Long non-coding RNAs in oncurology

Ilgiz Gareev a,1, Yulia Gileva a,1, Aleksandr Dzidzaria b,1, Ozal Beylerli a,1, Valentin Pavlov a, Murad Agaverdiev a, Bakhodur Mazorov a, Ilfat Biganyakov a, Andranik Vardikyan a, Mei Jin c,**, Aamir Ahmad d,ε

a Bashkir State Medical University, Ufa, Republic of Bashkortostan, 450008, Russia
b Urology Department, Russian Scientific Center of Radiology of the Ministry of Health of the Russian Federation, Moscow, Russia
c The First Affiliated Hospital of Harbin Medical University, 23 Youzheng St, Harbin, 150001, Heilongjiang Province, China
d Interim Translational Research Institute, Academic Health System, Hamad Medical Corporation, Doha, Qatar

ABSTRACT

For several decades, research in tumor biology has focused on the involvement of genes encoding a protein. Only recently has it been discovered that a whole class of molecules called non-coding RNAs (ncRNAs) play a key regulatory role in health and disease. Long noncoding RNAs (lncRNAs) are a group of noncoding RNAs longer than 200 nucleotides. It has been found that lncRNAs play a fundamental role in the biology of many types of tumors, including tumors of the genitourinary system. As a result, hundreds of clinical trials dedicated to oncurology have begun, using lncRNA as new biomarkers or treatments. Identifying new specific biomarkers, in the form of lncRNAs, will increase the ability to differentiate the tumor and other processes, determine the localization and extent of the tumor, and the ability to predict the course of the disease, and plan treatment. Therapy of tumors, especially malignant ones, is also a difficult task. When surgery and chemotherapy fail, radiation therapy becomes the treatment choice. Therefore, the possibility that lncRNAs could represent innovative therapeutic agents or targets is an exciting idea. However, the possibility of their use in modern clinical practice is limited, and this is associated with several problems at the pre-, analytical and post-analytical stages. Another problem in the study of lncRNAs is the large number and variety of their functions in tumors. Therefore, solving technological problems in lncRNAs study in oncurology may open up new possibilities for lncRNAs use in modern clinical practice.

1. Introduction

Tumors are one of the leading causes of death in the world, second only to cardiovascular diseases [1]. They represent an extensive and diverse class of diseases that manifest themselves in various forms, with varying degrees of severity and varying responses to treatment. Over the past several decades, certain success has been achieved in studies of the pathological and molecular mechanisms of the emergence and development of tumors. The study of pathogenesis is necessary in the search for new strategies for the diagnosis, prognosis and treatment of this deadly disease [2]. Oncurology occupy a special place in oncology. Despite advances in the treatment of these malignancies, urologists still face the challenge of improving diagnosis in the early or “pre-early” stages of the disease by developing methods that can detect neoplasms, bypassing the side effects of biopsy and other traditional diagnostic approaches [2]. In this regard, extracellular molecules in biological fluids embedded in microvesicles or protected by RNA-binding proteins/lipids are likely to provide diagnostic, prognostic, or even therapeutic targets in the fight against this type of tumor.

Non-coding RNAs (ncRNAs) refers to RNA molecules that are not translated, that is, proteins are not synthesized by their sequence. NcRNAs encompass a huge number of RNA classes and perform a wide range of biological functions, such as regulating gene expression, protecting the genome from exogenous DNA, and controlling DNA synthesis [3]. One of these classes of ncRNAs that are widely studied are long non-coding RNAs (lncRNAs). LncRNAs are a group of ncRNAs over 200 nucleotides in length, and they do not code for proteins. They play a regulatory role in health and disease. Long noncoding RNAs (lncRNAs) are a group of noncoding RNAs longer than 200 nucleotides. It has been found that lncRNAs play a fundamental role in the biology of many types of tumors, including tumors of the genitourinary system. As a result, hundreds of clinical trials dedicated to oncurology have begun, using lncRNA as new biomarkers or treatments. Identifying new specific biomarkers, in the form of lncRNAs, will increase the ability to differentiate the tumor and other processes, determine the localization and extent of the tumor, and the ability to predict the course of the disease, and plan treatment. Therapy of tumors, especially malignant ones, is also a difficult task. When surgery and chemotherapy fail, radiation therapy becomes the treatment choice. Therefore, the possibility that lncRNAs could represent innovative therapeutic agents or targets is an exciting idea. However, the possibility of their use in modern clinical practice is limited, and this is associated with several problems at the pre-, analytical and post-analytical stages. Another problem in the study of lncRNAs is the large number and variety of their functions in tumors. Therefore, solving technological problems in lncRNAs study in oncurology may open up new possibilities for lncRNAs use in modern clinical practice.

** Corresponding author. The First Affiliated Hospital of Harbin Medical University, 23 Youzheng St, Harbin, 150001, Heilongjiang Province, China.
* Corresponding author. Interim Translational Research Institute, Academic Health System, Hamad Medical Corporation, Doha, Qatar.
1 These authors contributed equally to this work.

https://doi.org/10.1016/j.ncrna.2021.08.001
Received 31 July 2021; Received in revised form 24 August 2021; Accepted 25 August 2021
Available online 26 August 2021
2468-0540/© 2021 The Authors. Published by KeAi Communications Co., Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
nucleotides in length. Because of their length, IncRNAs nucleotide chains have the unique ability to accept many complex secondary and tertiary structures, allowing them to perform specific functions necessary for the existence of an organism. IncRNAs cannot encode protein, but they can modulate gene expression at epigenetic (eg, DNA methylation, histone modification), transcriptional (eg, recruitment of transcription factors) and post-transcriptional (eg, regulation of microRNA (miRNA) and messenger RNA (mRNA) stability) levels [4]. An increasing number of studies have demonstrated deregulation or aberrant expression of IncRNAs in various types of human diseases [5]. Many studies have also shown aberrant IncRNAs expression in various tumors, as in tumors of the genitourinary system, which was directly associated with carcinogenesis, metastasis and disease stages (Table 1) [6–12]. Moreover, IncRNAs can be found in human biological fluids such as blood and urine [13]. The so-called circulating IncRNAs can be secreted from tumor cells into human biological fluids in extracellular vesicles (EVs), like microvesicles or exosomes. Such IncRNAs are resistant to the effects of RNases, which makes them attractive as new diagnostic and prognostic non-invasive biomarkers [13]. It has been proven that exosomes play an important role in intercellular communication. Exosomes, in addition to transferring IncRNAs, are used to transfer other information like DNA, proteins, etc. from one cell to another, and tumor cells play a particularly important role in the production of exosomes [14]. Now, many promising studies have studied circulating IncRNAs as non-invasive biomarkers in tumors of the genitourinary system (Table 2) [15–20]. As an example, IncRNA prostate cancer antigen 3 (PCA3), which is the most striking example of the use of IncRNA as a non-invasive biomarker in prostate cancer (PC), approved by the FDA (Food and Drug Administration) [15].

Aberrant expression of IncRNAs in tumor cells is a hallmark of a tumor, and IncRNAs may play a role as suppressors of tumor genes or oncogenes, depending on the cellular context and different functions of the target genes. Tumor IncRNAs have certain properties of oncogenes that can specifically control the regulation of the expression of tumor suppressor genes with subsequent inhibition of their expression. Thus, indirectly promote the development of the tumor. In addition, such IncRNAs are mainly overexpressed in the tumor cell. In other words, their expression level increases in the case of neoplastic transformation of normal cells [13,14]. Antitumor IncRNAs can specifically control the regulation of the expression of oncogenes and inhibit their expression in tumors. Therefore, they can inhibit the transcription of target oncogenes and ultimately inhibit tumor growth or genesis. In contrast to the first, the level of expression of such IncRNAs in the tumor cell is reduced [14]. The study of IncRNAs in oncology is one of the most promising directions in modern fundamental research and can help in the discovery of a significant number of new potential targets for new generation targeted drugs, as well as for the development of gene therapy. In this review, we will consider the problems and ways of their possible solution related to the profiling of IncRNAs expression in oncology.

2. Methodological aspects of IncRNA expression profiling

2.1. Pre-analytical, analytical and post-analytical stages

With early detection of a tumor, there is a high probability of positive results with effective treatment. Early diagnosis leads to more effective therapy, as a result of which the duration and quality of life of patients are increased. Therefore, the search for reliable, accurate, and non-invasive biomarkers for early diagnosis, prognosis, and monitoring of tumor treatment is an acute problem to this day. Research on the study of DNA or RNA molecules as potential biomarkers is not innovative, but, unfortunately, despite this, their results do not correspond to their use in modern clinical practice. Profiling of IncRNA expression in samples of cells and tissues, as well as in biological fluids of the human body, is feasible using various methods [21]. Proteins as biomarkers are sensitive indicators of physiological and pathological processes, including tumors, as well as responses to therapy. However, in turn, proteins are inferior to IncRNA for several reasons (Fig. 1) [22,23]. An ideal biomarker should be easy to detect, requiring a simple measurement methodology. However, in the case of circulating IncRNA, some problems arise at the pre-analytical, analytical, and post-analytical stages, the need to solve which is an important task for the possible introduction of circulating IncRNA as non-invasive biomarkers into clinical practice.

Another factor limiting the use of circulating IncRNAs as a diagnostic tool in oncology is associated with the fact that the same IncRNAs reported as potential biomarkers are found in patients with different types of tumors. For example, circulating metastasis associated lung adenocarcinoma transcript 1 (MALAT1) has been found in overexpressed serum in patients with PC, bladder cancer (BC), and renal cell carcinoma (RCC). Moreover, the results are inconsistent even among very similar studies with the same diseases [23,24].

Reduced expression of endogenous IncRNA in tumor tissues may be the result of genetic changes or mechanisms of epigenetic regulation, but a decrease in the level of expression of circulating IncRNA in biological fluids can occur only if the tumor itself negatively affects the expression

| Table 1 | LncRNAs involved in carcinogenesis of tumors of the genitourinary system. |
|---------|----------------------------------------------------------------------------|
| LncRNA  | Type of tumor                  | Expression | Gene-Targets | Biological function                  | Ref.  |
| MEG3    | Clear cell renal cell carcinoma | Decreased  | Bcl-2, procaspase-9 | Tumor suppressor. Promotes apoptosis of tumor cells. | [6]  |
| MALAT1  | Clear cell renal cell carcinoma | Increased  | miR-200s, ZEB2 | Oncogenic properties. Promotes proliferation, migration and invasion of tumor cells. | [7]  |
| GAS6-AS2| Bladder cancer                 | Increased  | miR-298, CDK9   | Oncogenic properties. Promotes proliferation and metastasis. | [8]  |
| CASCI1  | Bladder cancer                 | Increased  | miR-150         | Oncogenic properties. Promotes proliferation, migration and invasion of tumor cells. | [9]  |
| CCAT1   | Prostate cancer                | Increased  | DDX5, miR-28-5p | Oncogenic properties. Promotes the proliferation of tumor cells | [10] |
| HOXD-AS1| Castration-resistant prostate cancer | Increased | WDR5         | Oncogenic properties. Promotes proliferation, castration resistance and chemoresistance. | [11] |
| XIST    | Prostate cancer                | Decreased  | RKIP, miR-23a   | Tumor suppressor. Suppression of tumor growth and progression. | [12] |

Abbreviations: LncRNA, Long non-coding RNA; miRNA, microRNA; MEG3, Maternally expressed 3; MALAT1, Metastasis associated lung adenocarcinoma transcript 1; GAS6-AS2, GAS6 antisense RNA 2; CASCI1, Cancer susceptibility 11; CCAT1, Colon cancer associated transcript 1; HOXD-AS1, HOXD cluster antisense RNA 1; XIST, X-inactive specific transcript; Bcl-2, B-cell lymphoma 2; ZEB2, Zinc finger E-box binding homeobox 2; CDK9, Cyclin-dependent kinase 9; DDX5, DEAD-Box Helicase 5; WDR5, WD Repeat Domain 5; RKIP, Raf kinase inhibitory protein.
of endogenous lncRNA in other cells or reduces their stability. In other words, a decrease in the level of expression of circulating lncRNA in biological fluids can be attributed to nonspecific responses to the presence of a tumor [25]. In addition, the presence of a tumor cannot be correlated with the activation of these lncRNAs. Due to the anticoagulant system of the blood, only a small number of tumors, such as advanced tumors, resulting in overexpression of specific circulating lncRNAs in the blood. Accordingly, it is more likely that the detection of circulating lncRNA in biological fluids is also the result of the response (s) to the presence of a tumor in the body [26].

One of the important properties of an ideal biomarker is its stability in a biological environment. There were opinions that lncRNAs are less stable in human tissues and biological fluids, and are more susceptible to degradation than miRNAs, which may have been caused by their nucleotide length. However, Kraus et al. showed that some lncRNAs (lncRNA LUCA-15-specific transcript (LUST), lncRNA IGF2-AS (IGF2AS), lncRNA-7SK, lncRNA HOXA6as, lncRNA neuroblastoma differentiation marker 29 (NDM29)) in healthy brain tissue are even more stable than miRNAs [27]. Other researchers also indicated that intragenic and cis-antisense lncRNAs (half-life more than 16 h) are more stable than most lncRNAs that form from intron regions within a gene [28]. The specific half-life of lncRNA depends not only on its coding site in genome modifications but also on subcellular localization and function [29]. Moreover, the presence of some circulating lncRNAs, such as H19, in plasma confirms the high stability during incubation of plasma in ethylenediaminetetraacetic acid (EDTA) tube overnight at room temperature [30].

The next question concerns the standardization of the total RNA
and hemolysis, blood cells release endogenous lncRNA into plasma or hemolyzed cells in plasma/serum, can affect the preparation of the Gene-Probe Inc., San Diego, Calif.) [36]. Urine samples are collected in for lncRNA PCA3 determination using the PROGENSA PCA3 kit (Hologic currently commonly used in all studies of PC markers, either to measure prepared tubes containing a stabilizing reagent. This processing process according to the absorption spectrum of a total RNA solution, the degree of indicators are determined by the absorption spectrum of the resulting process was developed after comparative studies to determine the process with the highest diagnostic accuracy for this marker. This manipulation is currently commonly used in all studies of PC markers, either to measure the total, native urine, or its sediments or supernatants. Norgen Biotek also offers kits that allow you to concentrate preserve and isolate lncRNAs in urine with the stability of up to 2 years at room temperature [8].

Another very important issue is the definition of qualitative and quantitative indicators. Using the NanoDrop-2000 spectrophotometer, you can determine the quantitative and qualitative indicators of total RNA. Biological fluids, in contrast to tissue or cell cultures, have very low total RNA concentrations (in the range of 15–100 ng/µl). Qualitative indicators are determined by the absorption spectrum of the resulting solution with total RNA at three wavelengths 230, 260, 280 nm. According to the absorption spectrum of a total RNA solution, the degree of RNA purification from proteins, polysaccharides, guanidine, phenol, and EDTA is approximately estimated. The absorption ratio at 260/280 nm should be approximately equal to 2 (1.9–2.1); if the absorption ratio was less than 1.9, then additional purification of total RNA from proteins and guanidine thiocyanate is necessary. If this ratio is greatly increased, this indicates the decay of total RNA. The absorption ratio at 260/230 nm should be slightly over 2 (2.2–3). If this ratio is less than the established value, then the sample is contaminated with phenol, polysaccharides, or EDTA and requires mandatory cleaning, since these substances inhibit many enzymatic reactions, including polymerase chain reaction (PCR) [32,37].

Using the correct housekeeping gene to normalize data remains problematic in measuring circulating lncRNA expression. In the absence of such genes, most studies with circulating lncRNA are based on other lncRNAs [36]. Inappropriate advice affects results and makes it difficult to compare different studies. Normalization problems have been observed in the case of expression studies with circulating miRNAs [38].
NGS is currently one of the best methods for detecting lncRNA, which is extremely sensitive and provides data on their relative expression in a sample with a large dynamic range compared to microarrays [48]. NGS is used to obtain small differential RNA expression profiles, including lncRNA, to study tissue developmental stages, tissue types, and pathological conditions such as oncology, with the potential to search for new biomarkers and therapeutic targets [49]. The main disadvantage of NGS is the creation of the necessary infrastructure, such as computer capacity and storage, as well as the experience of the staff to comprehensively analyze and interpret the subsequent data. In addition, you need to skillfully manage the volume of data in order to extract clinically important information into an understandable and reliable interface. The actual cost of NGS is significant. For example, current NGS technology can generate about 150,000,000 reads for about $1,300, while a single Sanger read typically costs less than $1. However, in order to make NGS cost-effective, large batches of samples would have to be run, which may require supra-regional centralization [50]. Thus, each technology has its own advantages and limitations. Therefore, the method should be selected based on the specific research requirements and the issues under consideration (Table 3) [51–53].

### 3. Blood or urine?

One of the key issues in the field of research on circulating ncRNAs, including lncRNAs as biomarkers, as the choice of the priority biological fluid (urine or blood), must be resolved in order to maximize the potential of circulating lncRNAs for diagnosis, prognosis and choice of therapy for tumors of the genitourinary system. Since the blood is in contact with all-important organs (e.g. kidney), it collects all the necessary information about changes in the body. Obviously, when looking for potential biomarkers for pathologies, blood should be used. At the same time, it is available with little or no harm. The question is how long the changes can remain in the blood. In this case, it depends on how quickly the biomarker is produced and enters the bloodstream, and how quickly it leaves the blood. Blood (plasma/serum) is one of the available biological fluids for profiling the expression of circulating ncRNAs in patients with tumors [54]. Plasma or serum has been shown to be informative for profiling the expression of circulating RNA for diagnosis, prognosis, assessment of response to therapy and tumor recurrence, as well as detection of emerging resistance to therapy in various human tumors, including BC, PC, RCC [17,20,22]. The detection of circulating lncRNAs in plasma/serum samples without measurable circulating tumor cells suggests that circulating lncRNAs in plasma/serum may provide useful information about tumors of the urinary system, regardless of the presence of circulating tumor cells. Several studies have reported the sensitivity of circulating tumor cells in the blood of patients with RCC ranging from 20% to 40% [55]. However, due to the presence of a filtration barrier in the urinary system (an analogy of the blood-brain barrier for the central nervous system), blood is not an ideal fluid for an accurate assessment of these biomarkers [56]. These studies have shown conclusively that the filtration barrier can be an obstacle preventing circulating tumor cells or circulating lncRNAs from entering the bloodstream. However, as in the case of brain tumors, a violation of the barrier function occurs, which allows various molecules, including circulating for lncRNAs, to penetrate from the urinary system into the bloodstream, so it is possible from the general bloodstream into the urine.

Urine is probably the best place to detect changes, as it is a blood filtrate and contains all soluble biomarkers including circulating lncRNAs. It is possible that urine will be a better source of biomarkers than blood for diseases of the genitourinary system, including tumors [57]. Unlike blood, urine is in direct contact with the organs of the urinary system (kidney and bladder) and is a suitable source of biomarkers for tumors of this system. In addition, urine is easier and safer to obtain than blood from venipuncture or tumor tissue from biopsy. Other examples are probably saliva and salivary glands, sweat and sweat glands, cerebrospinal fluid and brain.

As already reported, EVs are membrane-enclosed nanoparticles that are released from living tumor cells, either as a result of the fusion of the endosome with the plasma membrane (exosomes) or directly from the cell membrane (microvesicles) [11]. EVs are carriers of communication between different compartments of a tumor and its microenvironment since other tumor cells and normal cells absorb them [18]. It is important to note that EVs, which can be isolated from both blood and urine, are a rich source of tumor molecules such as DNA, ncRNA, proteins, lipids, and metabolites since the EV structure protects them from nucleases and proteases [18,26]. Since blood contains a large number of nucleases and proteases, the isolation of lncRNA from EV can give a higher concentration of RNA compared to non-vesicular forms of circulating lncRNA from whole blood, plasma, or serum [13].

In addition, the change in the expression profile of circulating lncRNAs in urine and blood in the same patient with a RCC or BC is unique because urine likely reflects local events of damaged tissue compared to blood flow. Moreover, a specific panel of circulating lncRNAs in urine can help distinguish a tumor of the kidney or bladder from other inflammatory, infectious and traumatic lesions of the urinary system.

### 4. Authors’ opinion

The rapidly growing number of newly discovered lncRNAs and the accumulation of experimental data explaining their multifaceted functionality promise a better understanding of tumor biology and their future use in clinical practice. However, current research aimed at comprehensively investigating lncRNAs in tumors faces several challenges. Currently, most new transcripts are discovered using NGS technologies, which face computational constraints in terms of short sequence length, mapping and de novo assembly of transcripts derived from the tumor genome with complex structural rearrangements (for example, large deletions or insertions, chromosome fusions, chromotripsis or chromoplexy).

Recent developments in fluorescence probe design, imaging and

| Methods | Specificity | Sensitivity | Flexibility | Productivity | Absolute quantification/accuracy | Possibility of identification of new lncRNAs | Data analysis | Problems |
|---------|-------------|-------------|-------------|--------------|----------------------------------|---------------------------------------------|--------------|----------|
| Real-time PCR | +++ | +++ | +++ | +++ | +++ | No | Relatively easy | Lack of consensus on data normalization |
| Microarray | ++ | + | +/- | +++ | + | No | Moderate. Depends on the applications used | High price. Multiple samples on one platform |
| NGS | +++ | + | +++ | +++ | + | Yes | Complicated | High price |
imaging technology enable the determination of (sub) cellular localization and measurement of the absolute expression of endogenous transcripts in individual cells with single molecule resolution in situ. Elucidation of the function of IncRNA is difficult due to their relatively low sequence conservatism. However, the main functionality of RNA can be found in its tertiary structure, determined by the laws of conservative sequences that promote RNA folding and are necessary for binding to proteins. This is demonstrated by the sequential assembly of Prostate cancer associated non-coding RNA 1 (PRNCR1) and IncRNA prostate cancer gene expression marker 1 (PCGEM1) with the androgen receptor (AR), the MEG3 structure required for its tumor suppressive function. Another key question that remains to be answered is what causes the strikingly specific expression of most IncRNAs in normal and tumor tissues. Genetic/epigenetic aberrations that control IncRNA expression should be investigated in the future to understand the role of IncRNA in the tumor process.

Changes seen in biological fluids usually reflect changes in tissues or cells. Theoretically, oncogenic circulating molecules, like oncoIncRNAs, should reflect the onset of the tumor process. However, not all tumor loci are identical. Thus, understanding the origin of these molecules, whether primary or metastatic, is a key challenge. In addition, despite the encouraging data, significant challenges remain before these tests are ready for clinical use. Both quantitative and qualitative changes in the expression of circulating IncRNA strongly depend on methodological aspects. Laboratory staff and clinicians must collaborate to address a range of issues related to consistent and feasible preanalytical and analytical conditions for selected biomarkers, as well as assay validation in well-designed and sufficiently powerful multicenter studies. It is important to describe the sampling, processing and measurement conditions as accurately as possible. The biological fluid chosen for research must also correspond to the question of interest to us. Some body fluids are more complex than others are (blood is more complex than urine), which can make analysis difficult.

Various studies have been published regarding the optimal approach to diagnosis and follow-up in patients with suspected bladder cancer. New FDA-approved tests based on detecting tumor-associated proteins, either in urine or in desquamated urothelium cells, as well as tests based on detecting chromosomal aberrations, have failed in the clinic. Several urinary IncRNA biomarkers have shown higher sensitivity and specificity than cytology, but have failed to replace invasive cytoscopy as a diagnostic standard. It can be expected that individual biomarkers or their combinations will be introduced into clinical practice in the near future, as suggested by the first results of the ongoing large prospective study of the European FP7 UROMOL project. Compared with PC and BC, there is little evidence for the diagnostic and prognostic potential of circulating serum/plasma or urine IncRNAs in patients with suspected RCC. Studies of IncRNA-based biomarkers in biological fluids remain a topic of great interest, and circulating IncRNAs have great potential for future use in medicine.

5. Conclusion

IncRNAs are currently considered as potential biomarkers and therapeutic targets in many pathological conditions in humans. The success of their implementation in personalized medicine will largely depend on the availability of a reference method that will effectively validate and verify reliable and specific biomarkers based on IncRNA. By focusing on certain forms of transport (eg, exosomes), improved sampling and isolation of total RNA, combined with absolute quantification without the use of housekeeping genes, may lead to the practical use of circulating IncRNAs as non-invasive biomarkers in oncology in the future. We need to know which biological fluid of the human body (whole blood, plasma/serum, or urine) and for which pathology, in particular tumors of the genitourinary system, is best suited for measuring the expression level of circulating IncRNA. In addition, the discovery of new IncRNAs should be further confirmed by independent studies. Using a panel of two or more selected IncRNAs may be more effective and guarantee specificity for a particular pathology, such as tumors of the genitourinary system. The solution of these issues will make it possible to redirect basic research with IncRNA in oncology to the practical application of IncRNA as therapeutic targets and biomarkers.

Funding

The reported study was funded by RFBR and NSFC, project number 21-515-53017.

Declaration of competing interest

The authors declare that no conflicts of interest exist.

References

[1] J. Samson, S. Cronin, K. Dean, BC020 (BCVRN1) - the shortest, long, non-coding RNA associated with cancer, Noncoding RNA Res 3 (3) (2018) 131–143, https://doi.org/10.1016/j.ncrna.2018.05.003.

[2] A. Heidenreich, P.A. Abrahamsen, W. Antipin, J. Catto, F. Montorsi, H. Van Poppel, M. Wirth, N. Mottet, European Association of Urology, Early detection of prostate cancer: European Association of Urology recommendation, Eur. Urol. 63 (3) (2013) 347–354, https://doi.org/10.1016/j.eururo.2013.06.051.

[3] M. Farhan, M. Aatif, F. Dandawate, A. Ahmad, Non-coding RNAs as mediators of tamoxifen resistance in breast cancers, Adv. Exp. Med. Biol. 1152 (2019) 229–241, https://doi.org/10.1007/978-3-030-20301-6_11.

[4] S. Gagliardi, C. Pandini, M. Garofalo, M. Bordoni, O. Pamarasa, C. Cereda, Long non coding RNAs and ASL: still much to do, Noncoding RNA Res 3 (2) (2018) 206, https://doi.org/10.1016/j.jncb.2019.103214.

[5] M. Wang, T. Huang, G. Luo, C. Huang, X.Y. Xiao, L. Wang, G.S. Jiang, F.Q. Zeng, Long non-coding RNA MEG3 induces renal cell carcinoma cells apoptosis by activating the mitochondrial pathway, J Huazhong Univ Sci Technolog Med Sci 35 (2015) 541–545.

[6] H. Xiao, K. Pan, P. Liu, K. Chen, J. Hu, J. Zeng, W. Xiao, G. Yu, Y. Wang, Y. Zhou, H. Li, Y. Pan, A. Li, Z. Ye, J. Wang, H. Xu, Q. Huang, lncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging mir-200s in clear cell kidney carcinoma, Oncotarget 6 (2015) 38905–38915.

[7] X. Rui, L. Han, P. Tu, S. Shao, J. Leng, LncRNA GAS6-AS2 promotes bladder cancer proliferation and metastasis via GAS6-AS2/miR-298/CD99 axis, J Cell Mol. Med. 23 (2) (2019) 865–876, https://doi.org/10.1111/jcmm.13986.

[8] H. Liao, C. Xu, W. Le, B. Gu, T. Wang, IncRNA CASC11 promotes cancer cell proliferation in bladder cancer through miRNA-150, J. Cell. Biochem. 120 (8) (2019) 13487–13493, https://doi.org/10.1002/jcb.28622.

[9] Z. You, C. Liu, C. Wang, Z. Ling, Y. Wang, Y. Wang, M. Zhang, S. Chen, B. Hu, H. Bai, X. Chen, M. Chen, LncRNA OCAT1 promotes prostate cancer cell proliferation by interacting with DDX5 and MIR-28-SP, Mol. Canc. Therapeut. 18 (12) (2019) 2469–2479, https://doi.org/10.1158/1535-7163.MCT-19-0095.

[10] P. Gu, X. Chen, R. Xie, J. Han, W. Xie, B. Dong, C. Chen, M. Yang, J. Jiang, Z. Chen, J. Huang, T. Lin, IncRNA HOXD-AS1 regulates proliferation and chemo-resistance of castration-resistant prostate cancer via recruiting WDR5, Mol. Ther. 25 (8) (2017) 1959–1973, doi.org/10.1016/j.ymthe.2017.04.016.

[11] Y. Du, X.D. Weng, L. Wang, X.H. Liu, H.C. Zha, J. Guo, J.Z. Ning, C.C. Xiao, LncRNA XIST acts as a tumor suppressor in prostate cancer through sponging miR-23a to modulate RIKP expression, Oncotarget 8 (35) (2017) 94358–94370, https://doi.org/10.18632/oncotarget.21719.

[12] M. Sarfi, M. Abbastabar, E. Khalili, Long noncoding RNAs biomarker-based cancer assessment, J. Cell. Physiol. 234 (10) (2019) 16971–16986, https://doi.org/10.1002/jcp.28417.

[13] M.Y. Kim, Long non-coding RNAs in cancer, Noncoding RNA Res 4 (2) (2019) 45, https://doi.org/10.1016/j.jncb.2019.02.003.

[14] H. Helmsmorett, C. Everaert, N. Lumen, P. Ost, J. Vandesompele, Detecting long non-coding RNAs in prostate cancer liquid biopsies: hype or hope? Noncoding RNA Res 3 (2) (2018) 64–74, https://doi.org/10.1016/j.jncb.2018.05.001.

[15] S. Ren, F. Wang, J. Shen, Y. Sun, W. Xu, J. Liu, M. Wei, C. Xu, C. Wu, Z. Zhang, X. Gao, Z. Liu, J. Hou, J. Huang, Y. Sun, Long non-coding RNA metastasis associated in lung adenocarcinoma transcript 1 derived miniRNA as a novel plasma-based biomarker for detecting prostate cancer, Eur. J. Canc. 49 (13) (2013) 2949–2959, https://doi.org/10.1016/j.ejca.2013.04.026.

[16] G. Li, Y. Zhang, J. Mao, P. Hu, Q. Chen, W. Ding, R. Pu, IncRNA TUC388 is a potential diagnostic biomarker for bladder cancer, J. Cell. Biochem. 120 (10) (2019) 18014–18019, https://doi.org/10.1002/jcb.20104.

[17] S. Zhang, D. Lu, L. Wang, X. Jiang, Y. Zhan, J. Li, K. Yan, W. Duan, Y. Zhao, L. Wang, Y. Wang, Y. Shi, C. Wang, Evaluation of serum exosomal LncRNA-based biomarker panel for diagnosis and recurrence prediction of bladder cancer, J. Cell. Mol. Med. 23 (2) (2019) 1396–1405, https://doi.org/10.1111/jcm.14942.
I. Gareev et al.

[19] J. Wang, K. Yang, W. Yuan, Z. Gao, Determination of serum exosomal H19 as a noninvasive biomarker for bladder cancer diagnosis and prognosis, Med Sci Monit 24 (2018) 5907–5916, https://doi.org/10.12659/MSM.912016.

[20] Y. Wu, Y.Q. Wang, W.W. Weng, Q.Y. Zhang, X.Q. Yang, H.L. Gan, Y.S. Yang, P. Zhang, M.H. Sun, M.D. Xu, C.F. Wang, A serum-circulating long noncoding RNA signature can discriminate between patients with clear cell renal cell carcinoma and healthy controls, Oncogene 36 (2018), e192, https://doi.org/10.1038/onc.2015.48.

[21] S. Rehman, M. Aatif, Z. Rafi, M.Y. Khan, U. Shahab, S. Ahmad, M. Farhan, Effect of.social media on body image and self-esteem among adolescent girls, J. Med. Sci. 20 (2020) 351–356.

[22] M. Xue, W. Chen, X. Li, Extracellular vesicle-transferred long noncoding RNAs in bladder cancer, Clin. Chim. Acta 516 (2021) 34–45, https://doi.org/10.1016/j.cca.2021.01.003.

[23] M. Rasool, A. Malik, S. Zahid, M.A. Basit, A. Asif, Z. Azeem, M. Arshad, A. Raza, M.S. Jamal, Non-coding RNAs in cancer diagnosis and therapy, Noncoding RNA Res 1 (2016) 1–69, https://doi.org/10.1039/c6nr00011a.

[24] M. Rasool, A. Malik, S. Zahid, M.A. Basit, A. Asif, Z. Azeem, M. Arshad, A. Raza, M.S. Jamal, Non-coding RNAs in cancer diagnosis and therapy, Noncoding RNA Res 1 (2016) 1–69, https://doi.org/10.1039/c6nr00011a.

[25] A. Sanchez Calle, Y. Kawamura, Y. Yamamoto, F. Takeshita, T. Ochiya, Emerging roles of long non-coding RNAs in cancer, Expert Rev. Mol. Diagn 11 (2) (2011) 137–144, https://doi.org/10.1586/14737519.2011.543765.

[26] J. Qin, T.L. Williams, M.R. Fernando, A novel blood collection device stabilizes mRNA, microRNA and lncRNA as novel bladder tumor markers, J. Transl. Med. 15 (2017) 141, https://doi.org/10.1186/s12967-017-1018-2.

[27] E. Wieczorek, E. Reszka, mRNA, microRNA and lncRNA as novel bladder tumor markers, J. Transl. Med. 15 (2017) 141, https://doi.org/10.1186/s12967-017-1018-2.

[28] X. Zhou, C. Yin, Y. Dang, F. Ye, G. Zhang, Identification of the long non-coding RNA H19 in human bladder cancer, Expert Rev. Mol. Diagn 16 (6) (2016) 599–607, https://doi.org/10.1080/14737519.2016.1229371.

[29] E. Dinger, J.S. Mattick, Genome-wide profiling of long non-coding RNAs in cancer, Semin. Canc. Biol. 30 (2016) 37–44, https://doi.org/10.1016/j.semcancer.2016.01.002.

[30] Y. Wu, Y.Q. Wang, W.W. Weng, Q.Y. Zhang, X.Q. Yang, H.L. Gan, Y.S. Yang, P. Zhang, M.H. Sun, M.D. Xu, C.F. Wang, A serum-circulating long noncoding RNA signature can discriminate between patients with clear cell renal cell carcinoma and healthy controls, Oncogene 36 (2018), e192, https://doi.org/10.1038/onc.2015.48.

[31] A. Sanchez Calle, Y. Kawamura, Y. Yamamoto, F. Takeshita, T. Ochiya, Emerging roles of long non-coding RNAs in cancer, Expert Rev. Mol. Diagn 11 (2) (2011) 137–144, https://doi.org/10.1586/14737519.2011.543765.

[32] J. Wang, K. Yang, W. Yuan, Z. Gao, Determination of serum exosomal H19 as a noninvasive biomarker for bladder cancer diagnosis and prognosis, Med Sci Monit 24 (2018) 5907–5916, https://doi.org/10.12659/MSM.912016.

[33] Y. Wu, Y.Q. Wang, W.W. Weng, Q.Y. Zhang, X.Q. Yang, H.L. Gan, Y.S. Yang, P. Zhang, M.H. Sun, M.D. Xu, C.F. Wang, A serum-circulating long noncoding RNA signature can discriminate between patients with clear cell renal cell carcinoma and healthy controls, Oncogene 36 (2018), e192, https://doi.org/10.1038/onc.2015.48.

[34] X. Zhou, C. Yin, Y. Dang, F. Ye, G. Zhang, Identification of the long non-coding RNA H19 in human bladder cancer, Expert Rev. Mol. Diagn 16 (6) (2016) 599–607, https://doi.org/10.1080/14737519.2016.1229371.

[35] E. Wieczorek, E. Reszka, mRNA, microRNA and lncRNA as novel bladder tumor markers, J. Transl. Med. 15 (2017) 141, https://doi.org/10.1186/s12967-017-1018-2.

[36] X. Zhou, C. Yin, Y. Dang, F. Ye, G. Zhang, Identification of the long non-coding RNA H19 in human bladder cancer, Expert Rev. Mol. Diagn 16 (6) (2016) 599–607, https://doi.org/10.1080/14737519.2016.1229371.