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REVIEW

Non-coding RNAs in human health and disease: potential function as biomarkers and therapeutic targets

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Abstract

Humandiseases have been a critical threat from the beginning of human history. Knowing the origin, course of action and treatment of any disease state is essential. A microscopic approach to the molecular field is a more coherent and accurate way to explore the mechanism, progression, and therapy with the introduction and evolution of technology than a macroscopic approach. Non-coding RNAs (ncRNAs) play increasingly important roles in detecting, developing, and treating all abnormalities related to physiology, pathology, genetics, epigenetics, cancer, and developmental diseases. Noncoding RNAs are becoming increasingly crucial as powerful, multipurpose regulators of all biological processes. Parallel to this, a rising amount of scientific information has revealed links between abnormal noncoding RNA expression and human disorders. Numerous non-coding transcripts with unknown functions have been found in addition to advancements in RNA-sequencing methods. Non-coding linear RNAs come in a variety of forms, including circular RNAs with a continuous closed loop (circRNA), long non-coding RNAs (lncRNA), and microRNAs (miRNA). This comprises specific information on their biogenesis, mode of action, physiological function, and significance concerning disease (such as cancer or cardiovascular diseases and others). This study review focuses on non-coding RNA as specific biomarkers and novel therapeutic targets.

Keywords Non-coding RNA · Biomarker · And Drug discovery

Abbreviations

ncRNA	Non-coding RNA
lncRNA	Long non-coding RNA
miRNA	MicroRNA
circRNA	Circular RNA
snRNA	Small nuclear RNA
snoRNA	Small nucleolar RNAs
siRNA	Small interfering RNA
rRNA	Ribosomal RNA
piRNA	PIWI-interacting RNA
FANTOM	Functional Annotation of the Mammalian Genome
ENCODE	Encyclopedia of DNA Elements
Nt	Nucleotide

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Introduction

History of RNA biology

In 1958, Francis Crick established the central dogma of molecular biology by discovering the sequence of events in the passage of genetic material contained in DNA to the functioning of biological processes through proteins. However, with the development of new technologies and robust next-generation sequencing, large international consortiums such as the Functional Annotation of the Mammalian Genome (FANTOM) and the Encyclopaedia of DNA Elements (ENCODE) have described pervasive transcription (that 80% of the DNA is transcribed into RNA but only a 1.5% of that RNA translates into protein) (Carninci et al. 2005; Hangauer et al. 2013). Recent technological advances, like next-generation deep sequencing, have shown that the bulk of the genome is translated into RNAs. The universe of RNA is divided into two halves: (1) RNAs with coding potential and (2) RNAs without coding potential, sometimes known as non-coding RNAs, because of only 1 and 2% of the human genome codes for proteins (The ENCODE Project Consortium 2012). Although mRNAs have been studied in depth, most RNAs are ncRNAs. Even though

ncRNAs were formerly regarded as "evolutionary junk," new research shows that they substantially impact several molecular pathways. According to the hypothesis known as the "RNA universe," RNA was the earliest form of life, and as DNA became more solid, RNA's function as a messenger was left unfilled. However, it was eventually discovered that RNA is the most practical possibility in disease, epigenetics, and unknown regulatory features since it has a wide range of latent catalytic capabilities and can store genetic information (Bhatti et al. 2021). During evolution, RNA is thought to have evolved alongside proteins and DNA (Robertson and Joyce 2010). Understanding their intricate relevance in numerous biological processes, including homeostasis and development, is critical (Amaral et al. 2013). Figure 1 demonstrates the molecular events relate to non-coding RNA (Li et al. 2021a, b; Chhabra 2021).

A relatively broad size criterion is used to classify ncRNAs into two subclasses. Small or short non-coding RNAs (ncRNAs) are ncRNAs that are less than 200 nucleotides (nt), while long non-coding RNAs are ncRNAs that are more than 200 nt (lncRNAs). These two groups are quite different

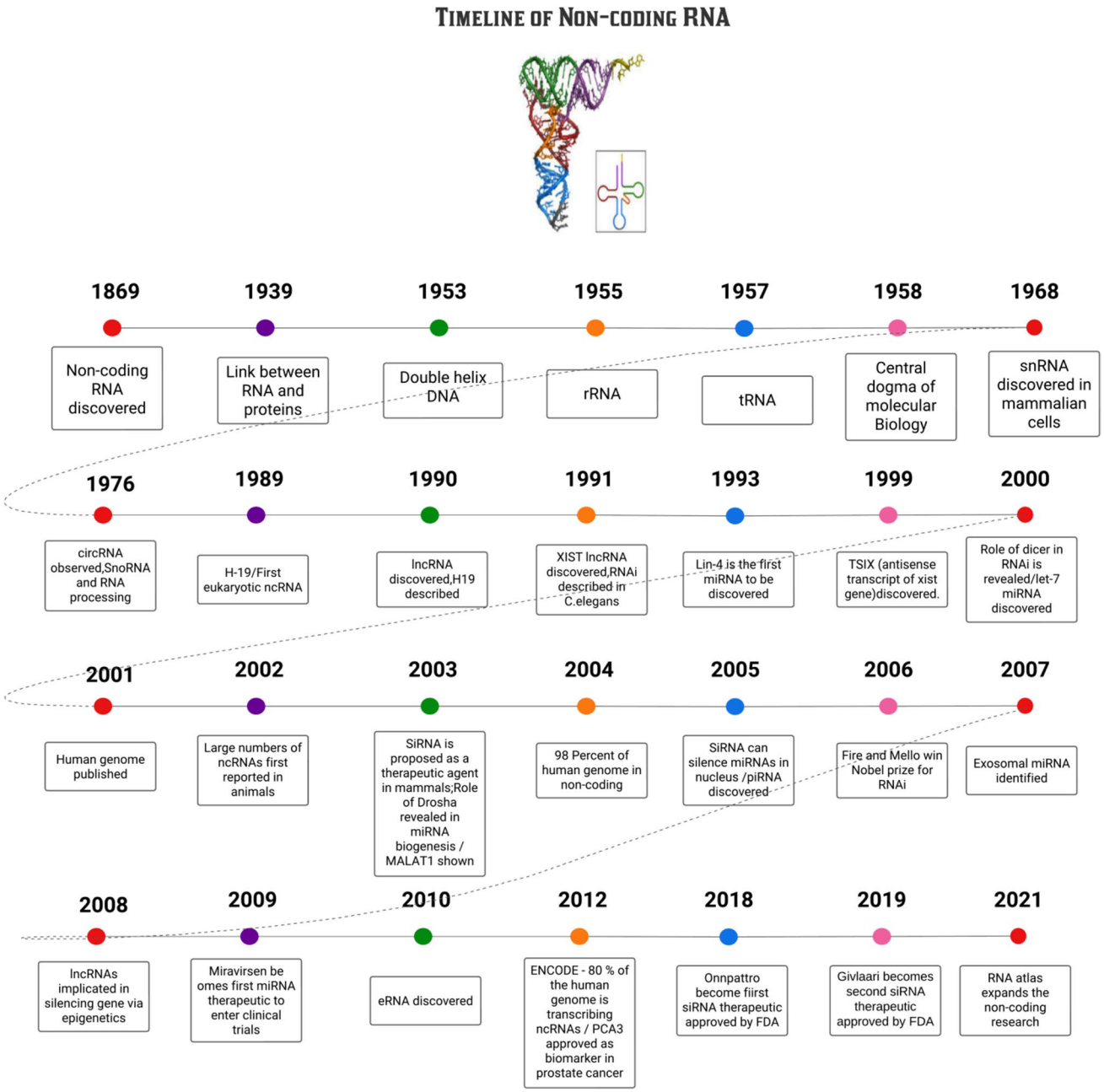

Fig. 1 Timeline of molecular discoveries of non-coding RNA

from one another. LncRNAs can be as significant as several kilobases, and small ncRNAs can be as small as a few to 200 nt. The most well-known class of tiny ncRNAs, microRNAs (miRNAs), have a length of 20 nucleotides or less and have undergone substantial research (Kim et al. 2009). The other non-coding such as siRNA and piRNA. The complexity of these animals' physiology, characteristics, and development, from lower non-chordates to humans, produces an increase in introns and intergenic sequences that are translationally modified by alternative splicing processes, leading to a further decrease in the size of this proteome (Mattick 2001).In addition, eukaryotes have more sophisticated and complex systems for RNA processing, trans induction, DNA methylation, imprinting, RNA interference (RNAi), post-transcriptional gene silencing, chromatin modification, gene editing, splicing, dosage compensation, gene regulation mechanisms, and transcriptional gene silencing (Mattick 2004). Non-coding RNA act as regulatory signal messengers for the stimuli received at sensory genetic elements (Guttman et al. 2011). The evolutionary history of prokaryotes supports their continued reliance on protein-based regulatory architecture, in contrast to eukaryotes, who have evolved new regulatory features and mechanisms to control the expression of phenotypic traits, the penetrance and expressivity of disease, and developmental programming using a variety of ncRNAs. Therefore, research on ncRNA about these linked pathways is essential to comprehend their function in health and disease (GAGEN 2005).

Distribution and types of ncRNA

RNA comes in a variety of forms in live cells. ncRNAs are typically split into two domains based on their transcript length: short ncRNAs (under 200 nucleotides) and long ncRNAs (over 200 nucleotides). ncRNA is important in several processes, including RNA maturation, RNA processing, signaling, gene expression, and protein synthesis (Kung et al. 2013; Morris and Mattick 2014). The amount of ncRNA and the degree of species conservation are remarkably correlated. According to estimates, each cell has 107 ncRNA molecules, most of which are snRNA, snoRNA, miRNA, rRNA, and lncRNA. Although about 53,000 distinct human lncRNAs identified, only about 1000 are present in adequate quantities to legitimately support their functional significance (Djebali et al. 2012). Other types of RNA and their specificities are mentioned in this study (Bhatti et al. 2021). The overview of non-coding RNA and its functions is mentioned in Table 1. The different types of RNA are mentioned in Fig. 2.

Biogenesis and functions of different types of ncRNA

RNA molecules are much more than just a blueprint for protein production. Since non-coding transcripts are expected to function similarly to proteins and can regulate the majority of cellular functions, RNA may interact with DNA, proteins, and other RNA molecules to form three-dimensional (3D) structures. The two main regulatory RNA groups—small and long ncRNAs—are partly defined by their length. Additionally, functional ncRNAs with lengths between 20 and thousands of nucleotides have grown significantly in number and classification over the past ten years. This review focuses on significant ncRNAs such as miRNA, lncRNA, and circRNA. Few other RNA will be mentioned such as piRNA, snRNA, snoRNA, and siRNA. This ncRNA will play a significant role in developmental processes and disease conditions. Numerous genes are involved in the production of ncRNAs across the whole human genome, and

Table 1 Overviewof non-coding RNA and its functions

Types of RNA	Full form	Functions	References
Housekeeping ncRNA			
rRNA	ribosomal RNA	Translational machinery	Fu 2014
tRNA	Transfer RNA	Amino acid carriers	
snRNA	Small nuclear RNA	RNA processing	
snoRNA	Small nucleolar RNA	RNA modifications	
TRNA	Telomere RNA	Chromosome end synthesis	
Regulatory ncRNA			
miRNA	MicroRNAs	RNA stability and translation control	Fu 2014
lncRNA	Long non-coding RNA	Imprinting, epigenetics, nuclear structure	
circRNA	Circular RNA	Inhibiting miRNA activity	
endo-siRNA	Endogenous siRNA	RNA degradation	
rasiRNA	Repeat associated-derived RNA	Transcriptional control	
eRNA	Enhancer-derived RNA	Regulation of gene expression	
piRNA	PIWI-interacting RNA	Silencing transposon and mRNA decay	
PATs	Promoter-associated RNA	Transcription initiation and pause release	

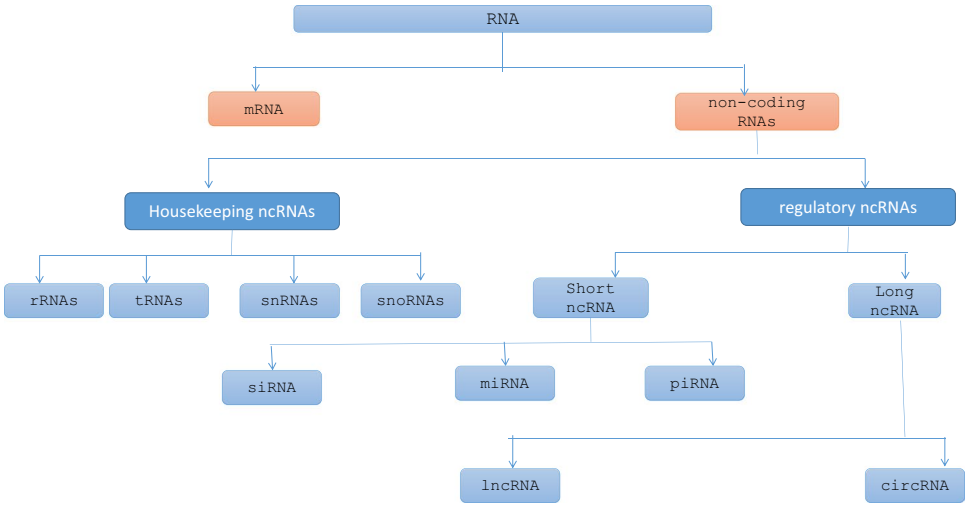

Fig. 2 Different types of RNA and major non-coding RNAs

there may potentially be distinct transcriptional units that function independently. Transcription, nuclear maturation, export to the cytoplasm for processing, and production of functional RNA are all steps in this biogenesis process. The detailed mechanism of non-coding RNA biogenesis is mentioned in this paper (Bhatti et al. 2021). The description of specific ncRNA and the description of biogenesis are mentioned in Table 2. Non-coding RNA is an integral part of genomics and proteomics. According to the "RNA world" hypothesis, RNA may have played a role in the emergence of life, which must be able to carry and duplicate its genetic material (Joyce 1989). In contemporary organisms that have evolved to use more effective methods to copy and express their genetic material along the central axis from DNA to RNA to protein, ncRNAs seem to have retained the majority, if not all, of their original characteristics and functions. Many RNA functions are transferred to proteins while others are kept because of the exploration of selective benefits of proteins and RNA during evolution. To grasp ncRNA function and mechanism, it may be instructive to compare ncRNA function with that of proteins.

Comparison of miRNA, lncRNA, and circRNA in RNA biology

The mechanistic characterization of lncRNAs is far less thorough than that of miRNAs. This is partly because lncRNAs can control gene expression through intricate biochemical pathways at various levels inside the cell. Despite being present in a group of species (Guttman and Rinn 2012), such as plants (Swiezewski et al. 2009), yeast (Houseley et al. 2008), prokaryotes (Bernstein et al. 1993), and viruses (Reeves et al. 2007), lncRNAs are not as well conserved as miRNAs in terms of the nucleotide sequence. Even though lncRNAs with diverse nucleotide compositions can exhibit the same 3D structure and, consequently, the exact molecular function, this restricts the selection of cellular and animal models for researching lncRNA functions (Derrien et al. 2012). It is increasingly becoming clear that lncRNAs play a role in virtually every cellular process and that the expression of these non-coding molecules is carefully regulated in both normal conditions and several human diseases, including cancer (Tano and Akimitsu 2012).

Unlike coding genes, lncRNAs can be produced in many ways from practically any location in the human genome. Contrary to those that overlap coding genes on the antisense strand, unlike coding genes, lncRNAs can be produced in a wide range of ways from practically any location in the human genome. Contrary to those that overlap coding genes on the antisense strand, sense lncRNAs are made from segments that overlap one or more exons of another coding transcript (antisense lncRNAs); sense lncRNAs are made from segments that overlap one or more exons of another coding transcript. Other lncRNAs are produced by regulatory components like enhancers or non-coding DNA sequences like introns. Some have promoters and regulatory elements expressed from intergenic regions that do not overlap other known coding genes (Thum and Condorelli 2015). It becomes clear that just a tiny portion of the theoretically infinite number of lncRNAs that could exist have been studied thus far. However, those studied have demonstrated the capacity to control the transcriptional and post-transcriptional stages of gene expression by interacting with nucleic acids and proteins in a manner that is specific to both sequences and structures (Mercer et al. 2009; Wilusz et al. 2009). The categorization and annotation of putative lncRNAs must be carefully examined to remove protein-coding RNAs. While being categorized as non-coding molecules, some lncRNAs have recently been shown to be able to code for micro peptides (Anderson et al. 2015). Before concluding a lncRNA's regulatory role, it is essential to prove that the skeletal muscle-specific RNA, which was previously thought

Table 2 Description of ncRNA and its biogenesis

Type of RNA	Full_form	Biogenesis description	Functions	References
miRNA	microRNA	Biogenesis of miRNAs begins with DNA sequences known as miRNA genes or clusters of genes that are only transcripted as miRNA molecules or collectively as polycistronic transcripts. MiRNAs can also be found in an intron or untranslated region (UTR) of a protein-coding gene	miRNA plays a vital role in post-transcriptional gene regulation. By inhibiting translation and destabilizing mRNA, miRNAs regulate their targets in eukaryotic cells	Annese et al. 2020
lncRNA	Long non-coding RNA	lncRNAs are RNA-type molecules with a 5′ methylcytosine cap and a 3′ poly(A) tail transcribed by RNA polymerase II (Pol II). 31 LncRNAs are categorized into many different categories based on their various features. lncRNAs, for example, can be classified into five categories based on their genetic origins: sense, antisense, bidirectional, intronic, and intergenic. LncRNAs are categorized into three categories based on their function: rRNA, tRNA, and cRNA	A new class of epigenetic regulators called lncRNAs is crucial to regulating epigenetic processes. LncRNAs modulate histone or DNA modification, primarily methylation, and acetylation, to control epigenetic modification primarily in the nucleus, which controls gene transcription at the transcriptional level	Liu et al. 2021a, b
snRNA	Small nuclear RNA	snRNA can be transcribed from a promotor (similar to mRNA) and encoded within intronic sequences	Splicing of introns from primary genomic transcripts is a critical function of small nuclear RNAs	Matera et al. 2007
snoRNA	Small nucleolar RNA	Except for a tiny subset of snoRNAs that RNA polymerase II transcriptions autonomously, most snoRNAs in vertebrates are encoded in the introns of protein-coding or non-coding genes. Most intronic snoRNAs are produced through co-transcription with the host gene, splicing, debranching of the intron lariat, and nucleoplasmic exonucleolytic digestion. The maturation of snoRNAs, which is co-transcriptionally induced, depends on the recruitment of ribonucleoproteins to the nascent intronic snoRNAs. Additional SnoRNPs are sent to Cajal bodies, carrying out additional maturation and processing operations. Shq1, Naf1, and NUFLP are additional auxiliary elements that contribute to snoRNP assembly and maturation. Both processing stability and nucleolar localization depend on these proteins	The function of snoRNA is to participate in rRNA processing, regulation of mRNA processing, involvement in stress response, and metabolic changes. snoRNA has a more and influential role in cancer	Liang et al. 2019
siRNA	Small interfering RNA	The cascade leading to the synthesis of mature siRNA begins with transcription by RNA polymerase II (in mammals), RNA polymerase III (from an shRNA template), or RNA polymerase IV (in plants), creating double-stranded RNA (dsRNA) (dsRNA)	siRNA is frequently employed in molecular biology to silence desired genes temporarily. Upon binding to their target transcript, they trigger RNAi based on the complementarity of their sequences	Carthew and Sontheimer 2009
piRNA	PIWI-interacting RNA	Lengthy RNA precursors are transcribed in the nucleus and exported into the cytoplasm. In the cytoplasm, piRNA precursors are further processed to form mature piRNAs that get loaded into Piwi proteins	piRNA has essential roles in embryonic development, the preservation of germline DNA integrity, the generation of heterochromatin, the silencing of transposon transcription, the suppression of translation, and the epigenetic regulation of sex determination	Wu et al. 2020a, b

Table 2 (continued)

Type of RNA	Full_form	Biogenesis description	Functions	References
circRNA	Circular RNA	CircRNAs often result from exon or intron circularization and splicing activities. Exonic circRNAs can be produced by a procedure known as back splicing, dependent on spliceosomal splicing. Exons are spliced in the opposite direction by combining an upstream and a downstream 3′ and 5′ splice site, resulting in a circular product. Exon skipping, which creates a lariat structure containing exons and introns, is another method that leads to exonic circRNAs. The intron is cut out of this precursor during self-splicing, and the lariat is circularized	CircRNAs control target gene expression by inhibiting miRNA activity as a miRNA sponge. Through several miRNA binding sites, one circRNA can control one or more miRNAs	Beermann et al. 2016

to be a lncRNA, is encoded for a functional micro peptide. Evidence from recent studies revealed that conventional processes do not just regulate ncRNA expression. Circular RNAs are produced due to a back-splicing expression variation (circRNA). Since CircRNAs are made up of a covalently closed continuous loop, they lack a 5′ cap and a 3′ tail. This RNA species is more tissue-specific, moderately stable, and highly conserved (Jeck et al. 2012). The functions of each of these ncRNA were mentioned in this paper (Beermann et al. 2016). The discovery of associations between non-coding RNAs and diseases has created new therapeutic and diagnostic possibilities. Numerous miRNAs have already been effectively demonstrated to act as diagnostic or therapeutic targets for various diseases. There is specific evidence that circRNAs and lncRNAs behave similarly.

Non-coding RNA and human diseases

Functional RNA molecules known as non-coding RNA (ncRNA) cannot be translated into proteins (Djebali et al. 2012). Initially, there are only a few ncRNAs were found and studied. Later technological advancements, ncRNA types were classified into many, and each ncRNA has specific functions that lead to biomarkers and novel therapeutic approaches. Despite not all of their functions being understood, several ncRNA species play crucial roles in controlling the transcription and translation of genes and the transcription of ncRNAs. Therefore, it is no surprise that ncRNAs are crucial in normal physiologic functions, complex human traits, and human diseases (Li et al. 2018a, b). This review will mention the different types of diseases and their ncRNA as potential biomarkers and interactions in Table 3.

Transposons: unexpected players in different diseases with different ncRNA

Transposable elements (TEs) are considered essential factors in the plasticity and evolution of the genome. Since TEs are so prevalent in the human genome, particularly the Alu and Long Interspersed Nuclear Element-1 (LINE-1) repeats, they are thought to be the molecular cause of several diseases. This encompasses a number of the molecular processes discussed in this article, including insertional mutation, DNA recombination, chromosomal rearrangements, changes in gene expression, and changes to epigenetic controls. Additionally, some of the more well-known and/or more recent cases of human disorders where TEs play a role are provided in this article (Chénais 2022). TEs are frequently linked to the genesis of human malignancies, whether through the insertion of LINE-1 or Alu elements that result in chromosomal rearrangements or epigenetic alterations. Numerous more clinical disorders may have their molecular roots in

Table 3 Non-coding RNA and its biomarkers

Disease	ncRNA as biomarker	References
Genetic disease		
Duchenne muscular dystrophy	miR-1, miR-21, miR-29, miR-30c, miR-31, miR-133, miR-181a, miR-206, miR-208a, miR-208b, miR-499;lnc-31, linc-MD1;	Salvatore et al. 2011; Hu et al. 2014; Ballarino et al. 2015; Cacchiarelli et al. 2011; Chen et al. 2006; Eisenberg et al. 2007; Giordani et al. 2014; Greco et al. 2009; Mizuno et al. 2011; Naguibneva et al. 2006; Perry and Muntoni 2016; Twayana et al. 2013; van Rooij et al. 2008; Wang et al. 2012; Yuasa et al. 2008; Zaharieva et al. 2013
Myotonic dystrophy (type 1)	miR-1, miR-133a/b, miR-206;MALAT1	Gambardella et al. 2010; Fritegotto et al. 2017; Wheeler et al. 2012
Familial dysautonomia	miR-203a-3p	Hervé and Ibrahim 2016
Amyotrophic lateral sclerosis	miR143-3p, miR-206, miR-208b, miR-374b-5p, miR-499;NEAT1_2	Salvatore et al. 2011; Williams et al. 2009; Gagliardi et al. 2018
Ullrich congenital muscular dystrophy	miR-30c, miR-181a	Paco et al. 2015
Cystic fibrosis	miR-9, miR-93, miR-145-5p, miR-181b, miR-454, miR-509-3p;XIST, TLR8, HOTAIR, MALAT1, TLR8-AS1, BLACAT1, MEG9, BGas	Gillen et al. 2011; Hassan et al. 2012; Ramachandran et al. 2012; Balloy et al. 2017; Fabbri et al. 2014; Fabbri et al. 2017; McKiernan et al. 2014; Oglesby et al. 2013; Pierdomenico et al. 2017; Saayman et al. 2016; Sonneville et al. 2017
Rett syndrome	miR-29b, miR-92, miR-122a, miR-130, miR-146a, miR-146b, miR-199a, miR-199b, miR-221, miR-296, miR-329, miR-342, miR-382, miR-409;AK081227, AK087060	Salvatore et al. 2011; Petazzi et al. 2013; Urdinguio et al. 2010
Pulmonary arterial hypertension	miR-9, miR-124, miR-130, miR-206;MEG3, LnRPT	Kim et al. 2015; Sun et al. 2017; Chen et al. 2018a, b
Facioscapulohumeral muscular dystrophy	miR-411; DBE-T	Harafuji et al. 2013
Sézary syndrome	miR-18a, miR-21, miR-31, miR-199a2, miR-214, miR-233, miR-342, miR-486	Salvatore et al. 2011; Qin et al. 2012; Ballabio et al. 2010; Narducci et al. 2011
Lesch–Nyhan disease	miR-9, miR-181a, miR-187, miR-424	Guibinga 2015
Multiple osteochondromas	miR-21, miR-140, miR-145, miR-195, miR-214, miR-451, miR-483	Salvatore et al. 2011; Zuntini et al. 2010
Hailey–Hailey disease	miR-99a, miR-106, miR-125b, miR-181a	Manca et al. 2011
Li-Fraumeni syndrome	miR-605	Id Said & Malkin 2015
Hepatoblastoma	miR-125a, miR-148a, miR-150, miR-214, miR-199a, miR-492	Magrelli et al. 2009
MELAS (mitochondrial encephalopathy syndrome)	miR-9;LINC01405, SNHG12, RP11-403P17.4, CTC-260E6.6, RP11-357D18.1	Meseguer et al. 2015; Wang et al. 2017a, b
X-Chromosomal schizophrenia	let-7f-2, miR-188, miR-325, miR-509–3, and miR-510, miR-660	Feng et al. 2009
β-Thalassemia	miR-15a, miR-16–1, miR-26b, miR-96, miR-144, miR-155, miR-181a/c, miR-210, miR-320, miR-451, miR-486-3p, miR-503;DQ583499, XIST, lincRNA-TPM1, MRFS16P, lincRNA-RUNX2-2, HMI-LNCRNA, NR_001589, NR_120526, T315543	Gasparello et al. 2017; Leecharoenkiat et al. 2017; Lulli et al. 2013; Ma et al. 2017; Morrison et al. 2018; Roy et al. 2012; Saki et al. 2016; Siwaponanan et al. 2016; Srinoun et al. 2017
Cardiovascular disease		
Coronary artery disease	miR-1, miR-133a/b,miR-208a/b, aHIF, ANRIL, APOA1-AS,AWPPH, BANCR,CHROME, CoroMarker, H19, HOTTIP, LIPCAR, lincRNA-p21, LINC00968, MALAT1, MIAT, NEXN-AS1, SMILR	Broadbent et al. 2007; D'Alessandra et al. 2013; Fichtlscherer et al. 2010; Hennessy et al. 2018; Hu et al. 2019; Toraih et al. 2019; Wang et al. 2016a, b, c; Xiong et al. 2019; Yang et al. 2015
Cardiomyopathy	miR-1,miR-423-5p	D'Alessandra et al. 2013; Fan et al. 2015

Table 3 (continued)

Disease	ncRNA as biomarker	References
Heart failure	miR-1, miR-133a/b, miR-208a/b,miR-499, ANRIL,BACE1-AS, Chaer, Chast, CHRF, EGOT, H19, HEAT2,HRCR, HOTAIR, LIPCAR, lincRNA-ROR, LOC285194, MEG3,MHRT, MIAT, NRON,RMRP, RNY5, SOX2-OT, SRA1	Gidlöf et al. 2013; Greco et al. 2017; Greco et al. 2016; Viereck et al. 2016; Wang et al. 2015a, b; Wang et al. 2016a, b, c
Aterial hypertension	AK098656, ANRIL,GAS5, Giver,Lnc-Ang362, NR_027032, NR_034083, NR_104181	Jin et al. 2018; Bayoglu et al. 2016; Wang et al. 2016a, b, c; Leung et al. 2013a, b
Atrial fibrillation	miR-1, miRNA-26, miRNA-499, miRNA-328, miRNA-21, miRNA-133, miRNA-590, miRNA-206, PANCR, TCONS_00075467, KCNQ1OT1, NPPA-AS1,lncRNA-HBL1,PVT1, GAS5,LICPAR, MIAT, NRON, TCONS_00032546, TCONS_00026102	Lu et al. 2015; Luo et al. 2013; Ling et al. 2013; Lu et al. 2010; Shan et al. 2009; Zhang et al. 2015; Holmes and Kirchhof 2016; Li, Wang, et al. 2017a, b; Shen et al. 2018; Ke et al. 2019a, b; Liu et al. 2017a, b; Zhao et al. 2020a, b; Wang et al. 2020; Yao et al. 2020; Sun et al. 2019; Wang, et al. 2015a, b
Atherosclerosis	LIPCAR, aHIF, ANRIL, KCNQ1OT1, MIAT, MALAT1, Coro-Marker, LncPPARδ	Kumarswamy et al. 2014; Vausort et al. 2014; Cai et al. 2016; Bayes-Genis et al. 2017
Acute myocardial infarction	miR-1, miR-133a/b, miR-208a/b, miR-423-5p,miR-499, miR-400, miR-320a,miR signature, aHIF, ANRIL,APF, CARL, CDR1AS, FTX, GAS5, H19, HOTAIR, KCNQ1OT1, LIPCAR, Lnc-Ang362, MALAT1, MDRL, MEG3, MHRT, Mirt1/2, n379519, NONRATT021972, NRF, PCFL, TTTY15, UCA1, UIHTC, Wisper,ZFAS1	Cheng et al. 2010; Widera et al. 2011; Bauters et al. 2013; Liu et al. 2015a, b; Zeller et al. 2014; Vausort et al. 2014; Jakob et al. 2016; Semenza 2014; Wang et al. 2015a, b; Wang et al. 2014a, b, c; Zhang et al. 2016a, b, c; Long et al. 2018; Du et al. 2019; Zhou et al. 2018; Gao et al. 2017; Chen et al. 2020a, b; Wang et al. 2019a, b, c; Wang et al. 2014a, b, c; Wu et al. 2018; Zhang et al. 2016a, b, c; Ishii et al. 2006; Zangrando et al. 2014 l Wang et al. 2018a, b; Chen et al. 2018a, b; Wang et al. 2016a, b, c; Huang et al. 2019a, b; Chen et al. 2019; Zhang et al. 2018a, b, c; Micheletti et al. 2017
Tachycardia	miR-1,miR-133a/b	SUN et al. 2015a, b
Takotsubo cardiomyopathy	miR-1,miR-133a/b	Jaguszewski et al. 2013
Viral myocarditis	miR-208a/b,miR-499	Corsten et al. 2010
Acute coronary syndromes	miR-1, miR-133 a/b,miR-208 a/b, miR-499, miR-150, miR-132, miR-186, MACE prediction after STEMI	Cheng et al. 2010; Widera et al. 2011; Bauters et al. 2013; Liu et al. 2015a, b
Neurological disorders		
Alzheimer's disease	let-7b, miR-106b, miR-128, miR-34a, mIr132/212, miR-142a-5p, miR-146a-5p, miR-155-5p, miR-455-5p, miR-15/107, miR-16, miR-200b/c, miR-25, miR-29a/b-1,miR-29c, miR-33, miR-34a, miR-485-5p,miR-873-5p, miR-338-5p, BC1, BC200, LncRNA -17A, MEG3, MIAT, NDM29, NEAT1, P3Alu/SINE	Zhang et al. 2018a, b, c;Li et al. 2018a, b; Feng et al. 2018; Mus et al. 2007; Wang et al. 2019a, b, c; Massone et al. 2011; Yi et al. 2019; Ke et al. 2019a, b; Polesskaya et al. 2018
Parkinson's disease	miR-126, miR-126-5p, miR-133a/b,miR-133b, miR-153, miR-16–1, miR-183,miR-205, miR-22, miR-221, miR-27a/b, miR-342-3p, miR-34b/c, miR-494, miR-494,miR-7, miR-7/miR-153,miR-96, circSNCA, HOTAIR, NEAT1, NORAD, p21, SNHG1, U1 spliceosomal lncRNA, RP11-462G22.1, tRNA-derived fragment, UCHL1-AS, NEAT1, PINK1-AS, CDR1-AS, circDLGAP4	Wang et al. 2017a, b;Sang et al. 2018;Kim et al. 2016;Wu et al. 2019;Lin et al. 2019;Liu & Lu 2018;Qian et al. 2019;Magee et al. 2019;Carrieri et al. 2015;de Mena et al. 2010;Fragkouli and Doxakis 2014;Zhang and Cheng 2014;Gao et al. 2018a, b;Cho et al. 2012;Espinoza et al. 2020;Kabaria et al. 2015;Xiong et al. 2014;Dong et al. 2018a, b

Table 3 (continued)

Disease	ncRNA as biomarker	References
ALS (amyotrophic lateral sclerosis)	ncRNACCND1, tiRNAs (tRNA-derived RNA fragments), Lhx1as, LncMN-1, LncMN2, miR-17 ~ 92, miR-155, miR-206,miR-218, miR-375-3p, miR-375, miR-92a-3p, miR-125b-5p, miR-124-3p, miR-92a-3p, miR-20b-5p miR-223b-3p,hsa_circ_0063411, hsa_circ_0023919, hsa_circ_0088036,hsa_mir-9,ABCA12, DYRK2, POTEM, MALAT1, NEAT1, C9ORF72-AS	Ruffo et al. 2021
FTD (frontotemporal disorders)	C9ORF72 (repeat expansion), MALAT1, MEG3, NEAT1, U12 snRNA, Hsrw	Ruffo et al. 2021
HD (Huntington's disease)	miR-9*, miR-10b-5p, miR-22, miR-27a,miR-34a-5p, miR-34b, miR-214, miR-125b, miR-146a, miR-150, miR-125b, miR-146a, miR-150, miR-124, miR-124a, miR-128a, miR132, miR-212/miR-132, miR-196a, miR-196a, miR-19, miR-146a, miR-432, HAR1F, HAR1R, DGCR5, MEG3, NEAT1, NEAT1-L, NEAT1-S, TUG1, TUNA, LINC00341, RPS20P22, LINC00342, HTT-AS	Chang et al. 2017;Hoss et al. 2015;Ban et al. 2017;Reynolds et al. 2018;Gaughwin et al. 2011;Prajapati et al. 2019;Ghose et al. 2011;Das et al. 2013;Das et al. 2015;Kocerha et al. 2014;Fukuoka et al. 2018;Kunkanjanawan et al. 2016;Her et al. 2017;Cheng et al. 2013;Bañez-Coronel et al. 2012;Johnson et al. 2010;Johnson et al. 2008;Johnson 2012;Chen et al. 2020a, b;Cheng et al. 2018;
SMA (spinal muscular atrophy)	variant of U1 snRNA (vU1), miR-183	Wu & Kuo 2020
SCA (spinocerebellar ataxia)	ATXN8-OS,SCAANT1	Salta & De Strooper 2017
Metabolic diseases		
Type 1 diabetes	LINC01370, PLUT, MALAT1, TUG1	Lodde et al. 2020
Type 2 diabetes	miR-16, CDR1,circRNA-HIPK3, hsa_circ_0054633, circANKRD36(Enhanced expression), miR-376, miR-432,miR-200, miR-184, miR-204, miR-24, miR-26, miR-148, miR-182, miR-9, miR-130a, miR-130b, miR-152, miR-187,miR-7, miR-708, miR-34a, m,iR-146a, miR-182-5p, miR-33, miR-37, miR-802, miR-122-5p,miR-106b, microRNA let-7a, let-7d, miR-29, miR-192, miR-122, miR-27a-3p, miR-27b-3p, H19, MEG3, MALAT1	Chi et al. 2021
Osteoporosis	DANCR, miR-23a, miR-30c, miR-34c, miR-133a, miR-135a, miR-205, miR-217, miR-206, miR-29b, miR-433-3p, miR-103,miR-21,miR-223, miR-146a, miR-2861, miR-214,miR-21, miR-23a, miR-24, miR-25, miR-100, miR-125b, miR-22-3p, miR-328-3p, let-7 g-5p, miR-21, miR-133a, miR-130b-3p, miR-151a-3p, miR-151b, miR-194-5p, miR-590-5p, miR-660-5p, miR-194-5p, miR-125b, miR-30, miR-5914, miR-365, miR-10b, miR-0129-3p, miR-671-5p, miR-141, miR-25, miR-21-5p, miR-93-5p, miR-100-5p, miR-125b-5p, miR-320a, miR-483-5p, miR-152-3p, miR-30e-5p, miR-140-5p, miR-324-3p, miR-19b-3p, miR-335-5p, miR-19a-3p, miR-550a-3p, miR-17-5p, miR-133a-3p	Tong et al. 2015; Foessl et al. 2019
Cancer		
Breast cancer	miR21, CamK-A, EPIC1, HOTAIR, LINK-A, PLK1	Slack and Chinnaiyan 2019
Lung cancer	mIR-16, miR-21, miR-34a, MALATI1	Slack and Chinnaiyan 2019
Colorectal cancer	miR-1290, CCAT1, CCAT2, HOTAIR, circCCDC66, ciRS-7	Slack and Chinnaiyan 2019

Table 3 (continued)

Disease	ncRNA as biomarker	References
Gastric cancer	miR-506, H19, circCTNNB1, PLK1	Slack and Chinnaiyan 2019
Ovarian cancer	miR-506, FAL1, HOTAIR, PLK1	Slack and Chinnaiyan 2019
Pancreatic cancer	miR-10b, miR-50b, HOTAIR, PKN3, APN401	Slack and Chinnaiyan 2019
Prostate Cancer	miR-21, miR-221, miR-375,miR-1290, MALAT1, NEAT1, PCA3, PCAT-1, PCAT-14, SChLAP1, circAR,	Slack and Chinnaiyan 2019
leukemia	miR-21,miR-155	Slack and Chinnaiyan 2019
Infectious diseases		
COVID-19	miR-1275, miR-766-3p, miR-214, miR-17 and miR-574-5p, miR-98,miR-223	Plowman and Lagos 2021
Viral hepatitis	miRNA-122	Bhatti et al. 2021
Dengue virus	miRNA-378	Bhatti et al. 2021
Japanese encephalitis virus	miR-15b	Bhatti et al. 2021
Enterovirus 71 (EV71)	miR-296-5p	Bhatti et al. 2021
Human immunodeficiency virus	miRNA-34a and miRNA − 217	Bhatti et al. 2021
Tuberculosis	miR-155, miR-16, miR-200, Let-7 family, miR-486, miR-223, miR-99, miR-29, miR-21, miR-193, miR-365, miR-30, miR-20, miR-146, miR-31,miR-150	Pattnaik et al. 2022
Autoimmune diseases		
Rheumatoid arthritis	lncRNA AC000061, HOTAIR, GAPLINC, ZFAS1, GAS5	Lodde et al. 2020
Systemic lupus erythematous	NEAT1, Linc00513, GAS5, TUG1	Lodde et al. 2020
Multiple sclerosis	NEAT1, TUG1, RN7SK, PVT1, FAS-AS1, THRIL, GAS5, MALAT1, MEG9, NRON, ANRIL, TUG1, XIST, SOX2OT, MIAT, HULC, BACE-1AS, lncAC007278.2, IFNG-AS1-001, IFNG-AS1-003	Lodde et al. 2020
Osteoarthritis	ARFRP1, LOXL1-AS1, HOTAIR, H19, NEAT1, DANCR, etc. (up). XIST, MEG3 etc. (down). miR-455-3p, miR-411, miR-27a (up), miR-149-5p, miR-26a-5p etc.(down), Circ_0136474, CircHIPK3, ciRS-7 etc. (up), CircRNA-9119, CircSERPINE2, circANKRD36	Ghafouri-Fard et al. 2021

gene structure and/or expression changes or chromosomal recombination caused by TE. Hemoglobinopathies, metabolic, neurological, and joint disorders are among the many conditions this group of diseases represents.

Additionally, TEs may influence aging. The epigenetic derepression and mobility of TEs, which can result in disease development, appear to be significantly impacted by the pressures and environmental toxins that people are exposed to. As a result, a greater understanding of TEs may result in the development of novel possible disease diagnostic markers (Pradhan and Ramakrishna 2022).

Differences between exosomal and non-exosomal non-coding RNAs in human health and diseases

Circulating ncRNA transfer via exosomes is an intriguing method. As mediators for intercellular communication, ncRNAs can be enclosed by EVs (such as exosomes, microvesicles, and apoptotic bodies) and secreted from cells to control various diseases depending on the target cells (Li et al. 2021a). It has been demonstrated that ncRNAs exist in various bodily fluids, including serum, plasma, urine, saliva, and others, in addition to cells. The ncRNAs seen in biofluids are frequently called circulating or extracellular ncRNAs. The fact that extracellular ncRNAs are reasonably durable in plasma even though extracellular RNase activity is considerable in that environment suggests that circulating ncRNAs may be shielded from adverse circumstances. In this part, they examine how ncRNAs in exosomes and non-exosomes regulate physiological homeostasis and pathological events in health and disease (Li et al. 2021b).

Tools and methods

Investigating miRNA, lncRNA, circRNA, and other RNAs

The complete methods and investigation of ncRNA will be discussed. miRNA methods have already been thoroughly explained. Deep sequencing techniques or microarrays are the most used methods for miRNA detection. Deep sequencing is a more sensitive technique when compared to microarray-based techniques. Microarrays can lead to finding distinct RNA sequences despite using a fixed set of probes for detection (van Rooij 2011). However, the output analysis is more difficult because of the enormous volume of data and the critical requirement for bioinformatics expertise. Quantitative real-time PCR allows for the comparatively inexpensive and low-effort validation of screening results (qRT-PCR). Because the transcript is so brief, previous difficulties prompted the construction of the primer for reverse transcription. Target-specific stem-loop reverse transcription primers are currently offered on many platforms. Northern blotting and in situ hybridization are other techniques for identifying identified miRNAs. To find a miRNA's targets, bioinformatics platforms are commonly implemented. The miRNA-related database is mentioned in Table 4. Luciferase tests are frequently used to verify expected targets of miRNAs following bioinformatics-based predictions of such targets. To completely comprehend the entire transcriptional regulatory scenario, small RNAs play a critical role in transcriptional regulation. Their abnormal expression profiles are believed to be linked to cellular dysfunction and diseases. Numerous studies are concentrating on detecting, predicting, or quantifying short RNA expression, particularly miRNAs, to better understand human health and disease.

The efficient and reasonably good next-generation sequencing approach allows the collection of large data sets with excellent accuracy. Appropriate bioinformatic procedures must be used to use the collected data and analyze for lncRNAs. Additionally, you can buy commercial arrays to look at the deregulation of a specific set of lncRNAs (e.g., Arraystar, Qiagen, Biocat). Another method to investigate the effect of lncRNAs is to use a genome-wide shRNA library to target a specific subset of lncRNAs. This library and additional studies might be used to ascertain how lncRNA inhibition influences signaling pathways or cell behavior. For instance, the lncRNA TUNA was discovered in mouse embryonic stem cells with Oct4-GFP using an shRNA library targeting 1280 lincRNA (Lin et al. 2014). The pros and cons of RNAi approaches are effectively summed up in a review written by Mohr et al. (Mohr et al. 2014).

Designing primers that only detect the ncRNA transcript is crucial for validating a screen's results for lncRNAs. To identify coding from non-coding regions, this design is essential. A lncRNA often has modest levels of expression. In addition, lncRNA annotation is continuously evolving and may not be consistent across all databases (like Refseq, UCSC, and Ensembl). Since pseudogenes typically produce lncRNAs, the actual gene and the long non-coding transcript can be recognized using the same primers. Another difficulty arises when lncRNAs are expressed sense- or antisense-to a recognized protein-coding gene. LncRNAs are primarily found in cell nuclei. There are many challenges associated with pulling down lncRNA/protein complexes since it may provide false-positive outcomes. A highly reproducible RNA antisense purification (RAP) method was described in this paper (McHugh et al. 2015). In vitro, lncRNAs can be suppressed using a variety of compounds. It is also critical to confirm the length of annotated sequences for newly discovered lncRNAs. The rapid amplification of cDNA ends (RACE) method can amplify a lncRNA between a specific point inside the lncRNA and the sequence's 3′ or 5′ end. The actual sequence can then be found or verified

Table 4 miRNA based tools and databases

Tools/databases	Description	Website	References
RNAcentral: The non-coding RNA sequence database	RNAcentral is a comprehensive database of non-coding RNA of sequences and functional annotation. It has 296 species; visualize the 2D RNA structure. It has a lot of inter-connected databases	https://rnacentral.org/	Sweeney et al. 2018
RNALOSS	Designing RNA sequences with low folding energy and distribution of locally optimum secondary structures that would suggest quick and robust folding could be done using the tool RNALOSS	http://clavius.bc.edu/~clotelab/RNALOSS	Clote 2005
RNAdb	The creation of a thorough mammalian non-coding RNA database (RNAdb) with over 800 different experimentally examined non-coding RNAs (ncRNAs), many of which are linked to illnesses and/or developmental processes	http://research.imb.uq.edu.au/RNAdb	Pang 2004
Rfam	Rfam is a library of covariance models and numerous sequence alignments for non-coding RNA families. The user can explore numerous sequence alignments and family annotations and search a database of covariance models using a query sequence. The INFERNAL package (http://infernal.wustl.edu/) enables local searches utilizing the database as well as the flat file download	http://www.sanger.ac.uk/science/tools/rfam	Griffiths-Jones 2003
EICO	They have created a specialized integrated database for researching imprinted disease genes	http://fantom2.gsc.riken.jp/EICODB/	Nikaido 2004
NONCODE	NONCODE database includes all information relates to non-coding RNAs. It has a lot of integrated databases available	http://noncode.bioinfo.org.cn	Bu et al. 2011
ChIPBase v2.0	ChIPBase also has a ChIP-Function tool and a genome browser that can predict gene functions and analyze ChIP-seq data. This research will help better understand how ncRNAs and PCGs regulate transcription	http://rna.sysu.edu.cn/chipbase/	Zhou et al. 2017
FARNA	A database about inferred functions of non-coding RNA has broad areas of human cells and tissues	http://cbrc.kaust.edu.sa/farna	Alam et al. 2017
NRDTD	ncRNAs represent a novel class of drug development targets since they may influence gene expression and disease course. We created the ncRNA Therapeutic Targets Database (NRDTD), which had 165 entries of ncRNAs that were supported by clinical or experimental research as potential drug targets	http://chengroup.cumt.edu.cn/NRDTD	Chen et al. 2017
BLAST	A blast is an online tool used for sequence analysis. The prediction algorithm used here is BLAST E-value	https://blast.ncbi.nlm.nih.gov/Blast.cgi	McGinnis & Madden 2004

Table 4 (continued)

Tools/databases	Description	Website	References
Blat	Blat is similar to the BLAST alignment tool. However, BLAT requires an exact or close match to find a hit. It finds similarities in DNA and proteins quickly. As a result, Blat is less adaptable than BLAST	https://genome.ucsc.edu/cgi-bin/hgBlat	Kent 2002
Infernal	This tool will build a consensus on RNA secondary structure. The model used for infernal is the covariance model	http://infernal.janelia.org/	Nawrocki et al. 2009
FastR	This tool will detect the ncRNA		Bafna and Zhang 2004
ERPIN	ERPIN-Easy RNA profile identification. This tool searches for RNA motifs	http://rna.igmors.u-psud.fr/Software/erpin.php	Gautheret and Lambert 2001
QRNA	An application extends the AMBER simulation approach with extra constraints and allows for fine-grained modification of nucleic acid structures	http://genesilico.pl/QRNAS/QRNAS_data.tar.gz	Stasiewicz et al. 2019
RNAz	RNAz effectively screens for putative ncRNAs by identifying evolutionarily conserved and thermodynamically stable RNA secondary structures in numerous sequence alignments	https://www.tbi.univie.ac.at/~wash/RNAz/	Washietl 2007
Evofold	Evofold will detect the functional RNA structure using multiple sequence alignment	https://github.com/bowhan/kent/blob/master/src/hg/makeDb/trackDb/drosophila/evofold.html	Knudsen & Hein 1999
MASTR	The algorithm MASTR (Multiple Alignment of STructural RNAs) iteratively enhances sequence alignment and structure prediction for a set of RNA sequences by utilizing Markov chain Monte Carlo in a simulated annealing architecture	http://mastr.binf.ku.dk/	Lindgreen et al. 2007
CSTminer	Using a possible coding score, this tool can locate statistically significant conserved blocks and determine whether they are coding or non-coding	http://www.caspur.it/CSTminer/	Castrignano et al. 2004
ESTscan	This tool will detect gene discovery and other assembly roles to find the coding regions. The algorithm used is the Hidden Markov model	https://myhits.sib.swiss/cgi-bin/estscan	Iseli et al. 1999
CONC	This algorithm will predict the RNA secondary structure. It will distinguish the coding and non-coding RNA		(Zou et al. 2011),(Liu et al. 2006)
CPC	The CPC webservers visualize sequence characteristics and forecast the transcript input's coding potential	http://cpc.cbi.pku.edu.cn	Kong et al. 2007
RNAfold	This tool has an extensive collection of tools like folding, designing, and analyzing RNA sequences	http://rna.tbi.univie.ac.at/	Gruber et al. 2008
Mfold	This tool will predict the secondary structure of single nucleic acids. Its easy access to RNA and DNA folding	http://www.bioinfo.rpi.edu/applications/mfold	Zuker 2003

Table 4 (continued)

Tools/databases	Description	Website	References
A fold	This method will be able to fold the RNA molecule that finds a conformation of energy minimization values		Zuker and Stiegler 1981
GTEx	The Genotype-Tissue Expression (GTEx) project aims to create a tissue bank and database of resources for the scientific community. The link between genetic variation and gene expression in human tissues will be investigated using GTEx. The expression datasets can be downloaded from this database for ncRNA analysis	https://gtexportal.org/home/	Lonsdale et al. 2013
DARIO	It can access numerous available ncRNA databases to quantify and annotate ncRNAs	http://dario.bioinf.uni-leipzig.de/	Fasold et al. 2011
CPSS	Quantify and annotate ncRNAs with a focus on miRNAs	http://114.214.166.79/cpss2.0/	Wan et al. 2017
RNA-CODE	Combines de novo assembly and secondary structure. Relevant to ncRNA annotation in the absence of reference genomes	http://www.cse.msu.edu/~chengy/RNA_CODE	Yuan & Sun 2013
YM500v3	A resource that emphasizes piRNAs, tRFs, snRNAs, snoRNAs, and miRNAs and comprises more than 8000 short RNA-seq datasets	http://ngs.ym.edu.tw/ym500/	Chung et al. 2016
tRF2Cancer	A web server that can find tRFs and the expression of those genes in various cancers	http://rna.sysu.edu.cn/tRFfinder/	Zheng et al. 2016
MINTbase v2.0	MINTbase is a collection of nuclear and mitochondrial tRNA-derived fragments (or "tRFs") discovered in various human tissues	https://cm.jefferson.edu/MINTbase/	Pliatsika et al. 2017

by cloning and sequencing this amplicon (Beermann et al. 2016). Detail-oriented loss- or gain-of-function studies are essential to comprehend a lncRNA's activity in vivo (Bassett et al. 2014). Numerous lncRNA-related database was mentioned in Table 5.

By searching current RNA-sequencing data for circular RNAs, a brand-new set of probable circRNAs can be predicted (Salzman et al. 2012). Data from long-read RNA sequencing can be utilized to look for possible circRNAs. This particular class of molecules requires a specific algorithm because their production may have involved back-splicing. Two studies demonstrate how to build a computational pipeline to identify new circRNAs (Guo et al. 2014). Using these new techniques to analyze RNA-sequencing data provides suggestions for existing circRNAs. Because the gene from which they are derived has a distinct orientation, the validation of these ncRNAs is particularly unique. Exonic circRNAs must be separated from other RNA molecules that have undergone backspacing. Divergent primers can be used in qPCRs to access the expression and access the predicted circRNAs.

Regarding the genomic area, these primers do not amplify toward one another but are somewhat away from one another. The circle can be amplified without amplifying the genomic areas (Jeck and Sharpless 2014). The functional circRNA can be accessed through previous RNA studies, which are still evolving. Other new approaches should be implemented for the circRNA. New tools and approaches to small ncRNA and circRNA were mentioned in Tables 6 and 7.

Identifying non-coding RNAs (ncRNAs), which play a significant function in the cell, is a crucial topic in biological study. The discovery of ncRNAs is now conceivably feasible, thanks to recent developments in computational prediction technology and bioinformatics. This study introduces three key computational methods for ncRNA identification: homologous search, de novo prediction, and deep sequencing data mining. There are two methods for detecting the ncRNA identification Homologous information and machine learning approaches (i.e., common features)aforementioned computational

Table 5 lncRNA based tools and databases

Tools/databases	Description	Website	References
LNCipedia	A vast and extensive class of non-coding RNA genes are LNCRNAs. 21 488 annotated human lncRNA transcripts from various sources are available on LNCipedia. The database could help start small- and large-scale lncRNA studies	https://lncipedia.org	Volders et al. 2012
LNCBook	Long non-coding RNAs (lncRNAs) play essential roles in various biological functions. The integration and curation of human lncRNA and the data they are related to are the focus of LncBook. Many multi-omics data from expression, methylation, genomic variation, and lnc RNA-miRNA interaction are also integrated	http://bigd.big.ac.cn/lncbook	Ma et al. 2019
Lnc2Cancer v2.0	The new database Lnc2Cancer 2.0 presents thorough correlations between lncRNAs and human malignancies. In addition to adding new features and more data, it has recruited 4989 lncRNA-cancer correlations	http://www.bio-bigdata.net/lnc2cancer	Gao et al. 2018a, b
TANRIC	Long non-coding RNAs (lncRNA) have become prominent players in cancer biology. They have created TANRIC using recent large-scale RNA-seq datasets, particularly from The Cancer Genome Atlas (TCGA). It describes the lncRNA expression profiles in sizable patient cohorts with 20 cancer types	http://bioinformatics.mdanderson.org/main/TANRIC:Overview	Li et al. 2015
lnCaNet	Numerous human long non-coding RNAs (lncRNAs) have been found in malignancies and implicated in various carcinogenesis processes. LnCaNet is a comprehensive database of co-expression information for cancer genes and lncRNAs	http://lncanet.bioinfo-minzhao.org/	Liu & Zhao 2016
LncRNADisease 2.0	LncRNADisease 2.0 documents more than 200,000 lncRNA-disease correlations. The database lists the connections between lncRNAs, mRNA, and miRNA in transcriptional regulation. It incorporates connections between diseases and circular RNA that experiments have supported	http://www.rnanut.net/lncrnadisease/	Bao et al. 2018
The Cancer LncRNome Atlas	Long non-coding RNA (lncRNA) has significantly altered their understanding of cancer. Their findings imply that lncRNA expression and dysregulation are remarkably tumor-type specific. This paves the way for the creation of novel diagnostics and therapies	http://tcla.fcgportal.org/	Yan et al. 2015
SELER	Super-enhancers (SEs) are enriched in mediator binding sites, which play a vital role in the production of genes that are particular to different cell types. Through regulating SEs activity, long non-coding RNAs (SE-lncRNAs) play crucial roles in transcriptional regulation. Users can thoroughly examine the physiological and pathological activities of the data in the SELER database to fully comprehend the building blocks of living systems	http://www.seler.cn/	Guo et al. 2019a, b

Table 5 (continued)

Tools/databases	Description	Website	References
lncRNAdb v2.0	lncRNAdb is a large, manually curated reference library of 287 eukaryotic lncRNAs independently published in the scientific literature. The new features include incorporating Illumina Body Atlas expression profiles, nucleotide sequence data, a BLAST search tool, and simple export	https://ngdc.cncb.ac.cn/databasecommons/database/id/23	Quek et al. 2014
LncRNAWiki	A knowledge base of human long non-coding RNAs is called LncRNAWiki 2.0. (lncRNAs). The system has substantially improved with an updated database system and curation approach. Additionally, it offers more approachable online interfaces that make data curation, retrieval, and visualization easier	https://ngdc.cncb.ac.cn/lncrnawiki1/index.php/Main_Page	Liu et al. 2021a, b
MONOCLdb	The antiviral response is expected to significantly influence long non-coding RNAs (lncRNAs). To detect coronavirus causing severe acute respiratory syndrome and influenza A, we used whole RNA-Seq on virally infected lungs from eight mouse strains (SARS-CoV). The interactive database MOuse NOn-Code Lung makes these data completely available (MONOCLdb)	https://www.monocldb.org/	Josset et al. 2014
CANTATAdb	Long non-coding RNAs (lncRNAs) are effective gene expression regulators in many eukaryotes. We still know very little about these compounds in plants. A database named CANTATAdb is online and offers the data for free searching, viewing, and downloading	http://cantata.amu.edu.pl/	Szcześniak et al. 2015
CPPred	The SVM classifier and several sequence features, including unique RNA features, are the foundation of the CPPred method. Most newly hypothesized novel coding RNAs (91.1%) are ncRNAs, which is consistent with earlier studies. Surprisingly, the global description of encoding properties is crucial in predicting coding capability	http://www.rnabinding.com/CPPred	Tong and Liu 2019
CNIT	It remains challenging to categorize RNA transcripts into protein-coding or non-coding even as more high-throughput data has been generated by next-generation sequencing, especially for species with inadequate annotation. The CNIT (Coding-Non-Coding Identifying Tool) assesses the coding capacity of RNA transcripts more quickly and accurately. For most eukaryotic transcripts, CNIT is more accurate than CNCI and operates 200 times faster. 11 animal species' AUC values and 27 plant species' AUC values	http://cnit.noncode.org/CNIT	Guo et al. 2019a, b
LncSLdb	Long non-coding RNAs (lncRNAs) may become crucial to biological processes and cellular function. Although we still do not fully understand them, they might explain how they work. A program that handles and maintains user-gathered subcellular localization data is called lncSLdb	http://bioinformatics.xidian.edu.cn/lncSLdb	Wen et al. 2018

Table 5 (continued)

Tools/databases	Description	Website	References
LncATLAS	The location of long non-coding RNAs (lncRNAs) inside the cell provides essential hints about their molecular function. Based on data from RNA sequencing, LncATLAS is a comprehensive repository of lncRNA localization in human cells	https://lncatlas.crg.eu/	Mas-Ponte et al. 2017
LncLocator	Studies of long non-coding RNA (lncRNA) have drawn much interest in the discipline of RNA biology. According to recent research, their subcellular localizations include crucial information for comprehending their intricate biological roles. So far, there are no computational methods for predicting the locations of lncRNAs. The LncLocator tool will be able to locate the positions of lncRNA	http://www.csbio.sjtu.edu.cn/bioinf/lncLocator/	Cao et al. 2018
RMDB	Since the invention of high-throughput sequencing methods, RNA structure mapping data has risen considerably. To facilitate structural, thermodynamic, and kinetic comparisons, we created an RNA mapping database (RMDB). The database now contains 53 entries outlining more than 2848 trials	https://rmdb.stanford.edu/	Cordero et al. 2012
DMfold	To predict the secondary structure with pseudoknots, "DMfold" is proposed. The Deep Learning and Improved Base Pair Maximization Principles serve as the foundation. Their code is available at the github repository	https://github.com/linyuwangPHD/RNA-Secondary-Structure-Database	Wang et al. 2019a, b, c
SEEKR	Most long non-coding RNAs (lncRNAs) have unknown functions, and finding one lncRNA's function rarely reveals what the others do. A robust method for identifying connections between sequence and function in lncRNas is Kmer-based categorization	http://seekr.org/	Kirk et al. 2018
LNCediting	An RNA transcript can change a single base through the post-transcriptional process known as RNA editing. Most of these RNA editing sites are located in non-coding areas of the genome and have unclear functions. To forecast the functional impact of novel editing sites in lncRNAs, LNCediting offers specialized methods	http://bioinfo.life.hust.edu.cn/LNCediting/	Gong et al. 2017a, b
Ufold	It has long been challenging to infer RNA secondary structure from nucleotide sequences. UFold suggests a unique, image-like representation of RNA sequences that Fully Convolutional Networks can parse quickly. On within-family and cross-family datasets, it dramatically outperforms earlier techniques	https://ufold.ics.uci.edu	Fu et al. 2021
RNAInter	RNAInter (RNA Interactome Database) has been upgraded to version 4.0. An upgraded confidence-scoring algorithm and a more extensive data collection. Updated, user-friendly UI and > 47 million new entries. Overall, RNAInter will offer a platform that is easier to use	http://www.rnainter.org/	Kang et al. 2022
RISE	RNA regulation and function depend on RNA-RNA interactions (RRIs). There are 328,811 interactions in the RISE database, mostly involving people, mice, and yeast. mRNA and long non-coding RNAs make up more than 50% of the RRIs in RISE	http://rise.zhanglab.net/	Gong et al. 2017a

Table 5 (continued)

Tools/databases	Description	Website	References
IntaRNA	The prediction modes and output formats can be freely customized and upgraded with IntaRNAv2. The improved lowest energy profiles for RNA-RNA interactions are visualized using the expanded web interface. These make it possible to investigate interaction options in detail and may show many possible interaction sites	https://bio.tools/intarna	Mann et al. 2017
LncRRIsearch	lncRNAs, also known as long non-coding RNAs, are essential to many biological processes. A web server called LncRRIsearch provides thorough predictions of lncRNA-lncRNA interactions. The prediction was made using RIblast, a quick and reliable technique for predicting RNA-RNA interactions	http://rtools.cbrc.jp/LncRRIsearch/	Fukunaga et al. 2019
LnChrom	The control of chromatin by long non-coding RNAs (lncRNAs) affects several biological functions and disorders. LnChrom is a database of lncRNA-chromatin interactions that have been empirically verified. There are 382 743 mouse and human interactions in it	http://biocc.hrbmu.edu.cn/LnChrom/	Yu et al. 2018
Triplexator	Triplex production offers a robust targeting mechanism for genomic locations of interest for biotechnological and gene-therapeutic applications. The first computational framework for displaying the possibilities of triplex creation is called Triplexator	https://github.com/Gurado/triplexator	Buske et al. 2012
SFPEL-LPI	LncRNA-protein interactions are crucial for polyadenylation, splicing, translation, and post-transcriptional gene control. SFPEL-LPI uses a feature projection ensemble-learning frame to merge numerous features and similarities. The method predicts novel lncRNAs (or proteins) more accurately than other approaches	http://www.bioinfotech.cn/SFPEL-LPI/	Zhang et al. 2018a, b, c
lncRScan	Identify the lncRNA from the complex assemblies and distinguish it from mRNA		Sun et al. 2015a, b
iSeeRNA	It will detect lncRNA from large datasets		Sun et al. 2013
Annocript	It utilizes public databases and sequence analysis software to find lncRNA and confirm its high non-coding potential		Musacchia et al. 2015
LncRNA2Function	lncRNA annotation should be based on the idea that genes with comparable expression patterns can have related biological pathways and activities under different situations		Jiang et al. 2015

Table 6 Small ncRNA-based tools and databases

Tools/databases	Description	Website	References
ncPRO-seq	Discovering new ncRNA species by impartially detecting known small ncRNAs	http://ncpro.curie.fr/	Chen et al. 2012
CoRAL	Organizing the short ncRNA into functional groups according to biologically comprehensible characteristics other than sequence; Describe ncRNA in less well-known species	http://wanglab.pcbi.upenn.edu/coral	Leung et al. 2013a, b
DASHR 2.0	A database that incorporates mature products from all the main RNA classes and human small ncRNA genes	http://lisanwanglab.org/DASHR	Kuksa et al. 2019

detection techniques are mostly intended for short non-coding RNAs like miRNAs, tRNAs, siRNAs, and piRNAs. However, conventional methods like PT-PCR and Northern Blot are expensive. The calculation methods can never perform well when dealing with long non-coding RNAs (lncRNA). To the current knowledge, the primary lncRNA detection method is RT-PCR or CHIP-SEQ (Wang et al. 2013). The primary software tools and ncRNA discovery method tools are mentioned in Table 8. The techniques used for ncRNA discovery are mentioned in Table 9.

Applications of CRISPR/Cas9-mediated non-coding RNA editing in the targeted therapy of human diseases

Genome editing, also known as gene editing, refers to a range of scientific techniques that enable the modification of an organism's DNA. These techniques enable adding, removing, or modifying genetic material at specific genomic regions. There are several genome editing methods, including ZFNs, TALENs, and CRISPR/Cas9. Comparison of these three approaches was mentioned in this article (Li et al. 2021a, b). The detailed structure and mechanism of these three different approaches were mentioned in this article (Li et al. 2021a, b).

CRISPR-Cas9, which stands for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9, is a well-known example. The CRISPR/Cas9 system has evolved and developed quickly as a reliable, practical, user-friendly, and widely applied gene editing tool in just a few years. CRISPR/Cas9 has significantly impacted a wide range of industries, including agriculture, biotech, and healthcare. However, no industry has been affected by the technology more profoundly than cancer research, as indicated by the accumulating data in the rapidly expanding publications. The discovery and application of more specific Cas9 variants, limiting the duration of CRISPR/Cas9 activity, the use of inducible Cas9 variants, and the application of anti-CRISPR proteins (Zhang et al. 2021a, b). Further research is required to fully comprehend the governing principles of CRISPR/Cas9 specificity and to increase the sensitivity of off-target identification. Second, on-target mutagenesis typically occurs in double-strand breaks brought on by single-guided RNA/Cas9, leading to massive deletions (over several kilobases) and complex genomic rearrangements at the targeted loci, which can have pathogenic effects (Zhang et al. 2021a, b).

The research evidence accumulated to date has shown significant contributions made by genome editing systems to exploit therapeutic approaches for various types of human diseases, with the CRISPR/Cas9 system being particularly successful by directly affecting target gene loci or generating tools with multiple functions. There are other diseases these approaches were found to therapeutic drugs of clinical drugs mentioned in this article (Li et al. 2021a, b). The advancement of cell imaging, gene expression regulation, epigenetic modification, therapeutic drug development, functional gene screening, and gene diagnosis has also been aided by gene editing technologies at the same time. Innovative genome editing complexes and more focused nanostructured vesicles have improved efficiency and reduced toxicity during the delivery process, bringing genome editing technology closer to the clinic. It is reasonable to assume that genome editing technology has the potential to ultimately elucidate biological mechanisms behind disease development and progression, providing novel therapies and ultimately promoting the development of the life sciences, with further investigation into this technology (Li et al. 2020; Li et al. 2021a, b).

Non-coding RNA therapeutics

Long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), as well as other types of non-coding RNAs (ncRNAs), are intriguing targets for therapeutic intervention in the treatment of cancer and a variety of other diseases. Many antisense oligonucleotides and small interfering RNAs have been used in the clinical use of RNA-based treatments over the past ten years, and several

Table 7 circRNA-based tools and databases

Tools/databases	Description	Website	References
CIRI	A first and essential step in understanding the synthesis and function of circRNAs is the thorough discovery of these molecules using high-throughput transcriptome data. For the first time, they detect and experimentally validate the prevalence of intronic/intergenic circRNAs as well as segments particular to them in the human transcriptome by applying CIRI to ENCODE RNA-seq data	https://sourceforge.net/projects/ciri/	Gao et al. 2015
CIRCexplorer	This tool is used to identify the fragments mapped to circRNA. It will identify and quantify the circ-RNAs to understand their function	https://github.com/YangLab/CIRCexplorer	Ma et al. 2021
KNIFE	This tool is used to identify the circRNA and will read as a fastq file for further analysis. This tool is implemented using python and R	https://github.com/lindaszabo/KNIFE	Szabo et al. 2015
find_circ	This tool identifies and finds the particular circR-NAs implemented in python and R. The input sequence would read as fastq	https://github.com/rajewsky-lab/find_circ	Memczak et al. 2013
MapSplice2	This tool will map the accurate reads in the splice junction. For the alignment of RNA-Seq reads to splice junctions, the exact algorithm Mapslice is used	http://www.netlab.uky.edU/p/bioinfo/MapSplice2	Wang et al. 2010
segment	This tool will map the short sequence reads to the reference genome	https://www.bioinf.uni-leipzig.de/Software/segemehl/	Hoffmann et al. 2009
circRNA_Finder	This tool is used to identify the circular RNA in a coordinate-based expression filter. This tool was implemented in Perl	https://github.com/orzechoj/circRNA_finder	Di Liddo et al. 2019
ACFS	From single- and paired-ended RNA-Seq data, Acfs enables de novo, accurate, and quick identification and abundance quantification of circRNAs. It is primarily for alignment purposes	https://github.com/arthuryxt/acfs	You & Conrad 2016
NCLscan	This tool will detect the numerous non-colinear transcripts of circRNA	https://github.com/TreesLab/NCLscan	Chuang et al. 2015
DCC	This tool will be able to detect and quantify the circRNA. It will be used for the mapping and alignment process. It is implemented in python packages	https://github.com/dieterich-lab/DCC	Cheng et al. 2015
UROBORUS	It is a computational pipeline to detect the cir-cRNA using RNA-Seq data	https://github.com/WGLab/UROBORUS	Song et al. 2016
circBase	circBase allows users to access, download, and browse consolidated and unified data sets of circRNAs and the evidence demonstrating their expression within the genomic context. Additionally, circBase offers to find both known and novel circRNAs in sequencing data. The organism used is Human, Mouse, worm, fly, and coelacanth	http://www.circbase.org/	Glažar et al. 2014
circRNADb	The goal of circRNADb is to serve as a platform for biological information about circRNA molecules and related biological processes. The database allows the user to study a specific cir-cular RNA of interest and continuously update the database through data search, browsing, downloading, submitting, and feedback. The dataset primarily used in exonic circRNAs and organisms is human	http://reprod.njmu.edu.cn/circrnadb	Chen et al. 2016

Table 7 (continued)

Tools/databases	Description	Website	References
Circ2Traits	It is a collection of databases about disease-circRNA association. The first complete database of possible links between circular RNAs and human disease	http://gyanxet-beta.com/circdb/	Ghosal et al. 2013
CircNet	According to the search, the CircNet database is the first openly accessible database to include tissue-specific circRNA expression profiles and circRNA-miRNA-gene regulation networks. It not only adds to the most recent catalog of circRNAs but also offers a complete examination of the expression of both previously known and newly discovered circRNAs	http://circnet.mbc.nctu.edu.tw/	Liu et al. 2015a, b
circRNABase	The interaction database of circRNA-miRNA. The organism involved in this database is human, mouse, and worm	http://web.archive.org/web/20130922084530/starbase.sysu.edu.cn/mirCircRNA.php	Li et al. 2014
MiOncoCirc	Using exome capture sequencing, 2093 clinical human cancer samples were found to contain circRNA	https://nguyenjoshvo.github.io/	Zhao et al. 2020a, b
CSCD	A database that reports anticipated cellular location, RBP locations, and ORFs focuses on differentiating cancer-specific circRNAs from noncancerous circRNAs	http://gb.whu.edu.cn/CSCD	Xia et al. 2018
CircRiC	This study characterizes circRNAs in cancer cell lines and investigates potential circRNA biogenesis mechanisms and their therapeutic relevance. We also offer a data portal to help with related biomedical research	https://hanlab.uth.edu/cRic	Ruan et al. 2019
circMine	In order to view, search, analyze, and download data freely and to submit new data for further integration, circMine offers user-friendly web interfaces. It can be a valuable tool for finding significant circRNA in various diseases. It has 1,821,448 items of 1107 samples from 31 different human body sites, 136,871 circRNAs, 87 diseases, and 120 circRNA transcriptome datasets	http://hpcc.siat.ac.cn/circmine	Zhang et al. 2021a, b
CircAtlas	An integrated database of 1070 vertebrate transcriptomes and one million precise circular RNAs	http://circatlas.biols.ac.cn/	Wu et al. 2020a, b
CIRCpedia v2	A thorough circRNA annotation from more than 180 RNA-seq datasets from six distinct species is stored in a database	http://www.picb.ac.cn/rnomics/circpedia	Dong et al. 2018a, b
TSCD	They have conducted a thorough analysis to identify the characteristics of tissue-specific (TS) circRNAs in humans and mice. We found 302 853 TS circRNAs in the human and mouse genomes overall, with the brain having the highest density of TS circRNAs	http://gb.whu.edu.cn/TSCD	Xia et al. 2016

of these have acquired FDA approval. Trial findings, however, have been mixed up to this point, with some studies claiming strong effects and others showing minimal efficacy or toxicity. Clinical trials are being conducted on alternative entities like antimiRNAs, and interest is growing in lncRNA-based therapies (Winkle et al. 2021). In this review, the existing therapeutic RNA and clinical trial drugs will be mentioned in Table 10.

Challenges in using ncRNA as biomarkers and therapeutic targets

Non-coding RNAs may be potential biomarkers and therapeutic targets because mounting data suggests they are critical regulators of the pathophysiological processes leading to many diseases. However, its clinical use has not been examined and may face numerous difficulties. First, non-coding

Table 8 Common techniques, databases, and tools used in ncRNA

Tools/databases	Description	Website	References
starBase v2.0	The interaction database of circRNA-miRNA. The organism involved in this database is human, mouse, and worm	http://starbase.sysu.edu.cn/	Li et al. 2014
miRTarBase	A source of microRNA-target interactions that have been verified through experiments	http://mirtarbase.cuhk.edu.cn/php/index.php	Chou et al. 2018
miRmine	A repository of profiles of human miRNA expression	http://guanlab.ccmb.med.umich.edu/mirmine	Panwar et al. 2017
EVmiRNA	A database specializing in extracellular vesicle miRNA expression patterns	http://bioinfo.life.hust.edu.cn/EVmiRNA#!/	Liu et al. 2019
miRGate	A curated library of miRNA-mRNA targets in humans, mice, and rats	http://mirgate.bioinfo.cnio.es/miRGate/	Andrés-León et al. 2015
miRBase	A database of 271 organisms' microRNA sequences, including 48,860 mature microRNAs and 38,589 hairpin precursors	http://www.mirbase.org/	Kozomara et al. 2018
DIANA-TarBase v8	A reference database for indexing miRNA targets that has been supported by the experiment	http://www.microrna.gr/tarbase	Karagkouni et al. 2018
miRCancer	Currently, a database lists more than 9000 connections between 57,984 miRNAs and 196 types of human cancer	http://mircancer.ecu.edu/	Xie et al. 2013
Somalia 2.0	A repository of microRNA (miRNA) target sites and cancer-related somatic alterations may change the interactions between competing endogenous RNAs and miRNAs (ceRNA)	http://compbio.uthsc.edu/SomamiR/	Bhattacharya and Cui 2015
OncomiR	A platform that explores the deregulation of miRNAs in cancer	http://www.oncomir.org/	Wong et al. 2018
miRCancerdb	An accessible resource to research target genes involved in the emergence of cancer under the regulation of microRNAs	https://mahshaaban.shinyapps.io/miRCancerdb/	Ahmed et al. 2018
miR2Disease	A database to offer a thorough resource on microRNA dysregulation in different human diseases	http://www.miR2Disease.org	Jiang et al. 2009
MiRscan	An algorithm for determining the genes for microRNAs from pairs of conserved sequences that may fold back RNA	http://hollywood.mit.edu/mirscan/index.html	Lim 2003
miRanda	This tool will predict the miRNA targets	http://34.236.212.39/microrna/home.do	Betel et al. 2008
RNAhybrid	This tool will predict the miRNA target with unique features such as G:U base pairs in the seed region and a seed-match speed-up	https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid	Kruger & Rehmsmeier 2006
TargetScan	This tool will be able to detect the miRNA targets. It will predict the miRNA, which is a functional site	http://www.targetscan.org/	Agarwal et al. 2015
PicTar	PicTar predicts targets for single microRNAs and combinations of microRNAs with high accuracy	http://pictar.mdc-berlin.de/	Krek et al. 2005

Table 8 (continued)

Tools/databases	Description	Website	References
TargetFinder	TargetFinder is an interactive tool for choosing effective antisense oligonucleotides (AOs). A selection based on target mRNA secondary structures and mRNA accessible site tagging (MAST). TargetFinder is a helpful tool in the selection of AO target sites because of its graphical, user-friendly design	https://github.com/carringtonlab/TargetFinder	Bo and Wang 2004
TarBase	This tool will detect the miRNA targets. Tarbes is a database of experimentally verified miRNA targets in the fruit fly, worm, zebrafish, and human/mouse	http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?%20r=tarbasev8	SETHUPATHY 2005
RNA22	They outline a web-based tool for interactively exploring and visualizing miRNA target prediction methods in context. RNA22-GUI is now available for Caenorhabditis elegans, Drosophila melanogaster, Mus musculus, and Homo sapiens	https://cm.jefferson.edu/rna22/	Loher and Rigoutsos 2012
GenMiR + + (Generative model for miRNA regulation)	MicroRNAs regulate a considerable fraction of mammalian genes by inhibiting protein translation. The computational prediction of miRNA genes and the target mRNAs has received much attention. Here, we offer a new Bayesian model and learning algorithm that considers gene expression patterns	http://www.psi.toronto.edu/genmir/	Huang et al. 2007
PolymiRTS	MicroRNA (miRNA) polymorphisms impair miRNA function, altering physiological and behavioral traits and causing disease. It is now possible to locate miRNA-mRNA binding sites because of polymiRTS	http://compbio.uthsc.edu/miRSNP/	Bhattacharya et al. 2013
miRDB	Numerous gene targets are regulated by small non-coding RNAs called microRNAs (miRNAs). Given their functional significance, miRNAs are the subject of extensive research. An online database system for functional annotation and target prediction for miRNAs is called miRDB	http://www.mirdb.org/	Wang 2008
miRGator	MicroRNA (miRNA)-associated gene expression, target prediction, disease association, and genomic annotation are all included in the miRGator database. It attempts to make miRNA functional research easier. The reference database miRGator v2.0 is used to study miRNA expression and function	http://mirgator.kobic.re.kr/	Cho et al. 2011

Table 8 (continued)

Tools/databases	Description	Website	References
miRecords	miRecords is an integrated database for animal miRNA-target interactions. 11 well-known miRNA target prediction systems create predicted miRNA targets, which miRecords keeps. In seven animal species, the database has 1135 records of verified interactions between 301 miRNAs and 902 target genes	http://c1.accurascience.com/miRecords/	Xiao et al. 2009
mirSOM	Small non-coding RNAs called microRNAs bind to the mRNA of the target gene to control transcriptional activities. Animal miRNA target prediction is difficult because of the imperfection of this binding in animals. The prediction of miRNA targets may be more accurate due to machine learning. This tool is a miRNA target prediction tool that depends on the self-organizing map (SOM)	https://bioinformatics.uef.fi/mirsom/	Heikkinen et al. 2011
miRWalk	An open-source tool called miRWalk generates predicted and verified miRNA-binding sites for well-known genes using an easy-to-use interface. Python, MySQL, and an HTML/Javascript database are used to access the database	http://mirwalk.umm.uni-heidelberg.de/	Sticht et al. 2018
mirDIP	miDIP will be able to predict the 152 million for miRNA target prediction	http://ophid.utoronto.ca/mirDIP/	Tokar et al. 2018
psRNATarget	The high-throughput analysis of next-generation data focuses on the psRNATarget server's architecture. Three streamlined, user-friendly interfaces are included in the server front end. Along with providing online tools for bulk downloading, keyword searching, and results sorting. It reports the number of small RNA/target site pairs	http://plantgrn.noble.org/psRNATarget/	Dai and Zhao 2011
miRTarCLIP	They developed a methodical strategy for mining miRNA-target sites from CLIP-seq and PAR-CLIP sequencing data and then linked the technique with a graphical web-based browser, which offers an intuitive user interface and thorough MTI annotations. Additionally, they demonstrated the effectiveness of miRTarCLIP as a tool for comprehending miRNAs using actual-world situations	http://mirtarclip.mbc.nctu.edu.tw/	Chou et al. 2013
MiRTDL	Genes that are linked to a variety of disorders are regulated by microRNAs. A new convolutional neural network-based miRNA target prediction algorithm is called miRTDL. It has much greater sensitivity, specificity, and accuracy, measuring 88.43, 96.44, and 89.98%, respectively	http://nclab.hit.edu.cn/CCRM/	Shuang et al. 2016

Table 8 (continued)

Tools/databases	Description	Website	References
miRBShunter	According to the evidence, the classical rule about the seed matching between miRNA and target mRNAs is broken in roughly 60% of miRNA-binding activity. The in-house Ago2-dataset and an Auroglial dataset in stem cells were used to evaluate and experimentally validate miRBShunter. Overall, we offer suggestions for selecting a good peak detection algorithm and a novel technique for identifying miRNA-targets	https://github.com/TrabucchiLab/miRBShunter	Bottini et al. 2017
miRTar2GO	MicroRNAs (miRNAs) control gene expression by identifying and attaching to mRNAs' complementary regions. With more lax miRNA-target binding characteristics, miRTar2GO is developed to predict miRNA target sites. It enables the prediction of miRNA targets specific to different cell types	http://www.mirtar2go.org/	Ahadi et al. 2016
MMIA	Comprehensive human genome coverage is used by MMIA, along with categorization into different disease-associated genes, canonical pathways, and Gene Ontology	http://cancer.informatics.indiana.edu/mmia	Nam et al. 2009
mirConnX	A web-based program called mirConnX can infer, show, and parse mRNA and miRNA gene regulatory networks. It builds a disease-specific, genome-wide regulatory network using analysis of gene expression data and sequencing information. It is a valuable tool for developing and exploring hypotheses because of its user-friendly design and extensive database	http://www.benoslab.pitt.edu/mirconnx	Huang et al. 2011
MAGIA	A web program called MAGIA (miRNA and genes integrated analysis) is used to collectively analyze target predictions, miRNA, and gene expression data. MAGIA is accessible freely	http://gencomp.bio.unipd.it/magia	Sales et al. 2010
TargetMinner	This tool will be able to detect the miRNA target prediction. They outperform ten other target prediction algorithms with their approach. Based on a pool of 90 features, we attain a much higher sensitivity and specificity of 69 and 67.8%, respectively. The issue of systematic detection of non-target mRNAs is still unresolved	http://www.isical.ac.in/%C2%A0bioinfo_miu/	Bandyopadhyay and Mitra 2009

Table 8 (continued)

Tools/databases	Description	Website	References
ExprTarget	One important mechanism of gene regulation is the attachment of a class of tiny RNA molecules known as microRNAs to mRNA transcripts. Understanding gene regulation networks requires a comprehensive library of miRNA-regulated targets. ExprTarget considerably enhances both the sensitivity and specificity of miRNA target prediction	http://www.scandb.org/apps/microrna/	Gamazon et al. 2010
MirZ	MirZ web server makes statistical analysis and data mining tools available to experimental and analytical biologists that use the most recent databases of predicted miRNA target sites and sequencing-based miRNA expression profiles for species ranging from Caenorhabditis elegans to Homo sapiens	http://www.mirz.unibas.ch/	Hausser et al. 2009
mimiRNA	MicroRNAs are small non-coding RNAs that control gene expression by blocking their target mRNA genes. Their expression patterns offer substantial therapeutic and diagnostic potential and therefore are tissue- and disease-specific. To comprehend these patterns, a reliable collection of miRNA and mRNA expression data is needed. mimiRNA will be able to solve this problem	http://mimirna.centenary.org.au/	Ritchie et al. 2009
ViennaRNA	A crucial intermediate level of description of nucleic acids is their secondary structure. It captures most folding energy and is frequently well-conserved during evolution. Among the new features is a comprehensive toolbox for evaluating RNA-RNA interactions and constrained ensembles of structures. A popular collection of software tools relevant to RNA secondary structure is called the ViennaRNA Package	http://rna.tbi.univie.ac.at/	Lorenz et al. 2011
HMDD	Many miRNA-disease association entries are manually compiled from literature for the new Human MicroRNA Disease Database (HMDD v3.0). HMDD is openly available	http://210.73.221.6/hmdd	Huang et al. 2019a, b
mirPath	An online software package called DIANA-miRPath v3.0 is used to evaluate the regulatory functions of miRNAs and identify regulated pathways. The capabilities and database have been greatly expanded to accommodate all KEGG molecular pathway analyses and several Gene Ontology components	http://snf-515788.vm.okeanos.grnet.gr/	Vlachos et al. 2015

Table 8 (continued)

Tools/databases	Description	Website	References
ExoCarta	Different types of cells release vesicles called exosomes into the extracellular surroundings. Exosomes include RNA, proteins, and lipids. Hence, it is essential to understand their molecular contents. ExoCarta includes biological pathways of exosomal proteins and dynamic protein–protein interaction networks. Based on the number of investigations, users can download the most often detected exosomal proteins	http://www.exocarta.org/	Keerthikumar et al. 2016
SeqBuster	SeqBuster is the first bioinformatic tool to comprehensively characterize miRNA variants by integrating different analysis modules into a novel platform (isomiRs). SeqBuster was used to analyze small-RNA datasets from human embryonic stem cells, and the results showed that most miRNAs contain a variety of isomiRs, some of which are linked to stem cell development. SeqBuster's thorough description of the isomiRs may make it easier to spot miRNA variants important for both physiological and pathological processes	https://pypi.org/project/seqcluster/	Pantano et al. 2009
TransmiR	For more specific details on regulating transcription factor (TF)-miRNA, see the TransmiR v2.0 database. By manually curating 3730 TF-miRNA regulations across 19 species from 1349 papers and reviewing more than 8000 articles, more than 1.7 million tissue-specific TF-miRNA regulations based on ChIP-seq data were also added. TransmiR v2.0 would be a helpful tool for researching how miRNAs are regulated	http://www.cuilab.cn/transmir	Tong et al. 2019
dbDEMC	This database is anticipated to be a valuable resource for identifying cancer-related miRNAs, which will aid in advancing human cancer categorization, diagnosis, and treatment	http://www.picb.ac.cn/dbDEMC	Yang et al. 2010
miTALOS	Nearly all biological activities require microRNAs, which act as signaling pathway regulators. The expression of miRNA target and pathway genes varies across human tissues. The tool miTALOS v2 sheds light on how particular miRNAs regulate biological pathways in different tissues	http://mips.helmholtz-muenchen.de/mitalos	Preusse et al. 2016

Table 8 (continued)

Tools/databases	Description	Website	References
miRT	By compiling information from several experimental investigations that validate miRNA TSSs and make the whole datasets available for download, we present a novel database of validated miRNA TSSs in this study called miRT. We offer miRT as a web server that can convert TSS loci between various genome structures. For cutting-edge research on miRNA regulation, miRT may be a helpful tool	http://mirstart.mbc.nctu.edu.tw/	Bhattacharyya et al. 2012
miRandola	Small non-coding RNAs called microRNAs are crucial in the control of many biological processes. They are commonly dysregulated in cancer and have demonstrated considerable promise as diagnostic and prognostic indicators. miRandola is a comprehensive catalog of extracellular circulating miRNAs that have been extensively curated	http://mirandola.iit.cnr.it/	Russo et al. 2012
miRNEST	A comprehensive resource for microRNAs is the MiRNEST database. The user interface was enhanced, and download and upload options were added in version 2.0. In-depth miRNA predictions using deep sequencing libraries, assessments of the degradation of plants, and categorization of pre-miRNAs were also incorporated	http://rhesus.amu.edu.pl/mirnest/copy/	Szcześniak & Makałowska 2013
miR-EdiTar	The database of anticipated A-to-I edited miRNA binding sites known as miR-EdiTar is presented in this work. The database includes projected miRNA binding sites that A-to-I editing may modify and sites that A-to-I editing may cause to become miRNA-binding sites	http://www.tau.ac.il/~elieis/miR_editing	Laganà et al. 2012
SM2miR	The development of miRNA therapeutics will be aided by SM2miR's complete archive on the effects of small compounds on miRNA expression	http://210.46.85.180:8080/sm2mir/index.jsp	Liu et al. 2012
YM500	Researchers can use this interactive web interface to search this database for these four categories of analytical results. In addition to integrating data from dbSNP to help researchers distinguish between isomiRs and SNPs, YM500 enables researchers to specify the criteria for isomiRs. Integrating miRNA-related data with preexisting evidence from hundreds of sequencing datasets is made possible by a user-friendly interface. The discovered new miRNAs and isomiRs have the potential to be used in biotechnological and fundamental research	http://driverdb.tms.cmu.edu.tw/ym500v3/	Cheng et al. 2012

Table 8 (continued)

Tools/databases	Description	Website	References
isomiRex	To discover isomiRs and provide an on-demand graphical display of the differentially expressed miRNAs, we provide the open-access web platform isomiRex. The platform can handle many read counts and reports the annotated microRNAs from the plant, animal, and viral NGS datasets	http://bioinfo1.uni-plovdiv.bg/isomiRex/	Sablok et al. 2013
PHDcleav	Predicting the Dicer cleavage sites in pre-miRNA using the website PHDcleav. With the help of this tool, researchers can examine the effects of genetic variants and SNPs in miRNA on the Dicer cleavage site and gene silencing. Additionally, it would be helpful in the identification of miRNAs in the human genome and the creation of pre-miRNAs specific to Dicer for effective gene silencing	http://crdd.osdd.net/raghava/phdcleav/	Ahmed et al. 2013
PASmiR	To give thorough, searchable descriptions of miRNA molecular regulation in various plant abiotic stressors, PASmiR, a literature-curated and web-accessible database, was created. Users can receive miRNA-stress regulatory entries using the plant species, abiotic stress, and miRNA identifier as keywords in the PASmiR interface. There are presently 1038 regulatory connections between 682 miRNAs and 35 abiotic stressors in 33 plant species represented by data from almost 200 published research in PASmiR	http://pcsb.ahau.edu.cn:8080/PASmiR	Zhang et al. 2013
microTSS	The missing piece to incorporating the regulation of miRNA transcription into the modeling of tissue-specific regulatory networks is MicroTSS, which is easily adaptable to any cell or tissue sample	http://www.microrna.gr/microTSS/	Georgakilas et al. 2014
Chimera	A chimera is a web-based tool for small RNA-Seq data processing using microRNA (miRNA). Chimera produces data on miRNA expression based on counts for later statistical analysis. In order to map sequences to miRNA hairpin sequences, cleaning, trimming, and size selection are made automatically	http://wwwdev.ebi.ac.uk/enright-dev/chimira/	Vitsios and Enright 2015

Table 8 (continued)

Tools/databases	Description	Website	References
MirGeneDB	Individual gene sequences for microRNAs are conserved throughout the animal kingdom, making them unique. Genuine miRNAs may be easily distinguished from the countless other short RNAs produced by cells using particular and mechanistically understood characteristics. Previous microRNA annotations notably omitted > 2000 bona five microRNAs and had several false positives. MirGeneDB is a robust platform for microRNA-based research, offering a more substantial and in-depth understanding of the biology and evolution of miRNAs as well as biomedical and Biomarker research	http://mirgenedb.org/	Fromm et al. 2019
DREAM	A web server for identifying mature microRNA editing events is a website for detecting RNA editing linked to microRNAs. Raw reads from microRNA sequencing can be used as input. Custom scripts analyze the statistical significance, interpret the data, and look for potential modification spots	http://www.cs.tau.ac.il/~mirnaed/	Alon et al. 2015
Islamic Bank	A web server for identifying mature microRNA editing events is a website for detecting RNA editing linked to microRNAs. Raw reads from microRNA sequencing can be used as input. Custom scripts analyze the statistical significance, interpret the data, and look for potential modification spots	http://mcg.ustc.edu.cn/bsc/isomir/	Zhang et al. 2016a, b, c
TissueAtlas	Human tissue miRNA TSI levels are firmly ($P = 108$) linked with rat tissue miRNA TSI values. There were 1,364 miRNAs in 61 tissue biopsies from various organs. MiRNA abundance clustering showed that tissues, including various brain regions, grouped	https://ccb-web.cs.uni-saarland.de/tissueatlas/	Ludwig et al. 2016
miRNAme Converter	The central archive for miRNAs is the miRBase database. Inconsistencies in mature miRNA names result from name changes in various miRNA releases. The problems brought on by these inconsistencies are addressed by the software and online interface known as miRNAmeConverter. The primary method enables a high-throughput automatic translation of mature mi RNA names that are independent of species	http://163.172.134.150/miRNAmeConverter-shiny	Haunsberger et al. 2016

Table 8 (continued)

Tools/databases	Description	Website	References
mirSTP	Understanding how miRNAs are regulated in development and disease requires the identification of miRNA transcription start sites (miRNA TSSs). Researchers at Vanderbilt University created mirSTP, which offers a probabilistic method for determining active miRNA Tsss from developing transcriptomes	http://bioinfo.vanderbilt.edu/mirSTP/	Liu et al. 2017a, b
ParSel	Tumor micro-RNAs (miRNA) can determine a patient's prognosis and response to therapy. By examining their cooperative involvement in gene regulation, this methodology aims to rank the miRNAs. It uses parallel processing to examine a sizably large number of combinatorial scenarios	https://github.com/debsin/ParSel	Sinha et al. 2017
isomiR2 function	Non-coding RNAs (ncRNAs) have been implicated in post-transcriptional control by changing plants' transcriptional landscape. A standalone, quickly deployable tool called isomiR2Function enables the high-throughput and reliable discovery of both templated and untemplated isomiRs	https://github.com/347033139/isomiR2Function	Yang et al. 2017
miRsig	To fully utilize the potential of miRNA in diagnostic, prognostic, and therapeutic applications, it is crucial to decode the patterns of miRNA regulation in illnesses. Computational predictions of potential miRNA-miRNA interactions have only been made in a few research. To understand how these interactions contribute to the development of the disease, further research is needed. We created miRsig, an online tool for analyzing and visualizing the core miRNA-miRNA interaction associated with disease-specific signatures	http://bnet.egr.vcu.edu/miRsig/	Nalluri et al. 2017
misalign	This computational method detects miRNA in animals based on structure and sequence alignment. This tool has greater specificity and sensitivity compared to other tools	http://bioinfo.au.tsinghua.edu.cn/miralign	Wang et al. 2005
CID-miRNA	CID-miRNA uses secondary structure-based filtering algorithms and an algorithm based on stochastic context-free grammar trained on human miRNAs to identify miRNA precursors in a given DNA sequence	http://mirna.jnu.ac.in/cidmirna/	Tyagi et al. 2008
MiRank	To identify the novel miRNA using a rank-based approach		Xu et al. 2008
mirTool	To investigate miRNA through small RNA transcriptome	http://centre.bioinformatics.zj.cn/mirtools/	Zhu et al. 2010
snoSeeker	This tool has been developed to screen snoRNA genes in the human genome		Yang et al. 2006

Table 8 (continued)

Tools/databases	Description	Website	References
MiRanalyzer	This tool has been developed to identify novel miRNA and known miRNA using High-throughput sequencing experiments	http://bioinfo2.ugr.es/miRanalyzer/miRanalyzer.php	Hackenberg et al. 2011
UEA sRNA workbench	The UEA sRNA workbench is a collection of tools that replaces the web-based UEA sRNA Toolkit, although it is available for download and has several improved and extra features	http://srna-workbench.cmp.uea.ac.uk	Stocks et al. 2012
MicroPC	Users can thoroughly compare and predict plant miRNAs and their targets using a first online resource. It provides a foundation for the ongoing investigation into miRNA's conservation, use, and evolution across plant species and classification	http://www.biotec.or.th/isl/micropc	Mhuantong and Wichadakul 2009
HHMMiR	Modeling of miRNA hairpins		Kadri et al. 2009
miReader	Discovering the novel miRNA without using genomic/reference sequences. The algorithm used is Multi-boosting	http://scbb.ihbt.res.in/2810-12/miReader.php	Jha and Shankar 2013
miRPlex	To predict miRNA only through sRNA datasets without using reference genome	https://www.uea.ac.uk/computing/mirplex	Mapleson et al. 2013
miRdentify	This tool will predict the miRNA in different species	http://www.ncrnalab.dk/#mirdentify/mirdentify.php	Hansen et al. 2014
deepSOM	This tool will be able to detect the pre-miRNA precursor using sequence. The algorithm used is supervised machine learning	http://fich.unl.edu.ar/sinc/blog/web-demo/deepsom/	Stegmayer et al. 2017
Mirnovo	This tool will be able to detect the miRNA from small RNA seq data using a machine-learning algorithm	http://wwwdev.ebi.ac.uk/enright-dev/mirnovo/	Vitsios et al. 2017

RNAs are still being developed as biomarkers. Although RT-PCR, next-generation sequencing, and microarray analysis have been utilized in research examining the connection between non-coding RNAs and disease-specific traits, most of these investigations are still experimental. However, no research has examined the viability of choosing lncRNA/circRNA as novel biomarkers (Zhang et al. 2017a, b). The discovery of tissue- or organ-specific biomarkers would be beneficial for the early diagnosis, treatment, and intervention of organ failure, perhaps increasing the chance of disease-specific survival.

Because they differ from conventional medications, such as small-molecule and protein medicines, which are also known to work primarily on protein targets, RNA-based therapies are considered the next generation of therapeutics. First, RNA aptamers can produce pharmacological effects by blocking the activity of a particular protein target. Second, for controlling a specific disease, antisense RNAs (asRNAs), miRNAs, and siRNAs can be created to specifically target mRNAs or functional ncRNAs. Thirdly, to cure a monogenic condition, gRNAs may be used to precisely alter the target sequences of a particular gene. Thus, RNA therapies can potentially increase the number of druggable targets. On-coding RNAs are promising "next-generation" biomarkers since the issues mentioned earlier and difficulties can be resolved. Non-coding RNAs may one day serve as innovative treatment targets with the help of a more profound knowledge of the mechanism underlying those specific diseases.

Conclusion and future perspectives

The attractive new field of ncRNA research demonstrates a higher level of nature's diversity. The complexity of ncRNA research results from the more significant than specified based on ncRNAs in cellular biology. Nevertheless, even though ncRNAs have recently been discovered, there have been significant advancements in clinical applications and diagnostic methods. This research will likely expand into a new area of more potent and particular medications and personalized medicine techniques, elevating patient care to a new level. Rapid developments in bioinformatics,

Table 9 Different techniques used for ncRNA discovery

Techniques	Description	References
SHAPE (selective 20-hydroxyl analyzed by primer extension)	It is a method to decipher the lncRNAs secondary structure	Wilkinson et al. 2006
PARS (parallel analysis of RNA structure)	It is a technology recently developed with the Illumina platform (nextPARS) that can study changes in lncRNA structure that may occur in carcinogenesis in order to produce results with higher throughput and sample multiplexing	Saus et al. 2018
Frag-Seq (fragmentation sequencing)	It combines RNA-seq with methods that determine nuclease accessibility at the single base resolution to provide an assay for exploring RNA structure at the transcriptome-wide level	Uzilov and Underwood 2016
ICE-seq (inosine chemical erasing sequencing)	It is a method that can show how A-to-I editing of lncRNAs may become dysregulated in cancer, allowing for meaningful effects on their secondary structure and, later, on the interaction with other RNA molecules	Sakurai et al. 2010
BRIC-seq (50-bromo-uridine immunoprecipitation chase–deep sequencing)	It is a technique that can accurately calculate the half-life of RNA in cells under pathological and physiological settings	Imamachi et al. 2014
FISSEQ (fluorescent in situ sequencings)	It is a technique that uses SOLiD sequencing to detect spatial alterations in lncRNAs that occur during cancer	Lee et al. 2015
Gro-seq (global run-on assay sequencing)	It provides details about the location, orientation, and density of RNAs being actively translated by RNA pol II using an NGS-based approach	Gardini 2017
Tiling arrays	A technique using probes to find transcripts from particular genomic regions	Mockler and Ecker 2005
Microarrays	A technique for quickly analyzing the transcriptome's global or parallel expression that uses many oligonucleotide probes	Yan et al. 2012
RNA-seq	A method that is now the most popular sequencing technology for RNA expression detection and new RNA discovery	Wang et al. 2009
RNA capture sequencing	An alternative method that combines tilling arrays and RNA-seq	Mercer et al. 2011
Smart-seq	A full-length cDNA amplification technique-based method for scRNA-seq	Ramsköld et al. 2012
DP-seq	A heptamer-primer-based scRNA-seq technique	Bhargava et al. 2013
Quartz-seq	A technique for scRNA-seq that lowers background noise	Sasagawa et al. 2013
SUPeR-seq	RNA sequencing using a single-cell global polyadenylated tail method	Fan et al. 2015
RamDA-seq	a technique for studying single cells based on the full-length whole RNA sequencing	Hayashi et al. 2018
Small RNA-seq	This is the type of RNASeq that distinguish small RNA from larger RNA to understand better these novel RNAs	Landgraf et al. 2007
Small-seq	A technique that will detect the small RNAs in a single cell	Hagemann-Jensen et al. 2018
SLAM-seq	A technique that uses s4U-to-C conversion brought on by nucleophilic substitution chemistry to separate nascent RNA from total RNA	Herzog et al. 2017
TimeLapse-seq	A technique that uses the s4U-to-C conversion caused by an oxidative nucleophilic aromatic substitution process to discriminate between nascent and whole RNA	Schofield et al. 2018

Table 9 (continued)

Techniques	Description	References
AMUC-seq	A process for converting s4U into a cytidine derivative using acrylonitrile to differentiate between nascent and total RNA	Chen et al. 2020a, b
GRID-seq	A procedure that seeks to fully identify and pinpoint the locations of all possible chromatin-interacting RNAs	Li et al. 2017a, b, c
iMARGI	An approach that provides in situ mapping of the RNA-genome interactome	Yan et al. 2019a, b
ChAR-seq	A genome-wide RNA-to-DNA interaction map produced by chromatin-associated RNA sequencing	Bell et al. 2018
CLASH	An old technique for detecting direct RNA-RNA hybridization employs UV cross-linking	Kudla et al. 2011
RIPPLiT	A method for examining the 3D conformations of RNAs that are stably linked with specific proteins at the transcriptome level	Metkar et al. 2018
MARIO	A technique that uses a biotin-linked reagent to detect RNA-RNA interactions near every protein that binds to RNA	Nguyen et al. 2016
PARIS	High throughput and resolution investigation of RNA interactions and structures using psoralen	Lu et al. 2016
LIGR-seq	A technique for mapping RNA-RNA interactions in vivo at a global level	Sharma et al. 2016
SPLASH	A technique that provides genome-wide paired RNA-RNA pairing data	Aw et al. 2016
RIC-seq	In this method, using RNA in situ conformation sequencing to map all RNA-RNA interactions at the intra- and intermolecular level	Cai et al. 2020
RNA proximity sequencing	A process using high-throughput RNA barcoding of the particles in water-in-oil emulsion droplets	Morf et al. 2019
FISSEQ	A technique that will provide in situ RNA information at high throughput levels	Lee et al. 2015
CeFra-seq	A process for physically isolating subcellular spaces and locating their RNAs	Taliaferro et al. 2014
APEX-RIP	A technique can map organelle-associated RNAs in living cells using proximity biotinylation and protein-RNA cross-linking	Kaewsapsak et al. 2017

sequencing technologies, proteomics, and microarrays have identified a wide variety of non-coding RNAs (ncRNA), which comprise most cellular mechanism regulators principally linked to eukaryotic complexity. It seems more difficult to comprehend the unique function of these non-coding RNAs with these varied ncRNAs having integrated, complicated networks and biological pathways. The use of ncRNA therapies in formal drug development will increase.

Further information has to be obtained, possible ncRNA medicines' pharmacokinetics and dynamics need to be examined, and thorough toxicological studies are required. To advance the field, more tools are required. There will be more phase I/II clinical studies. This study aims to investigate and advance knowledge of the mechanisms and functions of ncRNAs in human health and disease and to pave the way for novel clinical diagnostic and therapeutic approaches. When dealing with the enormous quantity of ncRNAs that need to be analyzed, ML outperforms since it can quickly address the fundamental problem. By categorizing healthy and disease samples, the current analysis of ncRNAs using ML demonstrates reasonable accuracy, indicating that the differentiation pattern is apparent in those instances. Therefore, future research should concentrate on increasing the likelihood that the ML models will recognize the distinctive pattern of each disease. However, the use of ncRNAs may significantly rise in the following years, which will contribute to the development of successful precision medicine and more individualized therapies.

Table 10 Existing ncRNA therapeutic drugs and clinical trial drugs

Drug_name	Mode of drug admin	Target	Mechanism of Action	Disease	Company	Status of the drug	References
Fomivirsen	IVT (intravitreal administration)	CMV mRNA	Downregulates IE2	Cytomegalovirus (CMV) retinitis with acquired AIDS	Ionis Pharmaceutical, Novartis	FDA-approved (1998)	Vitravene Study Group 2002
Mipomersen	SC (subcutaneous Injection)	apo-B-100 mRNA	Downregulates ApoB	Homozygous familial hypercholesterolemia	Kastle Therapeutics, Ionis Pharmaceuticals, Genzyme	FDA approved (2013)	Santos et al. 2015
Nusinersen	ITH	SMN2 pre-mRNA	Splicing modulation	Spinal muscular atrophy	Ionis Pharmaceuticals, Biogen	FDA approved (2016)	Mercuri et al. 2018
Eteplirsen	IV (intravenous)	Exon 51 of DMD	Splicing modulation	Duchenne muscular dystrophy	Sarepta Therapeutics	FDA approved	Mendell et al. 2013
Inotersen	SC (subcutaneous Injection)	TTR mRNA	Downregulates transthyretin mRNA	Familial amyloid polyneuropathy	Ionis Pharmaceuticals	FDA approved (2018)	Benson et al. 2018
Golodirsen	IV(intravenous)	Exon 53 of DMD	Splicing modulation	Duchenne muscular dystrophy	Sarepta Therapeutics	FDA approved (2019)	Scaglioni et al. 2021
Milasen	Intrathecal	CLN7	Splicing modulation	Batten disease	Boston Children's Hospital	FDA approved (2018)	Kim et al. 2019
Casimersen	IV (intravenous)	Exon 45 of DMD	Splicing modulation	Duchenne muscular dystrophy	Sarepta Therapeutics	FDA approved (2021)	Shirley 2021
1018 ISS	IV (intravenous)	TLR9	Enhancement of cytotoxic effector mechanisms	Non-Hodgkin's lymphoma	Dana-Farber Cancer Institute, Brigham and Women's Hospital, Massachusetts General Hospital, University of Rochester	NCT00251394 (Phase II)	Friedberg et al. 2005
Apatorsen (OGX-427)	IV (intravenous)	HSP27	Inhibits expression of heat shock protein (Hsp27)	Urologic cancer, bladder cancer, prostate cancer, urothelial cancer, non-small-cell lung cancer, and other cancers	Achieve Life Sciences PRA Health Sciences	NCT00487786 (PhaseI), NCT01454089 (Phase-II)	Chi et al. 2016
Cenersen (EL625)	IV (intravenous)	TP53	Blocks the effects of p53	Acute myelogenous leukemia, lymphoma	Eleos, Inc	NCT00074737(Phase II)	Cortes et al. 2011
ARRx (AZD5312)	IV (intravenous)	AR	Suppression of human AR expression	Prostate Cancer	AstraZeneca	NCT02144051 (Phase I/II)	De Velasco et al. 2019

Table 10 (continued)

Drug_name	Mode of drug admin	Target	Mechanism of Action	Disease	Company	Status of the drug	References
Custirsen (OGX-011)	IV (intravenous)	ApoJ	Inhibition of clusterin expression	Prostate cancer, breast cancer, non-small-cell lung cancer	NCIC Clinical Trials Group, Achieve Life Sciences	NCT00054106 (Phase I),NCT00138658(Phase-II)	Laskin et al. 2012;Chi et al. 2005
Patisiran	IV (intravenous)	TTR mRNA	Transthyretin activity is decreased	Polyneuropathy caused by hATTR amyloidosis	Alnylam	FDA approved (2018)	Adams et al. 2018
Givosiran	SC (subcutaneous injection)	ALS1 mRNA	ALAS1 is decreased in expression	Acute hepatic porphyria	Alnylam	FDA approved (2020)	Balwani et al. 2020
Lumasiran	SC (subcutaneous injection)	HAO1 mRNA	Reduced glycolate oxidase activity	Primary hyperoxaluria type 1	Alnylam	FDA approved (2020)	Liebow et al. 2016
Inclisiran	SC (subcutaneous injection)	PCSK9	Proprotein convertase subtilsin/kexin type 9 is downregulated	Atherosclerotic cardiovascular disease	Novartis	FDA approved (2021)	Lamb 2021
TKM-080301	Intra-arterial/IV	PLK1	Activation of PLK1 is reduced	Hepatocellular cancer, cancer with hepatic metastases,	National Cancer Institute, Arbutus Biopharma Corporation	NCT01437007 (Phase-I), NCT02191878(Phase-II)	El Dika et al. 2018;Steegmaier et al. 2007
Atu027	IV(intravenous)	PNK3	The expression of PNK3 is silenced	Solid tumors, pancreatic cancer	Silence Therapeutics GmbH, Granzer Regulatory Consulting & Services	NCT00938574 (Phase-I), NCT01808638 (Phase -II)	Schultheis et al. 2014;Schultheis et al. 2020
siG12D LODER	Locally implanted through EUS biopsy procedure	KRASG12D	Blocks the expression of KRAS	Pancreatic cancer	Silenseed Ltd	NCT01676259 (Phase -I), NCT01188785 (Phase-II)	Golan et al. 2015; Zorde Khvalevsky et al. 2013
ARO-HIF2	IV (intravenous)	HIF2A	HIF2A deregulation	Clear cell renal cell carcinoma	Arrowhead Pharmaceuticals	NCT04169711 (Phase-I)	Cho & Kaelin 2016
APN401	IV (intravenous)	CBLB	Inhibition of Cbl-b enhances natural killer cell and T cell-mediated antitumor activity	Brain cancer, melanoma, pancreatic cancer, renal cell cancer	Wake Forest University Health Sciences, National Cancer Institute	NCT03087591,NCT02166255 (Phase-I)	Triozzi et al. 2015
Vutrisiran	SQ (subcutaneous injection)	TTR	It lowers the expression of the TTR protein	Transthyretin-mediated amyloidosis with or without cardiomyopathy	Alnylam	NCT03759379, NCT04153149 (Phase 3)	Habtemariam et al. 2020; Sekijima et al. 2005
Pegaptanib	Intravitreal	The heparin-binding domain of VEGF-165	inhibiting VEGF-165	Neovascular age-related macular degeneration	OSI Pharmaceuticals	FDA-approved (2004)	Gragoudas et al. 2004

Table 10 (continued)

Drug_name	Mode of drug admin	Target	Mechanism of Action	Disease	Company	Status of the drug	References
Defibrotide	IV (intravenous)	Adenosine A1/A2receptor	Adenosine A1/A2 receptor activation	Veno-occlusive disease in liver	Jazz Pharmaceuticals	FDA-approved (2020)	Richardson et al. 2017;Lee et al. 2021
NOX-A12	IV (intravenous)	CXCL12	Interferes with CXCR4-CXCL12 interactions	Pancreatic cancer, colorectal cancer, multiple myeloma	NOXXON Pharma AG, Merck Sharp & Dohme Corp	NCT01521533(Phase-I),NCT01521533(Phase-II),NCT03168139(Phase-I/II)	Park et al. 2019
NOX-E36	IV (intravenous)/SQ (subcutaneous)	CCL2	Suppresses the pro-inflammatory chemokine CCL2 by specifically binding to it	Diabetic nephropathy	NOXXON Pharma AG	Phase-II	Menne et al. 2016
BNT162b2	IM (intramuscular injection)	Immunogenicity and antibody response to SARS-CoV-2 S antigens	Expression of SARS-CoV-2 S antigens	COVID-19	BioNTech and Pfizer	FDA-approved (2020)	Polack et al. 2020
mRNA-1273	IM (intramuscular injection)	Immunogenicity and antibody response to SARS-CoV-2 S antigens	Expression of SARS-CoV-2 S(Spike protein) antigens	COVID-19	Moderna	FDA-approved (2020)	Baden et al. 2020
CVnCoV	IM (intramuscular injection)	Immunogenicity and antibody response to SARS-CoV-2 S antigens	Expression of SARS-CoV-2 S antigens	COVID-19	CureVac AG	NCT04652102 (Phase -III)	Kremsner et al. 2022
AZD8601	Epicardial	VEGF-A	VEGF-A expression is restored	Ischemic heart disease	AstraZeneca	NCT03370887 (Phase- II)	Anttila et al. 2020
MRT5005	Inhalation	CFTR	CFTR expression is restored	Cystic fibrosis	Translate Bio	NCT03375047 (Phase -I/II)	Yan et al. 2019a, b
mRNA-3704	IV (intravenous)/SQ (subcutaneous)	MUT	MUT expression is restored	Methylmalonic aciduria	Moderna	NCT03810690 (Phase -I/II)	Chandler and Venditti 2019

Table 10 (continued)

Drug_name	Mode of drug admin	Target	Mechanism of Action	Disease	Company	Status of the drug	References
BNT111	IV (intravenous)/ SQ(subcutaneous)	Targets four non-mutated TAAs (NY-ESO-1, MAGEA3, tyrosinase, and TPTE	Immune response induction against the four malignant melanoma-associated antigens (tyrosinase, New York-ESO-1 (NY-ESO-1), Melanoma-associated antigen A3 (MAGE-A3), and transmembrane phosphatase with tensin homology (TPTE))	Advanced melanoma	BioNTech SE	NCT02410733 (Phase -I)	Sahin et al. 2020
Miravirsen	SC (subcutaneous injection)	miR-122	miRNA-inhibitor	HCV	Roche/Santaris	NCT01200420(Phase- II)	Janssen et al. 2013
RG-012 (lademirsen)	SC (subcutaneous injection)	miR-21	miRNA-inhibitor	Alport syndrome	Sanofi	NCT03373786(Phase- II)	Gomez et al. 2014
Cobomarsen	IV/SQ	miR-155	miRNA-inhibitor	Cutaneous T cell lymphoma/mycosis Fungoides	miRagen	NCT03713320, NCT02580552(Phase -II)	Bedewy et al. 2017
MRG-110	Intradermal	miR-92a	miRNA-inhibitor	Wound healing	miRagen	NCT03603431(Phase -I)	Bonauer et al. 2009
AZD4076	SC (subcutaneous injection)	miR-103/107	miRNA-inhibitor	T2D with NAFLD	AstraZeneca	NCT02826525(Phase- I/IIa)	Trajkovski et al. 2011
RGLS4326	SC (subcutaneous injection)	miR-17	miRNA-inhibitor	Autosomal dominant polycystic kidney disease	Regulus Therapeutics Inc	NCT04536688(Phase -I)	Lee et al. 2019
CDR132L	IV (intravenous)/SQ (subcutaneous)	miR-132	miRNA-inhibitor	Heart failure	Cardio Pharmaceuticals GmbH	NCT04045405(Phase -I)	Täubel et al. 2020
TargomiRs	IV (intravenous)/SQ (subcutaneous)	miR-16	miRNA-mimic	Malignant pleural mesothelioma	EnGeneIC Limited	NCT02369198(Phase- I)	van Zandwijk et al. 2017
Remlarsen	Intradermal	miR-29	miRNA-mimic	Keloids, scleroderma	miRagen	NCT03601052(Phase -II)	Cushing et al. 2011
MRX34	IV (intravenous)/SQ (subcutaneous)	miR-34a	miRNA-mimic	Melanoma, liver cancer	miRNA Therapeutics, Inc	NCT01829971(Phase -I)	Beg et al. 2017

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