Translational Research in Urology

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Review

The Promising Role of MicroRNAs, Long Non-Coding RNAs and Circular RNAs in Urological Malignancies

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HIGHLIGHTS

- Non-coding RNA might be a predominant biomarker from a biological standpoint.
- Cancer control is a major challenge for public health.
- Cancers are more curable when detectd early.

ARTICLE INFO

Receive Date: 23 November 2021

Accept Date: 02 February 2022

Avaliable online: 05 March 2022

DOI: 10.22034/TRU.2022.315706.1088

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ABSTRACT

Nowadays, non-communicable diseases are the leading cause of death worldwide. Cancer management has been a significant challenge for public health in the last decade. Aging of the population and Urbanization have induced significant alters in population structure and increased burden of non-communicable diseases, like cancers. For several years, cancer genomics studies traditionally focused on coding genes. An explosion of studies into non-coding RNAs biology has shown that they could function as tumor suppressors and oncogenic drivers in nearly all cancer types. As a result, the uncovering of the role of functional RNAs in the formation and development of cancers is a promising frontier of cancer genetics.

Keywords: Non-Coding RNA; ncRNA; lncRNA; miRNA; circRNA

Introduction

Cardiovascular disease is the primary cause of mortality worldwide. As cardiovascular disease decreases in multiple countries, mortality from cancer will probably become the leading cause of death (1). For the past two decades, it has been shown that cancer arises from the transformation of normal cells into malignant cells in a multi-stage process. These changes result from the various genetic and epigenetic events in proto-oncogenes and tumor suppressor genes that involve numerous etiologies that function at various stages of tumor progression. Cancers are dynamic diseases. During the disease, cancers become more heterogeneous. Therefore, a timely and specific estimation of this malignancy and its development is vital. Intrapatient tumor heterogeneity presents myriad clinical challenges from the diagnostic workup to the treatment of the high grade of cancer disease. So, it is essential to identify the primary genetic changes that cause a tumor to grow and spread. Early genetic mutations occur in all cells, while subsequent changes appear only in some cells. Genetic analysis plays the leading role in determining the risk of developing cancers, screening, and sometimes medical treatment (2). For long periods, Somatic cell mutations can predispose a person to cancer such as breast, prostate, and gastrointestinal cancers. Many tumors can reduce the expression of tumor suppressor genes and lead to loss of function by increased methylation of CpG islands. Histone deacetylase (HDAC) inhibitors, 5-azacytidine, and decitabine have been used to reanimate promoter CpG islands of tumor suppressor genes silenced by methylation. Treatment of malignancies caused loss of function of tumor suppressor genes is too

challenging, although targeted therapies based on the recognition of oncogenic mutations have been expanding. Identifying inferior alterations that induce malignancy or contribute to its proliferation is a high priority (2).

Urologic cancers result from fast and abnormal cell growth that affects the bladder, testicles, prostate, and kidneys. Prostate cancer (PCa), bladder cancer (BC), and renal cell carcinoma (RCC) ranking third, 12th, and 16th, respectively, in terms of global incidence (1).

Renal cell carcinomas (RCC) (also called renal adenocarcinoma, hypernephroma, kidney, or renal cancer) are a common type of kidney cancer in which malignant cells form in tubules of the kidney. RCC accounts for 2 to 3% of all adult cancer. RCC can be divided into three significant subgroups such as chromophobe (chRCC), clear cell (ccRCC), and papillary (pRCC). The 5-year relative survival rate of kidney cancer ranges from 15-50%, depending on the type of cancer, the stage of the tumor, and the selection of treatment. The common symptoms of RCC are flank pain, high blood pressure, abdominal mass, and abnormal liver function (3, 4).

Bladder cancer is among the top ten most common cancer types globally. BC usually starts when normal cells in the bladder lining change and become malignant, forming a tumor mass. It is caused when epithelial cells that line the bladder become malignant. Bladder cancer is divided into muscle-invasive bladder cancer (MIBC) and non-muscle invasive bladder cancer (NMIBC). The five-year cancer-specific survival rate of bladder cancer ranges widely in different stages. The survival rate for patients with bladder cancer depends on disease-related factors, such as the stage and type of BC diagnosed. The survival rate for a patient with stage 1 or 2 bladder cancer over five years is approximately 97 percent. In contrast, the patients with stage 3 or 4 have a lower chance to survive with only a 5-year survival rate of 6% since the cancer cells have already spread or invaded to surrounding tissues and organs beyond where the tumor originated, which make it quite challenging to eliminate or kill Malignant cells. The most common symptoms of bladder cancer are urine, pain with urination, and low back pain (3, 5, 6). In men, germ cells are responsible for producing sperm. Testicular cancer is one of the most common cancers in young adult men. Although this cancer affects males of any age, most of it occurs in men between 14 and 44 (7, 8). Two of the most common germ cell tumors are seminoma and nonseminoma.There are four main types of non-seminomatous germ cell tumors (NSGCT) that can appear alone but most often appear as a "mixed" NSGCT, with more than one type present: choriocarcinomas, Endodermal sinus tumor or yolk sac tumors, teratomas, and embryonal cell carcinomas. Non-seminomatous germ cell tumors are very variable in appearance and prognosis. The success of the treatment will depend on multiple factors, such as the type and stage of cancer. Understanding these data help doctors decide which treatment will work best. Testicular cancer's most common presenting symptom is a painless lump or swelling (9-11).

Prostate cancer (PC) is the second most common no-cutaneous cancer diagnosis in males and the fifth leading cause of death worldwide. PC is a form of cancer that begins in the prostate gland cells, which is found only in males. Due to the gradual progression of prostate cancers and their nonspecific symptoms, they are usually detected at an advanced stage. Early detection of cancer elevates the chances for successful treatment. Therefore, a timely urologic cancer diagnosis is essential for good clinical outcomes and patient experience (3, 12).

Although remarkable progress has been made in the recent decade towards detecting proposed hallmarks of cancer progression and therapy, the clinical management of cancer remains one of the significant clinical challenges for the 21st. Some modern treatment modalities comprise radiation therapy, hormonal therapy, surgery, chemotherapy, immunotherapy, and targeted therapy. Although advances in cancer treatment, overall patient survival is still low (13, 14).

Early diagnosis of cancers is key to improving the survival rate of patients. The main challenge for cancer early detection is that they usually have no symptoms in their early stages. Therefore, the presence of a non-invasive diagnostic biomarker with high specificity and sensitivity holds promise for curing cancer and reducing the cost of treatment (3).

As the basis of genetics, the central dogma (i.e., DNA→RNA→protein) describes the flow of genetic information. Alexander Rich has first proposed the concept of the "RNA world" in the 1960s. He has pointed up RNA's potential in performing various vital tasks without the direct performance of proteins or DNA. In 1986, Walter Gilbert, the biochemist, and Nobel laureate, developed Rich's hypothesis and termed it "RNA World." The RNA world hypothesis challenged the "central dogma" view of the biological function of RNA. The RNA world hypothesis suggests that life on earth is initiated with a simple RNA molecule. The main reasoning behind the hypothesis is that RNA could replicate itself and carries the genetic information as it is needed for the construction of a protein (15). In humans, less than 2% of DNA comprises protein-coding genes. The other word vast majority of the genome often gives rise to RNA that does not produce proteins, called non-coding RNA (ncRNA) (16).

Over the last ten years, a large part of the genome was considered evolutionary junk DNA, regions of DNA that are not translated into functional proteins, but recent findings proved that these fragments could be transcribed into different kinds of ncRNAs. This evidence shows that the DNA - mRNAs correlation is significantly more complicated than predicted initially (17).

Functional RNAs perform a varied repertoire of

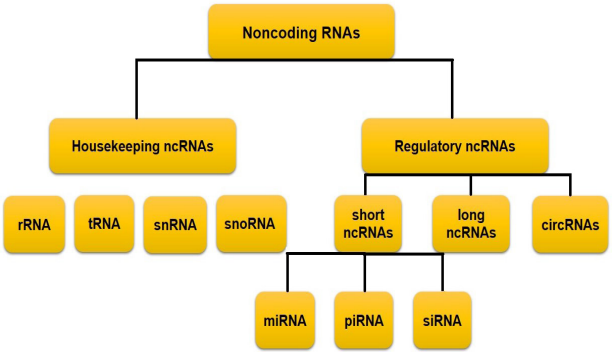

Figure 1. Classification of ncRNAs. Different types of non-coding RNAs on the basis of their function and their size

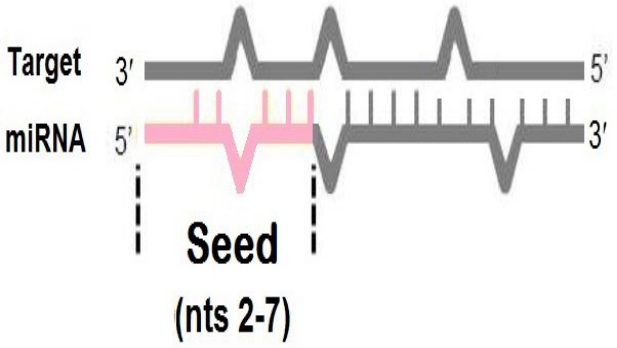

Figure 2. Seed sequences control the interactions between mRNAs and miRNAs. This region is mostly defined as the 2–7 nucleotides at the 5′ end of miRNA (16)

critical cellular processes. Although it is generally thought that proteins exchange most genetic information, the Latest documents propose that the lion's share of the genomes of complex organisms is transcribed into non-coding RNAs. Many of which are either alternative RNA splicing or processed into smaller products (18).

Classification of non-coding RNAs

There are various types of functional RNAs classified into different categories based on their lengths, Cellular function, and shapes. NcRNAs have been classified into regulatory and housekeeping ncRNAs. Housekeeping ncRNAs are usually small, constitutively expressed, and necessary for cell survival, such as snRNA (small nuclear), tRNA (transfer), rRNA (ribosomal), and small nucleolar RNAs (snoRNAs). Regulatory RNAs are expressed in tissues during developmental stages and certain diseases. Based on their shape and length, functional RNAs can be classified into long non-coding RNAs, short non-coding RNAs, and circular RNAs (16) (Figure 1).

In recent years, non-coding RNAs, particularly microRNAs, lncRNAs, and circRNAs, were associated with urologic malignancies occurrence and development. This review mainly focused on the importance of miRNAs, circRNAs, and lncRNAs. This may provide a foundation for developing particular diagnostic tools and more robust therapeutic strategies in the future.

MicroRNA

MiRNAs (MicroRNAs) are the large class of endogenously short ncRNAs, with 18 to 25 nucleotides in length that can act as a gene-regulator in animals and plants by pairing to the mRNAs of coding genes to direct their post-transcriptional repression (19). In addition to histone modifications and DNA methylation, small ncRNAs can act as a part of the epigenetics mechanism.

It has been shown that individual miRNAs can target hundreds of mRNAs and regulate the expression of complementary messenger RNAs involved in a functional interacting pathway regulated by a miRNA(20). Furthermore, microRNA can affect other miRNA and noncoding RNAs (21). MiRNAs can be divided into three main classes: more than half of the human microRNAs are placed in intergenic regions, and the other in intronic and exonic areas (22).

Other types of small nRNAs have been detected in plants and animals. siRNAs and piRNAs like miRNAs function as guide RNAs within the occurrence called RNA silencing (19).

A miRNA matches with its target in the seed sequence. This sequence is defined as the 2–7 nucleotides at the 5′ end of miRNA that can pair with the 3′ end of its messenger RNA target (19) (Figure 2). MiRNAs can regulate gene expression by mRNA cleavage, mRNA degradation, mRNA deadenylation, translational repression started by miRNA-guided and thus can play a role in regulating a vast range of biological mechanisms (23). According to the report, miRNAs have many roles in the biological mechanisms related to tumorigenesis, including inflammation, apoptosis, cell-cycle regulation, stress response, differentiation, Immune response, insulin secretion, and synthesis of neurotransmitters, are promising candidates for biomarker development (21). Despite the Regulatory performance of miRNAs as oncogenes or tumor suppressors, they may be regulated by tumor suppressors or oncogenes under certain conditions (21).

The Discovery of the lin-4, the first recognition microRNA in early 1993, by Ambros and his colleagues in Caenorhabditis elegans triggered a revolution in molecular biology. After seven years, let-7 miRNA was reported by Reinhart et al. in C. Elegans (19).

MiRNA Biogenesis

MicroRNA production is a multi-step process. Initial processing of All animal miRNA occurs in the nucleus. Canonical miRNA biogenesis begins with generating the large primary transcript (pri-miRNA), which is 5′ capped and 3′ polyadenylated in structure. miRNA genes are transcripted by RNA polymerase II Most of the time, but a

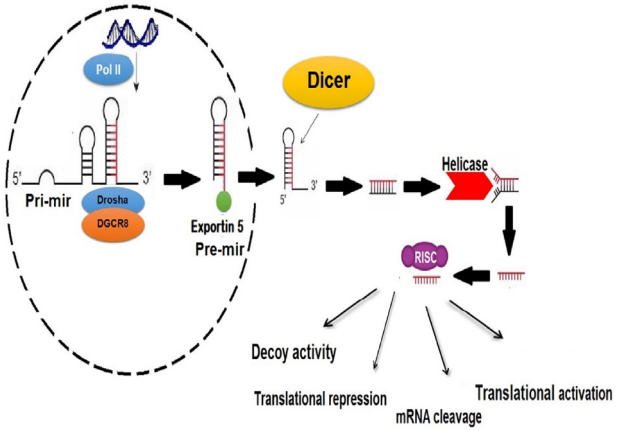

Figure 3. MiRNA Biogenesis. MiRNA biogenesis onset with the generation of the transcript of pri-miRNA. The Drosha complex cleaves the pri-miRNA to produce the pre-miRNA. The pre-miRNA is shuttled from the nucleus into the cytoplasm and processed by Dicer. The mature miRNA is loaded into the Argonaute to form a miRNA-induced silencing complex (RISC). Depending on miRNA-target complementarity, the RISC mediates mRNA degradation or translational repression (19, 20, 24).

small group associated with Alu repeats can be transcribed by RNA polymerase III. The microprocessor complex, consisting of Drosha and DGCR8, identifies specific motifs within the pri-miRNA and cleaves it at the stem of the hairpin structure, generating a 5′-monophosphate and a 3′-2-nt overhang on pre-miRNA, and releases the hairpin structure. This new miRNA structure is the pre-miRNA (precursor microRNA) Exportin5 and RanGTP shuttle pre-miRNAs from the nucleus into the cytoplasm to produce the mature miRNA duplex. The Dicer, RNase III endonuclease, removes the terminal loop of pre-miRNA in the cytoplasm. Finally, miRNAs appear as short RNA duplexes termed miRNA duplexes. After the duplex is unwound, either the 5p or 3p strands of the miRNA duplex are incorporated into the Argonaute (AGO) family to form a miRNA-induced silencing complex (RISC) and guides RISC to target mRNA. Generally, the strand which will remain preferentially loaded into AGO is the active strand, and it is named the leading strand or guide strand. The unloaded strand gets degraded by cellular machinery, and it is named the passenger strand (19, 20, 24) (Figure 3).

Identifying miRNAs, targets and functions

MiRNAs are an attractive topic for system modelling and computer science because of their roles in gene silencing mechanisms through the logic of complementary base pairing. The interactions between miRNA and mRNA are usually controlled by the seed sequence in the 5′ untranslated region of micro-RNA. Negatively regulation of gene expression is controlled by miRNA at the post-transcriptional level via either translational repression or mRNA degradation (20).

Given the crucial role of target prediction in miRNA functional characterization, various computer algorithms depend on the information from perfect pairing, evolutionary sequence conservation, and GC content of the target site that have been developed in the past years (25).

MiRNA can be extracted from body fluids, tissues, and cells (20). MiRNAs are secreted through exosomes and extracellular vesicles in stable bodily fluids by cells. For example, they have been extracted from blood, follicular fluid, urine, bile, and other bodily fluids. These secreted miRNAs can either be taken up by cells in the surrounding tissue or reach distant sites and are being checked out for efficacy as biomarkers for related diseases. Furthermore; microRNAs in body fluids may have communicated with their surroundings tissues (22). Multiple technological platforms have been progressed to detect miRNA levels in vivo and in vitro, such as Northern blotting, RNAse protection assay, microarrays, qPCR in situ hybridization, or bead-based detection (17).

Epigenetics and MicroRNAs

Genes expression at DNA and chromatin levels is regulated by epigenetic mechanisms, so it is necessary to study the epigenetic mechanisms in regulating the gene expression of malignant cells and the effect of some drugs on them. The definition of this mechanism was first introduced in the 1940s by Waddington. Epigenetics is described as changes in the expression of genes that are not attributed to alterations of the DNA sequences. Epigenetic inheritance is crucial in many biological processes such as aging, differentiation, silencing of the X chromosome of female mammals, and genomic imprinting (26).

Due to the role of microRNAs in growth, differentiation, and cell death, it has been shown that epigenetic factors can alter the expression of microRNAs in cells directly or indirectly. Deficiencies in these mechanisms can trigger the activation or inhibition of different signaling pathways and Cause diseases such as cancer. Epigenetic changes are involved in tumorigenesis by altering the activity of specific genes and inducing genomic instability. Pathologic epigenetic changes are conceived to replace chromosomal disorders and mutations in disrupting gene function. In cancer, these include hypermethylation of the CpG islands in the promoter regions of tumor suppressor genes, global DNA hypomethylation in tumors, chromatin alterations, and loss of imprinting. It has not been fully understood yet whether changes in the expression of microRNAs are the result of a pathological condition of cancer or cancer is the leading cause of these expression changes (26).

Epi-miRNAs as novel classes of miRNAs might be influential in cancer development. The expression of microRNAs can be altered by epigenetic changes like CpG islands methylation located in the promoter. For

Table 1. Consequences of microRNA dysregulation in human malignancies

microRNA Dysregulation	Targets	Examples
miRNA↑	Tumor suppressors↓	PTEN،P22،P57↓
miRNA↓	Oncogenes↑	BCL2, RAS, MYC↑
miRNA↓	DNA methyl transferases↑	p16, FHIT↓
miRNA↓	Chromatin silencers↑	Tumor suppressors↓

Table 2. OncomiRs/ TSmiRs involved in cancer formation and progression

Cancer	miRNA	Expression	MRNA target	Pathway	Reference
Bladder	miR-129	Up	SOX4, GALNT1	Signal transduction protein expression	(29)
	miR-221	Up	TRAIL pathway	Apoptosis	(29)
	miR-101	Down	EZH2	Gene expression	(29)
	miR-19a	Down	PTEN	Apoptosis mTOR pathway	(29)
	miR-125b	Down	E2F3	apoptosis proliferation	(29)
	miR-34a	Down	CDK6	Cell cycle control	(29)
	miR-145	Down	CBFB, PPP3CA, CLINT1	Signal transduction	(29)
Kidney	miRs-141/200	Down	ZEB2	EMT	(29)
	miR-23b	Up	Proline oxidase	Apoptosis	(29)
	miR-29b	Up	TIS11B	Angiogenesis	(29)
	miR-438-3p	Up	BBC3	Angiogenesis	(29)
Prostate	miR-20a	Up	E2F1-3	Apoptosis	(29)
	miR-148a	Up	CAND1	Cell cycle control	(29)
	miR-521	Up	Cockayne syndrome protein A	DNA repair	(29)
	miR-32	Up	BCL2L11(Bim)	Apoptosis	(29)
	miR-7	Down	ERBB-2 (EGFR, HER2)	Signal transduction	(29)
	miR-101	Down	EZH2	Gene expression	(29)
	miR-107	Down	Granulin	proliferation	(29)
Testicles	miR-372	**Up**	LAST2	Cell cycle control	(23)
	miR-373	Up	LAST2	Cell cycle control	(23)

instance, the expression of miR-127 is downregulated by methylation of the promoter in bladder cancers. However, its expression can be improved by using hypo ethylating agents such as 5-azacitidine. BCL6 as a candidate target of miR-127 is translationally suppressed after miR-127 upregulation by 5-azacitidine treatment; Therefor, it is inferred that suppression of histone deacetylase and DNA demethylation can activate the expression of miRNAs acting as tumor suppressors and inhibit the expression of BCL6 oncoprotein (27).

Micro RNAs in cancers

During the past few years, it has been demonstrated that miRNA plays a role in regulating a vast range of pathological and biological mechanisms, including the formation and development of most, perhaps all, human malignancies. MiRNAs relate to promoting malignancies by losing and gaining function in the Different mechanisms. MiRNA expression is dysregulated in human malignancies through different processes, such as epigenetic silencing, transcription factors disruption that target specific miRNAs, deletion/ amplification of miRNA genes, and defects in the miRNA biogenesis machinery. Malignant cells tend to Irregular expression of miRNA gene, so these small molecules provide essential opportunities for the improvement of miRNA-based therapies in the future (2) (Table 1,2).

The Preliminary evidence of the role of miRNAs in human cancer was discovered in the pathogenesis of chronic lymphocytic leukaemia (CLL). The 13q14.3 Deletions are the most frequent cytogenetic aberrations in More than 80% of B-CLL patients. Further research in this area indicates that the CLL suppressor gene was precisely within this small genomic region, with no protein-coding genes. These results showed that the miR-15a/16-1 cluster gene is deleted in approximately 50 percent of

Table 3. Functional annotation of the target genes and the relative miRNAs

Annotation	miRNA	Targets	Function	Reference
Apoptosis	miR-133b, miR-203	BCL2L2	Tumor suppressor	(34)
	miR-195, miR-203, miR-497	BIRC5	Tumor suppressor	(34)
	miR-200c ، miR-218	BMI1	Tumor suppressor	(34)
	miR-708	CASP2	Oncogene	(34)
	miR-145	SOCS7	Tumor suppressor	(34)
	miR-129	SOX4	Tumor suppressor	(34)
	miR-1	SRSF9	Tumor suppressor	(34)

cases, resulting in reduced expression of both miRNAs, and they function as a tumor suppressor gene in CLL (2). Regulation of miRNA-mediated gene expression is crucial for the cellular response to environmental stresses such as oxidative stress, starvation, DNA damage, and hypoxia. Interestingly, many miRNAs contribute to or repress the cancer phenotype by regulating the expression of tumor suppressors or oncogenes to act as either oncogene (oncomiRs) or tumor suppressor genes (Tsmir) depending on the functions of their targets. Commonly, oncomiRs are overexpressed in cancers, while TsmiRs are under-expressed (17, 28, 29) (Table 2). For instance, miR452-5p is one of the most impressive oncomirs in renal cell carcinoma. The overexpression of it leads to increase migration of tumor cells. The SMAD4 expression as a miRNA target is negatively associated with migration, invasion, and RCC metastasis. P65 can bind to the miR-452-5p promoter and stimulate the miR-452-5p expression or suppress the expression of SMAD4 and its downstream gene, SMAD7 (30).MiRNAs are often located at common breakpoint regions or fragile regions of chromosomes prone to chromosomal deletion, translocation, loss of heterozygosity, and amplification (31). Before describing microRNAs as a tumor suppressor or oncogene, it must be determined which cell or tissue to be examined because tissue type is essential for microRNA function. For example, the let-7 family of miRNA performs as a tumor suppressor, while one member of the family, let-7a-3, has an oncogenic function (17).

MiRNAs and Apoptosis

The term apoptosis comes from the Greek words "απο" and "πτωσιζ," meaning falling off, and refers to the falling of leaves and fruits from trees when they become ripe. Apoptosis is generally defined as the most common kind of programmed cell death by which the body eliminates damage without local inflammation. Cell shrinkage and pyknosis are the most characteristic feature of apoptosis.

This mechanism typically occurs during development and aging to ensure a homeostatic balance between cellular death and cell formation. Defects in the apoptotic process can lead to abnormal cell growth, proliferation, cancer, autoimmune disorders, etc. The apoptotic genes could be divided into two big subcategories: proapoptotic genes are involved in apoptosis, and the other group causes an inability to apoptosis and is called antiapoptotic. The balance between the pro and antiapoptotic signals within and around the cell determines whether a cell will undergo apoptosis or survive. Apoptotic-related miRNAs were divided into proapoptotic and antiapoptotic groups. miR-14 is one of the first known miRNAs associated with apoptosis in Drosophila (32-34) (Table 3).

Long non-coding RNAs (lncRNAs)

Long non-coding RNAs (lncRNAs) are a heterogeneous group of non-coding RNA with lengths exceeding 200 nucleotides that are not translated into proteins (35). Most lncRNAs are typically generated by RNA polymerase II but scarcely are some of them mediated by RNA polymerase III. The lncRNAs have little or no open reading frame (ORF) (36). Although most of them contain caps and poly-A tails at their 5’ and 3’ends, respectively, recent research identified lncRNAs that undergo unusual processing within their 5’ and 3’ends (37). Sequencing technology development and statistical analysis of its data have demonstrated that lncRNAs play a crucial role in regulating cellular pathways and biological mechanisms (38). Many ncRNAs are longer than 200 bp, like repeat or pseudogene-derived transcripts. Nonetheless, the abbreviated term lncRNA, often referred to as lincRNA, for long intergenic ncRNA, does not uniformly apply to all of these (39).

Due to the essential role of lncRNA in gene expression, they are abnormally expressed in various human malignancies, and suppressors amplify them (35). The essential biological processes, such as epigenetic control of gene expression, regulation of gene expression at the transcriptional or post-transcriptional level, genomic imprinting, RNA splicing, editing, turnover, cell differentiation, and development, are regulated or controlled by complex mechanisms in which ncRNAs are involved. Their various roles of lncRNAs in the regulation of cell invasion, migration, proliferation, and metastasis have allowed them to be known as diagnostic markers or therapeutic targets in malignancies (40). LncRNAs are involved in oncogenic events in genitourinary

malignancies, such as androgen receptor signaling in prostate cancer, activation of HIF pathway (hypoxia-inducible factor) in renal cell carcinoma, and invasiveness in bladder cancer, as well as several other progression and survival mechanisms (41).

Characterisation of lncRNAs

Most of the lncRNAs share many characteristics, including:

•Polyadenylation
•Epigenetic marks similar to a transcribed gene
•Regulation by specific transcription factors
•Tissue-specific expression patterns
•Transcription via RNA polymerase II (39).

LncRNAs have been classified into different categories based on their function, subcellular localization, and genomic localization.

Genomic localization

Depending on the locations on the genome, lncRNAs are classified into five types:

1) sense long noncoding RNAs: Sense lncRNAs originate from exons of the sense strand of protein-coding genes, and they could overlap with other exon transcripts.
2) Intronic long noncoding RNAs: They emanate from the introns of protein-coding genes.
3) Intergenic long noncoding RNAs are transcribed from the region between two protein-coding genes.
4) Bidirectional long noncoding RNAs emanate from the same promoter but in the opposite direction.
5) Antisense long noncoding RNAs: They originate from the opposite strand of coding or none coding genes. They can moderate their sense of gene expression.

Antisense lncRNAs can appear in 3 forms

1) Transcripts from the antisense strand of protein-coding genes overlap an exon of a sense gene through lncRNAs' exons.
2) Transcripts from the intron of a sense gene do not have exon-exon overlap with this sense gene.
3) Transcripts cover the entire sequence of a sense gene through an intron (38, 42) (Figure 4).

Function of lncRNAs

LncRNAs often act as important modulators to activate or suppress protein-coding genes. Their expression levels have a remarkable impact on cis (on neighboring) or trans (distal) coding genes. Cis-acting RNAs are constricted to the site of synthesis and exert their function on genes, one or more, on the same chromosome. while trans-acting RNAs move and enforce their function on other chromosomes (36).

Scaffold lncRNAs

These transcripts interact with various molecules and

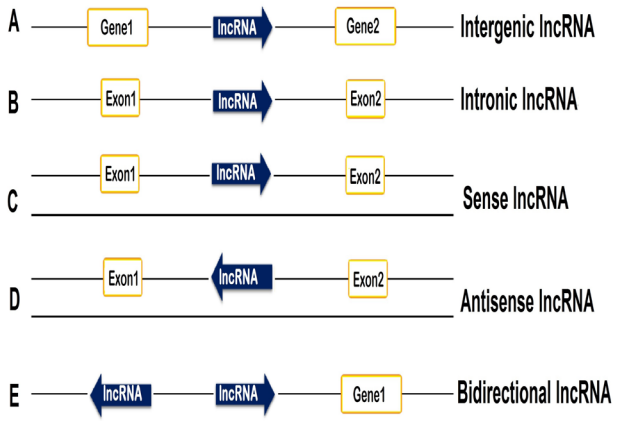

Figure 4. Genomic localization of lncRNAs. (A) Intergenic lncRNAs are transcribed in the genomic region between two coding genes; (B) Intronic lncRNAs originate from the introns of protein-coding genes; (C) Sense lncRNAs originate from exons of the sense strand of protein-coding genes and they could overlap with other exon transcripts; (D) Antisense lncRNAs are transcribed from the opposite strand of coding genes; (E) Bidirectional lncRNAs are transcribed from the opposite strand, in the opposite direction and within 1 kb of the promoter of coding genes (33,37).

provide platforms for aggregating multiple component complexes like ribonucleoprotein complexes. They may impact transcriptional repression or activation.

Guide lncRNA

Guide long non-coding RNAs are critical for the proper localization of factors at specific genomic loci to perform different functions such as chromatin modification and transcriptional regulation. These transcripts direct specific protein complexes to their target genes to precise locations in the genome at either adjacent or distant (cis or trans) sites from their locus of transcription.

Allosteric lncRNAs

Transcripts from the Allosteric class of lncRNAs interact with transcription factors or enzymes, causing structural modifications that modify their activity. They only bind their protein partner without interacting with the enzyme's substrate or the transcription factor's genomic target.

Signaling lncRNAs

Some LncRNAs are transcribed under specific temperature and cellular conditions, so they are packed into exosomes, transmitted to other cells, and used as markers.

Precursor

LncRNAs can code for functional micro peptides or process into miRNAs, acting in physiological settings.

Micro RNA sponge

LncRNAs can impair microRNA activity through

Table 4. Role of lncRNAs in the cancer development and progression

lncRNA	Cancer Type	Identified functions	Function	Chromosomal Localization	Reference
PCA3	Prostate	Unknown	Biomarker	9q21-q22	(36,53)
PCAT-1	Prostate	Promotes cell proliferation inhibits BRCA2	Oncogene	8q24.21	(36,53)
MEG3	Prostate	inhibits the progression of cancer by modulating miR-9-5p/QKI-5 axis	Tumor suppressor	14q32	(38,49,53)
	Bladder	Repression of MDM2			
	Kidney	Promotion of p53-dependent and p53-independent apoptosis			
DANCR	Prostate	Downregulation of metalloproteinase inhibitor	Oncogene	4q12	(4,38)
KCNQ1OT1	Bladder	KCNQ1OT1 aggravates cell proliferation and migration through modulating miR-145-5p/ PCBP2 axis	Oncogene	11p15	(36)
MALAT1	Bladder	Direct binding and activation of SUZ12 Upregulation of ZEB1, ZEB2 and SNAI2	Oncogene	11q13.1	(36,38)
	Kidney	Downregulation of multiple tumour suppressor genes through EZH2 binding			
	Prostate	Epigenetic reprogramming through EZH2			
XIST	Testicles	hypomethylation	Biomarker	Xq13.2	(5)

sequestration, effectively derepressing targets of that miRNA, therefore, upregulating the corresponding proteins.

Decoy

This type of lncRNAs is known as “molecular sinks” for target molecules. This type of activity occurs when lncRNAs bind and titrate target molecules away to suppress their function.

Recruitment of chromatin complex

Some of the lncRNAs bind to proteins with a chromatin-modifying role and recruit their catalytic activity to specific sites in the genome, thereby modulating chromatin states and impacting gene expression.

These long-chain molecules have also been shown to be involved in other physiological mechanisms like mRNA degradation, splicing regulation, and inhibition of translation mechanisms (36, 42, 43).

Subcellular Localization

LncRNAs can be found in many tissues and show condition-specific and Tissue-specific expression patterns more than protein-coding genes. They are present in different cellular compartments. According to the subcellular location, they are classified as cytoplasmic and nuclear types. Most of the lncRNAs tend to be located in the nucleus. Only small numbers of lncRNA are present can be detected exclusively in the cell nucleus, such as XIST and MALAT (44, 45).

Epigenetics and lncRNA

LncRNAs can mediate epigenetic processes by recruiting histone-modifying enzymes and DNA methyltransferases, called chromatin-remodeling complex, establishing chromatin conformation patterns. Misregulation of Some of lncRNA is associated with tumorigenesis. LncRNAs could influence gene expression or chromosome activity changes by DNA and protein modification, recruiting protein, RNA interaction, etcetera. CpG island hypermethylation has been reported in more than half of all cancer type (46).

LncRNA and genomic Imprinting

Imprinting is an epigenetic process in which one parent's copy of a gene is epigenetically silenced. Imprinted genes involve histone modification and DNA methylation without changing the genetic sequence. Approximately 25 imprinted genes have been identified to date, and loss of imprinting [LOI] is seen frequently in a large variety of human cancers. For example, increased expression of H19 is a marker of early recurrence in bladder cancer. The H19 and IGF2 genes are placed in the human chromosome at 11p15.5. The imprinted clusters in this area are implicated in a vast spectrum of human cancers. DNA methylation level of the DMR in the H19 gene could be higher in the patients with bladder cancer compared with normal bladder tissue (47).

LncRNA in cancers

lncRNAs are implicated in various diseases like cancers and therefore have emerged as potential tools for possible therapeutic intervention. For a disease as complex as cancer, emerging technologies show mutations on genomic sites that do not encode proteins but produce lncRNAs. Analysis of the functional pathways involved in lncRNAs shows that These molecules interact with chromatin, proteins, or RNAs to exert their cellular effects to modulate proliferation, migration, differentiation, apoptosis, and cell death (48).

Cancer susceptibility is partially due to the inheritance of genetic factors, and their effects may vary depending on the type of cancer. For example, Xu and colleagues found that the lncRNA, called TINCR, has been related to the formation and progression of bladder cancer. Furthermore, lncRNA TINCR SNPs have been correlated with bladder cancer susceptibility risk. The risk of BC in people carrying the rs2288947 G allele is 2.32 times higher than the A allele carriers, and The BC susceptibility risk of the rs8113645 T allele carriers is 0.33 times compared with the C allele carriers. The lncRNA TINCR rs2288947 A>G is associated with increased susceptibility, and rs8113645 C > T is associated with decreased bladder cancer risk (49).

LncRNAs have been found extensively in various genome regions, including gene deserts. The Parts of the genome that do not produce proteins are called gene deserts. They constitute an estimated 25% of the entire genome. Before discovering the RNA capture-Seq method, verifying cancer-related lncRNAs was challenging because of the diversity and extent of distribution of long ncRNAs in the genome (like exist in the gene deserts) and their low expression in some cases. This method helps to identify a large number of cancer-related lncRNAs which were previously unknown, but their performance remained unknown (50, 51).

The abnormal expression of many long functional RNAs in the various tumors determines the spectrum of disease promotion and may act as an autonomous predictor of disease outcome. Most lncRNAs have been known to play a functional role in regulating gene expression from the past till now. Therefore, they are mentioned as new goals in diagnosing and treating this disease. LncRNAs may serve as master gene regulators through various mechanisms mentioned earlier (52) (Table 4). In the following, we will briefly describe the function of some of these molecules.

Meg3: This gene is a maternally expressed imprinted gene that contains a 356-nucleotide nuclear retention element. This gene is expressed in many normal tissues, such as the Pituitary gland, but its expression is lost in multiple cancer cell lines of various tissue origins like bladder cancer. It also interacts with the MDM2 and inhibits it, Increases transcription of P53 target genes, and regulates their expression.

Deletion of meg3 increases angiogenesis in vivo. Experimental evidence has proven that MEG3 is a lncRNA tumor suppressor (53, 54).

MALAT 1: MALAT 1 (metastasis-associated lung adenocarcinoma transcript 1), also known as NEAT2 (noncoding nuclear-enriched abundant transcript 2), is 8,708 bp length and located on chromosome 11q13.1. It is expressed in most human tissue, but its expression is most prominent in the nervous system.

MALAT1 could serve as an oncogene and modulate cancer-related signaling pathways. Mutations in the MALAT1 gene are common in numerous cancerous tissues, such as bladder, kidney, and prostate cancers. Knocked down of this lncRNA can decrease Slung, ZEB1, and ZEB2 while increasing E-cadherin expression. MALAT1 activates cell migration and promotes EMT by activating WNT signaling in vitro. MALAT1 suppression considerably triggers cell cycle arrest in the G0 / G1 phase. Recent studies have begun to reveal that urine MALAT1 can function as a promising diagnostic biomarker for prostate cancer. MALAT1 has a suppressive effect on sex steroid hormone receptor genes, like pS2 and PSA that has been correlated with prostate cancer (55, 56). LINC00467: The expression level of LINC00467 is related to tumorigenesis and overall patient survival time. LNC00467 could regulate the AKT3 expression and affect total AKT phosphorylation in testicular cancer. So, it can develop the migration of TGCT cells (57).

KCNQ1OT1: KCNQ1 overlapping transcript 1, also known as KCNQ1OT1, is an ncRNA expressed from the paternal allele. Human chromosome band 11p15. Five houses a large cluster of genes, such as various lncRNAs and transcription factors often involved in developing urological malignancies. Activation of KCNQ1OT1 could trigger cell migration, EMT, and proliferation while Suppressing cell death. Increased expression of E-cadherin and decreased expression of N-cadherin is caused by a defect in KCNQ1OT1. LncRNA performs as a competing endogenous RNA of microRNA and regulates the function of miRNA downstream target gene. For example, KCNQ1OT1 facilitate cell migration by regulating the expression of miR145-5p/PCBP2 in bladder cancer (58).

LncRNA and apoptosis

Overexpression or downregulation of lncRNA could induce apoptosis in cancer cells. It suggests that lncRNAs can be considered therapeutic targets for various malignancies. It has been reported that Overexpressed lncRNA PlncRNA-1 promotes the proliferation and cell death of PC cells. Another example is LncRNA GAS5, which is a stimulant of apoptosis in prostate cancer (59). Multiple technological platforms have been developed for detection of miRNA levels in vitro and in vivo, such

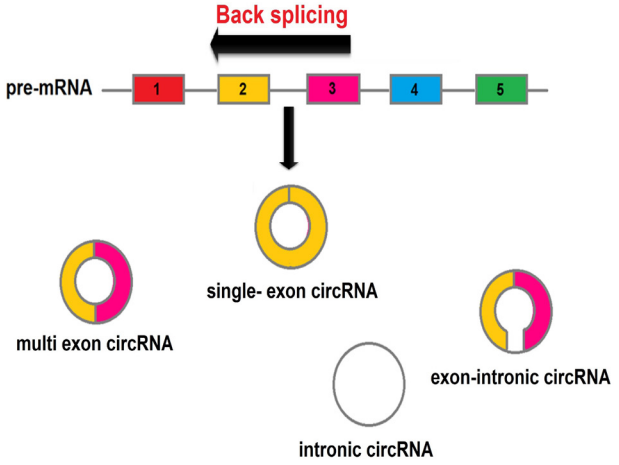

Figure 5. Biogenesis of circRNAs. The back-splicing process can take place because of exon skipping mechanism, which leads to lariat formation.

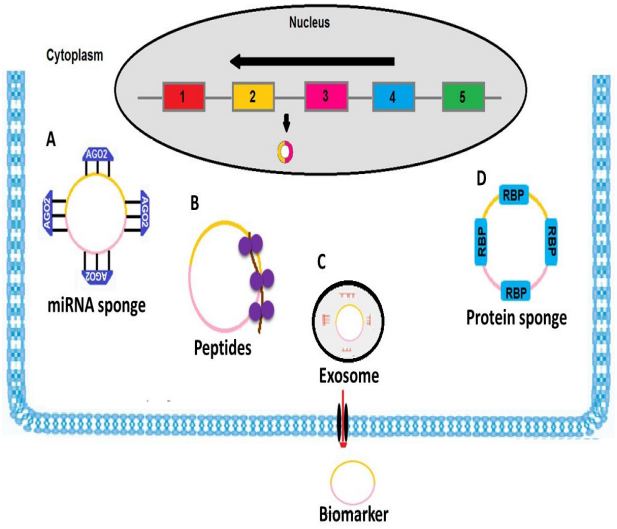

Figure 6. Functions of circRNAs. (A) circRNAs can act as miRNA sponges and subsequently control the expression of their target genes (B) the peptides or proteins can originate from different circRNA isoforms (c) circRNAs exist in the bodily fluids, and can function as molecular biomarkers (D) circRNAs bind to various proteins and mediate their functions.

as next-generation sequencing, expression microarrays, tiling array, RNAi, RIP assay, ChIRP ، northern blot, and CLIP- Seq (60, 61).

Circular RNAs

In 2012, the development of RNA-Seq and statistical analysis of its data and biochemical analysis in the next step had led to appear a complete surprise which named Circular RNA (62). circRNAs are a recently discovered form of RNA formed by exon back-splicing (circularization) and observed to regulate transcription in human cells (63). Back splicing is regarded as a kind of alternative splicing. They are single-stranded RNA molecules with specific functions and structures that were considered by-products of aberrant splicing. CircRNAs are evolutionarily conserved and more stable than linear RNAs because the lack of free terminal ends (lack of caps and poly-A tails) induces resistance to degradation by ribonuclease (1, 63, 64). Circular RNAs are a novel group of endogenous and covalently-closed circular molecules of single-stranded RNA with tissue-specific and cell-specific expression. They are generated by a non-canonical splicing event called back-splicing from linear mRNA.the 5′ and 3′ ends of circular RNAs are joined together to form loop structures (Figure 5). It has been found that the Circular RNAs are highly resistant to exonucleases and show the substantial stable state (65).

circRNAs were detected in the transcriptomes of metazoans, from worms and flies to mice, monkeys, and humans. Identification of DCC tumor suppressor gene transcripts was the first example of spliced circular RNAs in humans. These initial reports, in 1991, described the serendipitous discovery of transcripts produced from non-canonical splicing (scrambled exons).

During the following years, a handful of expressed genes were discovered in mammals using the RNA sequencing method, and they have been demonstrated to express isoforms of circRNAs at low levels. This method has allowed researchers to quickly examine the quantity and sequences of RNA in a sample. The best circular transcripts are determined in rodents.

Over the following years, a few genes were characterized to be processed into circRNA isoforms. Such as ANRIL, the MLL, ETS-1, NCX1 in monkeys, Sry gene, CDR1 loci, Cytochrome P450, mbl in Drosophila, and Dystrophin genes. All examples of human circular transcripts are expressed at low levels compared to the conventional linear isoform (62).

According to the origin sequences of circRNAs, they are classified into three types:

1.exonic circRNA: this type originates from only exons and is located in the cytoplasm

2.intronic circRNA: this type originates from the introns and is located in nuclei

exon-intronic circRNA (EIciRNA): this type originates from the introns at the area between exons and is mainly located in nuclei (66) (Table 5).

Characterisation of circRNA

Compared to linear RNAs, a circRNA has the following features:

1. It is resistant to RNA exonucleases since it has a covalent loop structure without 5'cap and 3'poly A tail.
2. Tissue-specific and developmental-stage specific.

Table 5. Origin sequences of circRNAs

Name	Type	Location	Joint site	Function
ciRNA	Intron	Nucleus	2'-5' phosphodiester bond	Regulation of gene transcription
EIciRNA	Exon-intron	Nucleus	3'-5' phosphodiester bond	Regulation of gene transcription
ecRNA	Exon	Cytoplasms	3'-5' phosphodiester bond	MiRNA sponges; interaction with RBP; translation

Table 6. Role of circRNAs in the cancer development and progression

circRNA	Cancer	miRNA	miRNA targets	Biological function	Function	Reference
circTCF25	Bladder	miR-103a-3p, miR-107	CDK6	Increase proliferation and migration	Oncogene	(69)
circMYLK	Bladder	miR-29a	VEGFA	Relieve the repression and activate Ras/ ERK pathway	Oncogene	(1)
circRIP2 (circ_0005777)	Bladder	miR-1305	TGF-β2, smad3	Promote tumor growth, metastasis and increase expression of TGF-β2, N-cadherin, Vimentin, smad3 and p-smad3	Oncogene	(1)
circFAM114A2 (circ_0001546)	Bladder	miR-762	ΔNP63	Reduce tumor growth	Tumor suppressor	(1,69)
circPCNXL2 (circ_406752)	Kidney	miR-153	ZEB2	Enhance tumor growth	Oncogene	(1)
circ_001895	Kidney	miR-296-5p	SOX12	Increase tumor growth, improve expression of N-cadherin	Oncogene	(1)
circMYLK (circ_0141940)	Kidney	miR-513a-5p	VEGFC	Enhance tumor growth and metastasis, increase expression of VEGFC	Oncogene	(1)
circABCC4 (circ_0030586))	Prostate	miR-1182	FOXP4	Increase cell proliferation, invasion and migration	Oncogene	(1)
circFOXO3 (circ_0006404)	Prostate	miR-29a-3p	SLC25A15	Increase cell proliferation and inhibit apoptosis	Oncogene	(1)
circFMN2 (circ_0005100)	Prostate	miR-1238	LHX2	Increase tumor growth and reduce the expression of E-cadherin	Oncogene	(1)

3. Predominantly found in an extracellular fluid such as blood and urine.
4. Evolutionary conservation in mice and humans.
5. Primarily located in the cytoplasm, sometimes in the nucleus
6. Often developing from the long exons and occasionally from the introns
7.The average half-life period is much more extended than that of mRNAs.

These features are common to most circRNAs and are not found in all types (1, 66).

Function

RNA circles may be prevalent invariant biological mechanisms because they have distinct properties that can be advantageous. RNA circles contain abundant miRNA binding sites to absorb the microRNAs like a sponge and regulate the expression of relevant target genes. Additionally, they have been found to function as miRNA reservoirs to regulate miRNA availability. It means that they can augment the accessibility of miRNAs for binding to target mRNA and repressing them. These Molecules can change the activity of proteins by interacting with them. In addition, they function as a translation template for protein or peptides synthesis and produce functional proteins. RNA circles act as molecular biomarkers for detecting and treating disease because they are in bodily fluids. Numerous studies have confirmed the crucial role of CircRNAs in tumor development, metastasis, and epithelial-mesenchymal transmission (EMT) (1) (Figure 6).

RNA circles in cancers

Studies of cancer metabolism in the 1920s have revealed that Altered energy metabolism provided required nutrients and energy to sustain cellular functions. Although metabolic pathways associated with carbohydrate, lipid, and amino acid are necessary for tumorigenesis, the major metabolic pathway in cancer cells is aerobic glycolysis (Warburg effect). These cells

Table 7. Summary and comparison list of the databases

Data bases	Sites	Data bases	Sites
miRNAs		**lncRNAs**	
miRWalk	http://mirwalk.uni-hd.de/	**lncRNome**	http://genome.igib.res.in/lncRNome/
miRBase	https://www.mirbase.org/	**NcFANs**	http://www.noncode.org/ncFANs/
miRDB	http://mirdb.org/	**NRED**	http://jsm-research.imb.uq.edu.au/nred/cgi-bin ncrnadb.pl
lncRNAs		**CircRNAs**	
LncRRIsearch	http://rtools.cbrc.jp/LncRRIsearch/	**CircBase**	http://www.circbase.org
lncRNADisease	http://cmbi.bjmu.edu.cn/lncrnadisease	**CircInteractome**	https://circinteractome.nia.nih.gov
Rfam	http://rfam.sanger.ac.uk/	**CircPedia**	http://www.picb.ac.cn/rnomics/circpedia/
Noncode	http://www.noncode.org/	**Starbase**	http://starbase.sysu.edu.cn/mirCircRNA.php
Rnadb	http://research.imb.uq.edu.au/rnadb/	**SomaMIR v2.0**	http://compbio.uthsc.edu/SomamiR

tend to lactate production and glucose uptake, even in oxygen. So, Cancer metabolism is an essential aspect of tumorigenesis. Metabolic pathways are regulated not only by carcinogenic proteins but by ncRNAs. Among them, circular RNA has become the focus of attention. RNA circles play a significant role in regulating cellular metabolism via binding with microRNAs or proteins (67, 68). They are essential in the formation and progression of cancers. The circRNA–miRNA–mRNA interaction network analysis suggests that circRNAs modulate carcinogenesis in multiple ways, especially by acting as miRNA sponges and regulating the driver genes. So, any disruption in the regulation of this network can play an essential role in causing cancer (1, 69)(Table 6).

Impairment of transcription factor activity Triggers the progression of malignant cells. For example, FAM114A2 upregulates the ΔNP63 (a transcription regulator that activates p53 target genes). Overexpression of circFAM114A2 hampered the migration and invasion of UCB cells in vitro and in vivo. MiR-762 could pair to TP63 and adjust it. circFAM114A2 increases the expression of ΔNP63 (an isoform of TP63 in UCB) by sponging miR-762. CircFAM114A2 performs as a ceRNA of miR-762 in regulating the expression of ΔNP63, so it inhibited bladder cancer promotion via circFAM114A2/miR-762/ΔNP63 axis (68).

Activation of the EMT process and the VEGF signaling pathway promotes cancer development. CircPRRC2A and circMYLK can increase the expression of N-cadherin and vitamins. These molecules abolish the tumor suppression effect of miR-514a-5p/miR-6776-5p and miR-513a-5p in renal cell carcinoma. In addition, TRPM3 and VEGFC could be upregulated by circPRRC2A and circMYLK, respectively. Moreover, these circRNAs facilitate tumor progression and aggressiveness in patients with RCC (1).

Role of circRNAs as Biomarker

CircRNAs are exceptionally stable molecules and are resistant to degradation by exonuclease. Circular RNAs can be transported from tissues into different body fluids by exosomes. Most of them are highly conserved, have tissue-specific expression patterns, and are distinctly different between patients with cancer and healthy controls (70). These features make RNA circles ideal biomarkers for the detection of human disease.

Databases

With the development of high-throughput sequencing technology, many ncRNA-related biological datasets have accumulated. Multiple ncRNA-related databases have been created (Tables 7). This Database allows users to check the ncRNAs expression, location, function, and other information related to them.

Conclusions

The emerging world of ncRNA is deceptive and displays a new level of the complexity of nature. Non-coding RNAs have been found to have roles in a large variety of biological processes. ncRNAs promote migration and metastasis of urological cancers. Numerous studies have documented that ncRNAs correlate with cancerous phenotypes of cancer patients. ncRNAs may act as tumor suppressors and oncogenic drivers in every primary cancer type. Due to the features of specific expression patterns in cancers and relatively high stability, ncRNAs could be considered as non-invasive diagnostic biomarkers for cancers. Increased knowledge about the role of non-coding RNAs in molecular processes leads to a better understanding of tumor biology and could provide new therapeutic targets for treating urological cancers.

Author's contributions

All authors contributed equally.

Acknowledgments

None.

Conflict of interest
The author declares that there is no conflict of interest.

Funding
There is no funding.

Ethical statements
Not applicable.

Data availability
Data will be provided on request.

Abbreviations

3′-UTR	3′-untranslated region
5′-UTR	5′-untranslated region
AR	Androgen receptor
BC	Bladder cancer
ChiRP-Seq	Chromatin Isolation by RNA purification
circRNA	Circular RNA
CLIP	Cross-linking immunoprecipitation
CLL	Chronic lymphocytic leukemia
FISH	Fluorescence in situ hybridization
HIF	Hypoxia-inducible factor
lncRNA	Long non-coding RNA
miRNA	MicroRNA
mRNA	Messenger ribonucleic acid
ncRNA	Non-Coding RNA
PC	Prostate cancer
PCR	Polymerase chain reaction
Qpcr	Quantitative polymerase chain reaction
RCC	Renal cell carcinoma
RIP	RNA immunoprecipitation
RNA	Ribonucleic acid
RNAi	RNA interference
RNA-Seq	RNA sequencing
TGCC	Testicular germ cell cancer

References

1. Yang L, Zou X, Zou J, Zhang G. Functions of circular RNAs in bladder, prostate and renal cell cancer (Review). Mol Med Rep. 2021;23(5).
2. Croce CM. Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet. 2009;10(10):704-14.
3. Ouyang H, Zhou Y, Zhang L, Shen G. Diagnostic Value of MicroRNAs for Urologic Cancers: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015;94(37):e1272.
4. Petejova N, Martinek A. Renal cell carcinoma: Review of etiology, pathophysiology and risk factors. Biomedical papers. 2016;160(2):183-94.
5. Chen Z, Chen X, Xie R, Huang M, Dong W, Han J, et al. DANCR Promotes Metastasis and Proliferation in Bladder Cancer Cells by Enhancing IL-11-STAT3 Signaling and CCND1 Expression. Mol Ther. 2019;27(2):326-41.
6. Zhang R, Wang J, Jia E, Zhang J, Liu N, Chi C. lncRNA BCAR4 sponges miR-370-3p to promote bladder cancer progression via Wnt signaling. Int J Mol Med. 2020;45(2):578-88.
7. Cheng L, Albers P, Berney DM, Feldman DR, Daugaard G, Gilligan T, et al. Testicular cancer. Nat Rev Dis Primers. 2018;4(1):29.
8. Kawakami T, Okamoto K, Ogawa O, Okada Y. XIST unmethylated DNA fragments in male-derived plasma as a tumour marker for testicular cancer. Lancet. 2004;363(9402):40-2.
9. Bremmer F, Behnes CL, Schweyer S. [Non-seminomatous germ cell tumours]. Der Pathologe. 2014;35(3):238-44.
10. Gillis AJM, Rijlaarsdam MA, Eini R, Dorssers LCJ, Biermann K, Murray MJ, et al. Targeted serum miRNA (TSmiR) test for diagnosis and follow-up of (testicular) germ cell cancer patients: a proof of principle. Mol Oncol. 2013;7(6):1083-92.
11. Fakhr Yasseri A, Behtash N, Asadi M, Mohseni MG. Compound Nevus with Severe Dysplastic Feature in Mixed Germ Cell Tumor: A Case Report. Translational Research in Urology. 2020;2(2):69-73.
12. Tamehri Zadeh SS, Taheri D, Shivarani S, Khatami F, Kazemi R. Liquid Biopsy in Prostate Cancer Diagnosis and Prognosis: A Narrative Review. Translational Research in Urology. 2020;2(4):139-46.
13. Zhan Y, Chen Z, Li Y, He A, He S, Gong Y, et al. Long non-coding RNA DANCR promotes malignant phenotypes of bladder cancer cells by modulating the miR-149/MSI2 axis as a ceRNA. J Exp Clin Cancer Res. 2018;37(1):273.
14. Gu C, Zhao K, Zhou N, Liu F, Xie F, Yu S, et al. UBAC2 promotes bladder cancer proliferation through BCRC-3/miRNA-182-5p/p27 axis. Cell Death & Disease. 2020;11(9):733.
15. Piras V, Tomita M, Selvarajoo K. Is central dogma a global property of cellular information flow? Frontiers in Physiology. 2012;3(439).
16. Panni S, Lovering RC, Porras P, Orchard S. Non-coding RNA regulatory networks. Biochim Biophys Acta Gene Regul Mech. 2020;1863(6):194417.
17. Schaefer A, Jung M, Kristiansen G, Lein M, Schrader M, Miller K, et al. MicroRNAs and cancer: current state and future perspectives in urologic oncology. Urol Oncol. 2010;28(1):4-13.
18. Mattick JS, Makunin IV. Non-coding RNA. Hum Mol Genet. 2006;15 Spec No 1:R17-29.
19. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136(2):215-33.
20. Lu TX, Rothenberg ME. MicroRNA. J Allergy Clin Immunol. 2018;141(4):1202-7.
21. Di Leva G, Garofalo M, Croce CM. MicroRNAs in Cancer. Annual Review of Pathology: Mechanisms of Disease. 2014;9(1):287-314.
22. Mohr AM, Mott JL. Overview of microRNA biology. Semin Liver Dis. 2015;35(1):3-11.
23. Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. Dev Biol. 2007;302(1):1-12.
24. Rusek AM, Abba M, Eljaszewicz A, Moniuszko M, Niklinski J, Allgayer H. MicroRNA modulators of epigenetic regulation, the tumor microenvironment and the immune system in lung cancer. Mol Cancer. 2015;14:34.

25. Wiemer EA. The role of microRNAs in cancer: no small matter. Eur J Cancer. 2007;43(10):1529-44.
26. Moutinho C, Esteller M. MicroRNAs and Epigenetics. Adv Cancer Res. 2017;135:189-220.
27. Yang N, Coukos G, Zhang L. MicroRNA epigenetic alterations in human cancer: one step forward in diagnosis and treatment. Int J Cancer. 2008;122(5):963-8.
28. Loh HY, Norman BP, Lai KS, Rahman N, Alitheen NBM, Osman MA. The Regulatory Role of MicroRNAs in Breast Cancer. Int J Mol Sci. 2019;20(19).
29. Catto JW, Alcaraz A, Bjartell AS, De Vere White R, Evans CP, Fussel S, et al. MicroRNA in prostate, bladder, and kidney cancer: a systematic review. European urology. 2011;59(5):671-81.
30. Zhai W, Li S, Zhang J, Chen Y, Ma J, Kong W, et al. Sunitinib-suppressed miR-452-5p facilitates renal cancer cell invasion and metastasis through modulating SMAD4/SMAD7 signals. Mol Cancer. 2018;17(1):157.
31. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci U S A. 2004;101(9):2999-3004.
32. Obeng E. Apoptosis (programmed cell death) and its signals - A review. Braz J Biol. 2021;81(4):1133-43.
33. Ambros V. The functions of animal microRNAs. Nature. 2004;431(7006):350-5.
34. Enokida H, Yoshino H, Matsushita R, Nakagawa M. The role of microRNAs in bladder cancer. Investigative and clinical urology. 2016;57 Suppl 1(Suppl 1):S60-S76.
35. Yang X, Xie Z, Lei X, Gan R. Long non-coding RNA GAS5 in human cancer. Oncol Lett. 2020;20(3):2587-94.
36. Dastmalchi N, Safaralizadeh R, Nargesi MM. LncRNAs: Potential Novel Prognostic and Diagnostic Biomarkers in Colorectal Cancer. Curr Med Chem. 2020;27(30):5067-77.
37. Yin QF, Yang L, Zhang Y, Xiang JF, Wu YW, Carmichael GG, et al. Long noncoding RNAs with snoRNA ends. Mol Cell. 2012;48(2):219-30.
38. Cao Y, Tian T, Li W, Xu H, Zhan C, Wu X, et al. Long non-coding RNA in bladder cancer. Clin Chim Acta. 2020;503:113-21.
39. Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. Cancer Discov. 2011;1(5):391-407.
40. Dianatpour A, Ghafouri-Fard S. Long Non Coding RNA Expression Intersecting Cancer and Spermatogenesis: A Systematic Review. Asian Pac J Cancer Prev. 2017;18(10):2601-10.
41. Flippot R, Beinse G, Boilève A, Vibert J, Malouf GG. Long non-coding RNAs in genitourinary malignancies: a whole new world. Nat Rev Urol. 2019;16(8):484-504.
42. Bresesti C, Vezzoli V, Cangiano B, Bonomi M. Long Non-Coding RNAs: Role in Testicular Cancers. Front Oncol. 2021;11:605606.
43. Romero-Barrios N, Legascue MF, Benhamed M, Ariel F, Crespi M. Splicing regulation by long noncoding RNAs. Nucleic Acids Res. 2018;46(5):2169-84.
44. Hutchinson JN, Ensminger AW, Clemson CM, Lynch CR, Lawrence JB, Chess A. A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. BMC Genomics. 2007;8:39.
45. Dinger ME, Pang KC, Mercer TR, Mattick JS. Differentiating protein-coding and noncoding RNA: challenges and ambiguities. PLoS Comput Biol. 2008;4(11):e1000176.
46. Chen Z, Chen X, Xie R, Huang M, Dong W, Han J, et al. DANCR Promotes Metastasis and Proliferation in Bladder Cancer Cells by Enhancing IL-11-STAT3 Signaling and CCND1 Expression. Mol Ther. 2019;27(2):326-41.
47. Byun H-M, Wong H-L, Birnstein EA, Wolff EM, Liang G, Yang AS. Examination of IGF2 and H19 Loss of Imprinting in Bladder Cancer. Cancer Research. 2007;67(22):10753.
48. Nandwani A, Rathore S, Datta M. LncRNAs in cancer: Regulatory and therapeutic implications. Cancer Lett. 2021;501:162-71.
49. Xu C, Liu M, Jia D, Tao T, Hao D. lncRNA TINCR SNPs and Expression Levels Are Associated with Bladder Cancer Susceptibility. Genet Test Mol Biomarkers. 2021;25(1):31-41.
50. Ozawa T, Matsuyama T, Toiyama Y, Takahashi N, Ishikawa T, Uetake H, et al. CCAT1 and CCAT2 long noncoding RNAs, located within the 8q.24.21 'gene desert', serve as important prognostic biomarkers in colorectal cancer. Ann Oncol. 2017;28(8):1882-8.
51. Yang G, Lu X, Yuan L. LncRNA: a link between RNA and cancer. Biochim Biophys Acta. 2014;1839(11):1097-109.
52. Zhang A, Xu M, Mo YY. Role of the lncRNA-p53 regulatory network in cancer. J Mol Cell Biol. 2014;6(3):181-91.
53. 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):2093-100.
54. Wu M, Huang Y, Chen T, Wang W, Yang S, Ye Z, et al. LncRNA MEG3 inhibits the progression of prostate cancer by modulating miR-9-5p/QKI-5 axis. J Cell Mol Med. 2019;23(1):29-38.
55. Chen D, Xu T, Chang HH, Song Q, Zhu Y, Han Y, et al. The Role of MALAT1 in Cancer. Journal of Cancer Science and Clinical Therapeutics 2019;3:5-27.
56. Martens-Uzunova ES, Böttcher R, Croce CM, Jenster G, Visakorpi T, Calin GA. Long noncoding RNA in prostate, bladder, and kidney cancer. European urology. 2014;65(6):1140-51.
57. Bo H, Zhu F, Liu Z, Deng Q, Liu G, Li R, et al. Integrated analysis of high-throughput sequencing data reveals the key role of LINC00467 in the invasion and metastasis of testicular germ cell tumors. Cell Death Discov. 2021;7(1):206.
58. Wang J, Zhang H, Situ J, Li M, Sun H. KCNQ1OT1 aggravates cell proliferation and migration in bladder cancer through modulating miR-145-5p/PCBP2 axis. Cancer Cell Int. 2019;19:325.
59. Rossi MN, Antonangeli F. LncRNAs: New Players in Apoptosis Control. International Journal of Cell Biology. 2014;2014:473857.
60. Spizzo R, Almeida MI, Colombatti A, Calin GA. Long non-coding RNAs and cancer: a new frontier of translational research? Oncogene. 2012;31(43):4577-87.
61. Xiu B, Chi Y, Liu L, Chi W, Zhang Q, Chen J, et al. LINC02273 drives breast cancer metastasis by epigenetically increasing AGR2 transcription. Mol Cancer. 2019;18(1):187.
62. Salzman J. Circular RNA Expression: Its Potential Regulation and Function. Trends Genet. 2016;32(5):309-16.
63. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB, Kjems J. The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet. 2019;20(11):675-91.
64. Su Y, Feng W, Shi J, Chen L, Huang J, Lin T. circRIP2 accelerates bladder cancer progression via miR-1305/Tgf-β2/smad3 pathway. Molecular Cancer. 2020;19(1):23.
65. Suzuki H, Aoki Y, Kameyama T, Saito T, Masuda S, Tanihata J, et al. Endogenous Multiple Exon Skipping and Back-Splicing at the DMD Mutation Hotspot. Int J Mol Sci. 2016;17(10).
66. Greene J, Baird A-M, Brady L, Lim M, Gray SG, McDermott R, et al. Circular RNAs: Biogenesis, Function and Role in Human Diseases. Frontiers in Molecular Biosciences. 2017;4.
67. Kato Y, Maeda T, Suzuki A, Baba Y. Cancer metabolism: New insights into classic characteristics. Jpn Dent Sci Rev. 2018;54(1):8-21.
68. Yu T, Wang Y, Fan Y, Fang N, Wang T, Xu T, et al. CircRNAs in cancer metabolism: a review. J Hematol Oncol. 2019;12(1):90.
69. Ng WL, Mohd Mohidin TB, Shukla K. Functional role of circular RNAs in cancer development and progression. RNA Biol. 2018;15(8):995-1005.
70. Fang J, Qi J, Dong X, Luo J. Perspectives on Circular RNAs as Prostate Cancer Biomarkers. Front Cell Dev Biol. 2020;8:594992.

Author (s) biosketches

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How to cite this article
Azodian Ghajar H, Koohi Ortakand R. The Promising Role of MicroRNAs, Long Non-Coding RNAs and Circular RNAs in Urological Malignancies.2022 Feb4(1):9-23.
DOI: 10.22034/TRU.2022.315706.1088
URL: https://www.transresurology.com/article_144211.html