorac. Surg. 11; 28, https://doi.org/10.1186/s13019-016-0427-x.

7. Yamashita T, Uramoto H, Onitsuka T, Ono K, Baba T, So T, So T, Takenoyama M, Hanagiri T, Oyama T, Yasumoto K.(2010) Association between lymphangiogenesis-/micrometastasis- and adhesion-related molecules in resected stage I NSCLC. Lung Cancer; 70: 320-328.

8. Fan KJ, Liu Y, Yang B, Tian XD, Li CR, Wang B.(2017) Prognostic and diagnostic significance of long non-coding RNA AGAP2-AS1 levels in patients with non-small cell lung cancer. Eur Rev Med Pharmacol Sci; 21: 2392-2396.

9. Sapalidis K, Zarogoulidis P, Pavlidis E, Laskou S, Katsaounis A, Koulouris C, Giannakidis D, Mantalovas S, Huang H, Bai C, et al.(2018) Aerosol Immunotherapy with or without Cisplatin for metastatic lung cancer non-small cell lung cancer disease: In vivo Study. A more efficient combination. J Cancer; 9: 1973-1977.

10. Bach DH, Kim D, Bae SY, Kim WK, Hong JY, Lee HJ, Rajasekaran N, Kwon S, Fan Y, Luu TT, et al.(2018) Targeting Nicotinamide N-Methyltransferase and miR-449a in EGFR-TKI-Resistant Non-Small-Cell Lung Cancer Cells. Mol Ther Nucleic Acids; 11: 455-467.

11. Guo Q, Lan F, Yan X, Xiao Z, Wu Y, Zhang Q.(2018) Hypoxia exposure induced cisplatin resistance partially via activating p53 and hypoxia inducible factor-1alpha in non-small cell lung cancer A549 cells. Oncol Lett; 16: 801-808.

12. Chen F, Li J, Qi X, Qi J.(2018) Diagnostic value of CYFRA 21-1 and carcinoembryonic antigen in diagnosis of operable lung cancer from benign lung disease. J Cancer Res Ther; 14: S400-S404.

13. Mercer T.R, Dinger M.E, Mattick J.S.(2009) Long non-coding RNAs: insights into functions, Nat. Rev. Genet. 10; 155–159, https://doi.org/10.1038/nrg2521.

14. Shi X, Sun M, Liu H, Yao Y, Song Y.(2013) Long non-coding RNAs: a new frontier in the study of human diseases, Cancer Lett. 339; 159–166, https://doi.org/10. 1016/j. canlet.2013.06.013.

15. M.C. Tsai, R.C. Spitale, H.Y. Chang.(2011) Long intergenic noncoding RNAs: new links in cancer progression, Cancer Res. 71; 3–7, https://doi.org/10.1158/0008- 5472.can-10-2483.

16. Ponting C.P, Oliver P.L, Reik W.(2009) Evolution and functions of long noncoding RNAs, Cell 136; 629–641, https://doi.org/10.1016/j.cell.2009.02.006.

17. Gupta S.C, Awasthee N, Rai V, Chava S, Gunda V, and Challagundla K.B.(2020) Long non-coding RNAs and nuclear factor-kB crosstalk in cancer and other human diseases. Biochim. Biophys. Acta Rev. Cancer; 1873, 188316.

18. Wang X, Yu H, Sun W, Kong J, Zhang L, Tang J, Wang J, Xu E, Lai M, and Zhang H. (2018) The long non-coding RNA CYTOR drives colorectal cancer progression by interacting with NCL and Sam68. Mol. Cancer; 17, 110.

19. Wu G, Ma Z, Cheng Y, Hu W, Deng C, Jiang S, Li T, Chen F, and Yang Y.(2018) Targeting Gas6/TAM in cancer cells and tumor microenvironment. Mol. Cancer; 17, 20.

20. Andrzejewska A, Dabrowska S, Nowak B, Walczak P, Lukomska B, and Janowski M. (2020)Mesenchymal stem cells injected into carotid artery to target focal brain injury home to perivascular space. Theranostics; 10, 6615–6628.

21. Ma M, Zhang Y, Weng M, Hu Y, Xuan Y, Hu Y, and Lv K.(2018) LncRNA GCAWKR promotes gastric cancer development by scaffolding the chromatin modification factors WDR5 and KAT2A. Mol. Ther; 26, 2658–2668.

22. Wei L., Wang X, Lv L, Liu J, Xing H, Song Y, Xie M, Lei T, Zhang N, and Yang M.(2019) The emerging role of microRNAs and long noncoding RNAs in drug resistance of hepatocellular carcinoma. Mol. Cancer; 18, 147.

23. Xie B, Bai B, Xu Y, Liu Y, Lv Y, Gao X, Wu F, Fang Z, Lou Y, Pan H, and Han W. (2019) Tumor-suppressive function and mechanism of HOXB13 in rightsided colon cancer. Signal Transduct. Target. Ther; 4, 51.

24. Zhao Y, Liu Y, Lin L, Huang Q, He W, Zhang S, Dong S, Wen Z, Rao J, Liao W, and Shi M.(2018) The lncRNA MACC1-AS1 promotes gastric cancer cell metabolic plasticity via AMPK/Lin28 mediated mRNA stability of MACC1. Mol. Cancer; 17, 69.

25. Liu X.L, Wang B.B, Wang Y, Wang Y.X, Yang C.H, Tan C, Zhang X, He Q.J, Ding J, and Meng, L.H.(2019) Unbiased screening reveals that blocking exportin 1 overcomes resistance to PI3Ka inhibition in breast cancer. Signal Transduct. Target. Ther; 4, 49.

26. Ding C.H, Yin C, Chen S.J, Wen L.Z, Ding K, Lei S.J, Liu J.P, Wang J, Chen K.X, Jiang H.L, et al.(2018) The HNF1a-regulated lncRNA HNF1A-AS1 reverses the malignancy of hepatocellular carcinoma by enhancing the phosphatase activity of SHP-1. Mol. Cancer; 17, 63.

27. Zhang C, Liao Y, Liu P, Du Q, Liang Y, Ooi S, Qin S, He S, Yao S, and Wang W.(2020) FABP5 promotes lymph node metastasis in cervical cancer by reprogramming fatty acid metabolism. Theranostics; 10, 6561–6580.

28. Kawamura E, Maruyama M, Abe J, Sudo A, Takeda A, Takada S, Yokota T, Kinugawa S, Harashima H, and Yamada Y.(2020) Validation of gene therapy for mutant mitochondria by delivering mitochondrial RNA using a MITO-Porter. Mol. Ther. Nucleic Acids; 20, 687–698.

29. Le Grand M, Mukha A, Püschel J, Valli E, Kamili A, Vittorio O, Dubrovska A, and Kavallaris M.(2020) Interplay between MycN and c-Myc regulates radioresistance and cancer stem cell phenotype in neuroblastoma upon glutamine deprivation. Theranostics; 10, 6411–6429.

30. Wang J, Zhu S, Meng N, He Y, Lu R, and Yan G.R.(2019) ncRNA-encoded peptides or proteins and cancer. Mol. Ther; 27, 1718–1725.

31. Hewes A.M, Sansbury B.M, Barth S, Tarcic G, and Kmiec E.B.(2020) Grna sequence heterology tolerance catalyzed by CRISPR/Cas in an in vitro homologydirected repair reaction. Mol. Ther. Nucleic Acids; 20, 568–579.

32. Li X, Wang M, and Xiang R.(2019) Clonal replacement of novel T cells: a new phenomenon in the tumor microenvironment following PD-1 blockade. Signal Transduct. Target. Ther; 4, 43.

33. Zhang L, Meng X, Zhu X.W, Yang D.C, Chen R, Jiang Y, and Xu T.(2019) Long non-coding RNAs in oral squamous cell carcinoma: biologic function, mechanisms and clinical implications. Mol. Cancer; 18, 102.

34. Li J, Zhu Y, Wang H, and Ji X.(2018) Targeting long noncoding RNA in glioma: a pathway perspective. Mol. Ther. Nucleic Acids; 13, 431–441.

35. Horita K, Kurosaki H, Nakatake M, Kuwano N, Oishi T, Itamochi H, Sato S, Kono H, Ito M, Hasegawa K, et al.(2019) lncRNA UCA1-mediated Cdc42 signaling promotes oncolytic vaccinia virus cell-to-cell spread in ovarian cancer. Mol. Ther. Oncolytics; 13, 35–48.

36. Fan J, Xu Y, Wen X, Ge S, Jia R, Zhang H, and Fan X.(2019) A cohesinmediated intrachromosomal loop drives oncogenic ROR lncRNA to accelerate tumorigenesis. Mol. Ther. 27; 2182-2194.

37. Peng Z, Liu C, and Wu M.(2018) New insights into long noncoding RNAs and their roles in glioma. Mol. Cancer; 17, 61.

38. Xie S, Yu X, Li Y, Ma H, Fan S, Chen W, Pan G, Wang W, Zhang H, Li J, and Lin Z. (2018) Upregulation of lncRNA ADAMTS9-AS2 promotes salivary adenoid cystic carcinoma metastasis via PI3K/Akt and MEK/Erk signaling. Mol. Ther. 26; 2766–2778.

39. Zhou H, Zhu P, Wang J, Toan S, and Ren J.(2019) DNA-PKcs promotes alcohol-related liver disease by activating Drp1-related mitochondrial fission and repressing FUNDC1-required mitophagy. Signal Transduct. Target. Ther. 4; 56.

40. Cristóbal I, Sanz-Alvarez M, Torrejón B, Santos A, Luque M, Rojo F, and García-Foncillas J.(2018) Potential therapeutic impact of miR-145 deregulation in colorectal cancer. Mol. Ther. 26; 1399–1400.

41. Prensner J.R, Iyer M.K, Balbin O.A, Dhanasekaran S.M, Cao Q, Brenner J.C, Laxman B, Asangani I.A, Grasso C.S, Kominsky H.D, et al.(2011) Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. Nat. Biotechnol; 29, 742–749.

42. Guo L, Zhao Y, Yang S, Zhang H, Wu Q, Chen F.(2014) An integrated evolutionary analysis of miRNA-lncRNA in mammals. Mol. Biol. Rep; 41, 201–207.

43. Parasramka M.A, Maji S, Matsuda A, Yan, I.K. Patel T.(2016) Long non-coding RNAs as novel targets for therapy in hepatocellular carcinoma. Pharmacol. Therap; 161, 67–78.

44. Roberts T.C, Wood M.J.A.(2013) Therapeutic targeting of non-coding RNAs. Essays Biochem; 54, 127–145.

45. Cha D.J, Franklin J.L, Dou Y, Liu Q, Higginbotham J.N, Demory Beckler M, Weaver, A.M.; Vickers, K.; Prasad, N.; Levy, S.; et al.(2015) KRAS-dependent sorting of miRNA to exosomes. eLife; 4, e07197.

46. Hinger S.A, Cha D.J, Franklin J.L, Higginbotham J.N, Dou Y, Ping J, Shu L, Prasad N, Levy S, Zhang B, et al.(2018) Diverse long RNAs are differentially sorted into extracellular vesicles secreted by colorectal cancer cells. Cell Rep; 25, 715–725.e4.

47. Dou Y, Cha D.J, Franklin J.L, Higginbotham J.N, Jeppesen D.K, Weaver A.M, Prasad N, Levy S, Coffey R.J, Patton J.G, et al.(2016) Circular RNAs are down-regulated in KRAS mutant colon cancer cells and can be transferred to exosomes. Sci. Rep; 6, 37982

48. Takahashi K, Yan I.K, Haga H, Patel T.(2014) Modulation of hypoxia-signaling pathways by extracellular linc-Ror. J. Cell Sci; 127, 1585–1594.

49. Mohankumar S, Patel T.(2016) Extracellular vesicle long noncoding RNA as potential biomarkers of liver cancer. Brief. Funct. Genom; 15, 249–256.

50. Hirsch F.R, Scagliotti G.V, Mulshine, Kwon R, Curran W.J Jr., Wu Y.L, L. Paz-Ares, (2017) Lung cancer: current therapies and new targeted treatments, Lancet (London, England) 389 (10066); 299–311.

51. T. Puri,(2017) Targeted therapy in nonsmall cell lung cancer, Indian J. Cancer 54 (1); 83–88.

52. D.V. Parums,(2014) Current status of targeted therapy in non-small cell lung cancer, Drugs Today (Barcelona, Spain: 1998) 50 (7); 503–525.

53. S. Chandra Gupta, Y. Nandan Tripathi,(2017) Potential of long non-coding RNAs in cancer patients: from biomarkers to therapeutic targets, Int. J. Cancer 140 (9); 1955–1967.

54. Li Y, Yang Z, Wan X, Zhou J.G, Zhang Y, Ma H, Bai Y.(2016) Clinical Prognostic Value of Metastasis-Associated Lung Adenocarcinoma Transcript 1 in Various Human Cancers: An Updated Meta-Analysis. Int. J. Boil. Markers; 31, 173–182.

55. Zhang C.G, Yin D.D, Sun S.Y, Han L.(2017) The use of lncRNA analysis for stratification management of prognostic risk in patients with NSCLC. Eur. Rev. Med. Pharmacol. Sci; 21, 115–119.

56. Moran C.A.(2011) Importance of Molecular Features of Non–Small Cell Lung Cancer for Choice of Treatment. 5Am. J. Pathol; 178, 1940–1948.

57. Lu T, Wang Y, Chen D, Liu J, Jiao W.(2018) Potential clinical application of lncRNAs in non-small cell lung cancer. OncoTargets Ther; 11, 8045–8052.

58. Bolha L, Ravnik-Glava˘c M, Glava˘c D.(2017) Long Noncoding RNAs as Biomarkers in Cancer. Dis. Markers 2017; 1–14.

59. Shi T, Gao G, Cao Y.(2016) Long Noncoding RNAs as Novel Biomarkers Have a Promising Future in Cancer Diagnostics. Dis. Markers 2016; 1–10.

60. Lemos A.E.G, Matos A.D.R, Ferreira L.B, Gimba E.R.P.(2019) The long non-coding RNA PCA3: An update of its functions and clinical applications as a biomarker in prostate cancer. Oncotarget; 10, 6589–6603.

61. Weber D.G, Johnen G, Casjens S, Bryk O, Pesch B, Jöckel K.H, Kollmeier J, Brüning T. (2013) Evaluation of long noncoding RNA MALAT1 as a candidate blood-based biomarker for the diagnosis of non-small cell lung cancer. BMC Res. Notes; 6, 518.

62. Tantai J, Hu D, Yang Y, Geng J.(2015) Combined identification of long non-coding RNA XIST and HIF1A-AS1 in serum as an effective screening for non-small cell lung cancer. Int. J. Clin. Exp. Pathol; 8, 7887–7895.

63. Li Y, Yang Z, Wan X, Zhou J.G, Zhang Y, Ma H, Bai Y.(2016) Clinical Prognostic Value of Metastasis-Associated Lung Adenocarcinoma Transcript 1 in Various Human Cancers: An Updated Meta-Analysis. Int. J. Boil. Markers; 31, 173-182.

64. Zhang C.G, Yin D.D, Sun S.Y, Han L.(2017) The use of lncRNA analysis for stratification management of prognostic risk in patients with NSCLC. Eur. Rev. Med. Pharmacol. Sci, 21, 115–119.

65. Sanchez Y, Huarte M.(2013) Long Non-Coding RNAs: Challenges for Diagnosis and Therapies. Nucleic Acid Ther; 23, 15–20.

66. Liu X.H, Liu Z.L, Sun M, Liu J, Wang Z, De W.(2013) The long non-coding RNA HOTAIR indicates a poor prognosis and promotes metastasis in non-small cell lung cancer. BMC Cancer; 13, 464.

67. Guo F, Cao Z, Guo H, Li S.(2018) The action mechanism of lncRNA-HOTAIR on the drug resistance of non-small cell lung cancer by regulating Wnt signaling pathway. Exp. Ther. Med; 15, 4885–4889.

68. Chery J, Näär A.(2016) RNA therapeutics: RNAi and antisense mechanisms and clinical applications. Postdoc. J; 4, 35–50.

69. Gutschner T, Haemmerle M, Eissmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Gross M, et al.(2012) The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res; 73, 1180–1189.

70. Wu J.L, Meng F.M, Li H.J.(2018) High expression of lncRNA MEG3 participates in non-small cell lung cancer by regulating microRNA-7-5p. Eur. Rev. Med. Pharmacol. Sci; 22, 5938–5945.

71. Zhao Y, Zhu Z, Shi S, Wang J, Li N.(2019) Long non-coding RNA MEG3 regulates migration and invasion of lung cancer stem cells via miR-650/SLC34A2 axis. Biomed. Pharmacother; 120, 109457.

72. Wang P, Chen D, Ma H, Li Y.(2017) LncRNA MEG3 enhances cisplatin sensitivity in non-small cell lung cancer by regulating miR-21–5p/SOX7 axis. Onco. Targets Ther; 10, 5137–5149.

73. Lu K.H, Li W, Liu X.H, Sun M, Zhang M.L, Wu W.Q, Xie W, Hou Y.(2013) Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer; 13, 461.

74. Schmitt A, Chang H.Y.(2016) Long Noncoding RNAs in Cancer Pathways. Cancer Cell; 29, 452–463.

75. Zhou W, Liu T, Saren G, Liao L, Fang W, Zhao H.(2019) Comprehensive analysis of differentially expressed long non-coding RNAs in non-small cell lung cancer. Oncol. Lett.; 18, 1145–1156.

76. Moran C.A.(2011) Importance of Molecular Features of Non–Small Cell Lung Cancer for Choice of Treatment. Am. J. Pathol; 178, 1940–1948.