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The Complexity Of Non-Coding Rnas: Implications For Cancer Diagnosis And Therapy

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Abstract:

Non-coding RNAs (ncRNAs) constitute a diverse family of RNA molecules that regulate various cellular processes, with implications spanning from basic molecular biology to clinical applications. This review explores the multifaceted roles of ncRNAs in gene regulation, focusing on their involvement in cancer biology and potential applications as diagnostic and therapeutic targets. NcRNAs encompass a wide array of molecules, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and others, each exerting regulatory effects on gene expression through various mechanisms. MiRNAs, for instance, regulate mRNA transcripts via sequence-specific interactions, while lncRNAs modulate gene expression at transcriptional and post-transcriptional levels. In cancer, dysregulated expression of ncRNAs contributes to tumorigenesis, metastasis, and drug resistance, highlighting their potential as biomarkers for diagnosis and prognosis. Liquid biopsies, utilizing circulating tumor-derived ncRNAs, offer less invasive alternatives to traditional tissue biopsies for cancer detection and monitoring. Additionally, advancements in RNA sequencing technologies enable comprehensive profiling of ncRNAs, aiding in the identification of cancer-specific signatures. Therapeutically, ncRNAs hold promise as targets for innovative treatments, such as RNA-based gene silencing therapies. Clinical trials investigating ncRNA-targeted therapies have shown encouraging results in diverse cancer types, although challenges remain in ensuring efficacy and safety. Overall, the burgeoning field of ncRNA research offers insights into the complex regulatory networks governing cancer biology and presents opportunities for the development of novel diagnostic tools and therapeutic interventions.

Keywords: Non-coding RNAs (ncRNAs), Cancer biology, Gene regulation, Diagnostic biomarkers, Therapeutic targets, Liquid biopsies, RNA-based therapies

Introduction to non-coding RNAs

"Frontiers in Non-Coding RNA: Regulation and Therapy"

Non-coding RNAs (ncRNAs) are a family of RNA molecules that play a critical or regulatory role in the process of protein synthesis, in contrast to messenger RNAs, which function as templates for the process. ncRNAs are essential for translation since they are the building blocks of ribosomes (rRNA) or transfer amino acids (tRNA) to the formed peptide. It was just discovered thirty years ago that additional non-coding RNAs (ncRNAs) regulate the expression of proteins or other metabolic processes. [1]. These later ones, which are commonly known as the regulatory ncRNA, attracted attention right away and continue to do so now as fresh information demonstrating their participation in processes like cell proliferation, apoptosis, and differentiation is being shown practically daily. [2]. Cytoplasmic regulatory non-coding RNAs (ncRNAs) are classified into two types based on their nucleotide count: microRNAs (miRNA) and long non-coding RNAs (lncRNAs)[3]. Through the identification of complementary sites at the UTR region of the mRNA, miRNAs interact with mRNA transcripts in a sequence-specific manner that results in transcriptional suppression or the destruction of the mRNA. [4]. LncRNAs are RNA molecules that have a length of more than 200 nucleotides. The primary way that these particles control expression is through their interactions with transcriptional regulatory elements. By competing with the enhancer or creating chromatin loops with target genes, lncRNAs can either positively or adversely impact enhancer activity. Furthermore, it has been demonstrated that lncRNAs interact with the transcript and prevent splicing.[3]. It's interesting to note that lncRNAs have the ability to draw in and bind miRNAs, thereby decreasing their activity. These layered relationships between various RNA types show how intricately these regulatory ncRNAs interact. [3]. ncRNAs influence gene expression, which has a myriad of impacts on different biological mechanisms.[5]. Many diseases in humans, including cancer, metabolic syndrome, heart disease, autoimmune disorders, and infectious diseases, can be brought on by dysregulated expression of non-coding RNAs. Many diseases in humans, including cancer, metabolic syndrome, heart disease, autoimmune disorders, and infectious diseases, can be brought on by dysregulated expression of non-coding RNAs. [6–9]. Because non-coding regulatory transcripts are highly stable and resistant to enzymatic degradation, they can be released into the extracellular space and bloodstream within exosomes. Consequently, ncRNAs can function as prognostic or diagnostic biomarkers.[10]. Lastly, regulatory non-coding RNAs are thought to be therapeutic agents for the management of several illnesses.[11]. A new class of medicines has been developed as a result of ncRNA-based gene silencing, which targets and inhibits genes linked to particular diseases, including cancer. Some of these therapies have received FDA approval. [12]. To create the best possible diagnostic techniques and therapeutic approaches, it is essential to comprehend the mechanisms behind the interactions between regulatory ncRNAs and their targets. Because non-coding RNA is involved in the pathophysiology of many different human diseases, such as inflammatory diseases, genetic abnormalities, and malignancies, it has become the focus of translational research. Because of its special ability to be produced quickly and energetically, RNA is an attractive target for therapeutic development. Based on the length of the transcript, non-coding RNAs (ncRNAs) are classified into two main classes in addition to the traditional functional subtypes such ribosomal RNA (rRNA), small nuclear RNA, small nucleolar RNA, and tRNA. MicroRNA (miRNA), small interfering RNA (siRNA), and PIWI-interacting RNA are examples of tiny ncRNAs (≤200 nucleotides), whereas RNAs longer than 200 nucleotides are referred to as long ncRNAs (lncRNAs). [13-14]

Clinical Advances in Short Non-Coding RNAs

Unconjugated sncRNAs

1. Age-related macular degeneration and diabetic macular edema

Age-Related Macular Degeneration with Diabetic Macular Edema The first human clinical trials using siRNA targeting vascular endothelial growth factor (VEGF) were retinal degeneration patients. [16]. The most common cause of significant vision impairment in Americans over 65 is exudative, or "wet," age-related macular degeneration (AMD). [15]. Dry AMD causes drusen to build up on the retina. The pressure this puts on the retinal pigment epithelium triggers an inflammatory reaction that increases VEGF, which in turn causes choroidal neovascularization. [15] The most common cause of blindness in people between the ages of 20 and 74 is diabetic macular edema (DME), which can develop when elevated VEGF increases blood-retinal barrier permeability, causing an excess of fluid to accumulate in the eye and edema. [17] Previous clinical trials have

demonstrated that VEGF is a useful target for treatments, most often antibodies, to reduce AMD or DME-related visual loss. Anti-VEGF antibodies, such ranibizumab, are the standard of care; however, because they must be administered intravitreally every 4 to 6 weeks, there is a risk of lens damage, intravitreal hemorrhage, endophthalmitis, and retinal tears. [15] A siRNA that targets VEGF mRNA is called bevasiranib (also called Cand5) [17]. The overexpression of VEGF is caused by mRNA stability rather than enhanced translation, which makes siRNA-based therapies superior to antibody-based therapies. Additionally, the use of siRNA theoretically permits downregulation rather than inhibiting the activity. [15] Because the VEGF mRNA that is already there is not completely destroyed, bevasiranib does exhibit a clear anti-angiogenic impact, which takes around 6 weeks to develop from the commencement of treatment. In this instance, anti-VEGF antibody combo therapy may be the most beneficial course of action. [15] NCT00557791 was a phase 3 clinical trial that was intended to investigate the advantages of this combination medication, however it was never initiated. Numerous investigations have revealed that bevasiranib primarily acts on the cell surface toll-like receptor 3 (TLR3) through RNA-mediated activation, which decreases CNV through intracellular signaling, rather than by inducing an RNAi response. [16] Since these siRNAs were not created with cell penetration in mind, it's possible that fewer of them than expected reach their intended target.[16] A phase 3 clinical trial for bevasiranib was stopped in 2009 due to early results indicating a very low chance of achieving the primary aim (NCT00499590).

Respiratory Syncytial Infection

The primary cause of hospitalization for infants in the United States is respiratory syncytial virus (RSV), in part due to the lack of a vaccination and the scarcity of treatment options for this infection.[18]. The most frequent community-acquired respiratory virus in lung transplant patients is RSV infection, which is linked to bronchiolitis obliterans syndrome, a major barrier to patient and graft survival [42]. Alnylam Pharmaceuticals created the siRNA ALN-RSV01, which targets the mRNA encoding the nucleocapsid protein, which is essential for RSV replication [18,43]. Delivery without a carrier is effective, as it can be given directly to the mucosa and destroyed by the nucleases if it enters the systemic circulation, as is the case with lung-targeted siRNAs. [21] Intranasal injection of 150 mg dosages given once or five times per day was shown to be safe and well-tolerated in safety and tolerability studies involving 101 healthy people [20]. Following an experimental RSV challenge in 88 healthy adults, 71.4% of the placebo group and 44.2% of the ALN-RSV01 group contracted the virus [18]. In Phase 2a trials, ALN-RSV01 was demonstrated to lower the risk of new or progressive bronchiolitis obliterans syndrome (BOS) when combined with standard of care in transplant patients who were naturally infected with RSV. It did not, however, advance to a phase 3 study and did not reach the primary goal of reduced day 180 BOS [19].

Pachyonychia Congenita

The dominant hereditary disorder known as pachyonychia congenita (PC) is characterized by thicker nails, keratoderma, leukokeratosis, and excruciating blisters that are mostly on the soles of the feet [42]. Without the assistance of an ambulatory device, more than 50% of patients are unable to walk [22]. Oral retinoids, topical keratolytics, and mechanical callus removal are the only effective symptom control options available for PC at this time [22]. Mutations in keratins K6a, K6b, K16, or K17 cause this syndrome. The most frequently altered gene, K6a mRNA, is the target of the siRNA treatment TD101 [42, 22]. The efficacy of TD101 intradermal injection in suppressing mutant K6a expression was confirmed by measuring in vivo mRNA levels using quantitative reverse transcription PCR (qRT-PCR). The same levels of mutant and wild-type K6a were expressed by PC-10 cells and patient callus samples that were obtained. Nevertheless, the administration of TD101 resulted in a 98% reduction in the expression of mutant K6a [42].

Hepatitis C

The most prevalent hepatic miRNA, miR-122, facilitates the spread of the hepatitis C virus (HCV). miR-122 binds to the 50 end of HCV RNA, shielding it from nuclease assault and hiding an RNA motif that could trigger an innate immune reaction [23]. Cirrhosis and ultimately hepatocellular cancer can result with chronic HCV [24]. Currently undergoing clinical trials is miravirsen, an anti-miR-122 ASO made of locked nucleic acid (LNA) ribonucleotides that hybridize to mature miR-122 and prevent its association with HCV RNA [28]. The second

oxygen molecule in LNAs is connected to the ribonucleotide's 40 carbons. This alteration can raise target affinity while shielding the oligonucleotide from nuclease degradation [24, 25].

Clinical investigations have shown that treatment with miravirsen reduces the viral load in individuals with chronic HCV in a dose-dependent manner while having no discernible impact on other miRNAs' plasma levels [23]. One week after the first dose in the experimental group, a placebo-controlled study of five weekly doses of miravirsen decreased plasma levels of miR-122 from 3.9 × 103/4 to 3.1 × 101/4 µL. In the highest-dose group, these values were sustained for the duration of the study. [23] By contrast, after one week of treatment, the mean plasma levels in the placebo group were 1.1 × 104/4 µL, compared to 1.3 × 104/4 µL at baseline. Following treatment, all dosed patients showed improvement, and some even had undetectable levels of miR-122. The HCV viral load did not correlate with the drop in miR-122 plasma levels, despite the fact that the viral load did in dosed patients. It is believed that a C3U nucleotide alteration in the 50 UTR region of the HCV RNA makes this process miR-122-independent and hence resistant to miravirsen in a large number of patients who experienced virological recurrence after taking the medication [26,27]. It has been suggested that miR-122 may also function as a tumor suppressor [35], which has sparked worries that receiving anti-miR-122 therapy may elevate the risk of hepatocellular carcinoma. In preclinical research, mice given miravirsen for five weeks did not grow tumors, nevertheless. Even yet, considering that hepatocellular carcinoma does arise in mir-122-knockout animal models [26, 35], this worry calls for additional safety research to assess the danger [28].

5. Acute Kidney Injury

The complex illness known as acute kidney injury (AKI) is marked by an abrupt drop in glomerular filtration rate, which is then followed by an increase in blood creatinine concentration or oliguria. AKI typically happens in the context of a recent or ongoing medical condition. About 20% of hospitalized patients are affected by it. The pooled incidence rate of AKI in clinical trials was 21.6%, and 10% of patients needed kidney replacement therapy [29, 30]. A p53-targeting siRNA called QPI-1002 (Teprasiran, Quark Pharmaceuticals) is used to prevent AKI and post-kidney replacement delayed graft function [31]. 10 mg/kg of QPI-1002 decreased the incidence, severity, and length of AKI following heart surgery in high-risk patients in a phase 2 clinical trial [31]. Nevertheless, a phase 3 clinical trial (NCT03510897) was abruptly stopped since the patients' results did not reach the efficacy objectives at day 90.

6. Alport’s Disease

A multifaceted miRNA, miR-21 is involved in inflammation, fibrosis, immunological response, and carcinogenesis [41,35,32,33]. Mutations in the genes encoding several α chains of collagen 4 result in the hereditary condition known as Alport syndrome. The kidney's and other organs' capillary membranes are jeopardized by altered collagen 4 function. Alport syndrome patients and genetic mice models exhibit elevated expression of miR-21 [34,36]. Subcutaneous administration of 25 mg/kg antimiR-21 ASO twice a week increased animal survival by 46% in the Col4a3−/− mouse model [34]. The development of glomerular crescents, periglomerular fibrosis, and glomerulosclerosis—all linked to the advancement of Alport syndrome—were markedly postponed by the anti-miR-21 ASO treatment. [34] Mechanistically, anti-miR-21 ASO therapy prolongs kidney function by preventing TGF-β-induced fibrosis and inflammation and by safeguarding PPARα/retinoid X receptor (PPARα/RXR)-dependent mitochondrial activity. Anti-miR-21 ASO (RG-021, now known as lademirsen) was administered subcutaneously to individuals with Alport syndrome in phase 1 clinical trials at a dose of 1.5 mg/kg, either as a single dose or as four doses spaced 14 days apart (NCT03373786). Following a well-tolerated course of treatment, individuals with Alport syndrome are currently being actively recruited for a phase 2 clinical trial to assess the therapeutic efficacy of lademirsen in maintaining kidney function (NCT02855268).

7. cardiovascular disease

Targeting miR-92a-3p, MRG-110 is an LNA-modified ASO that is used to treat wound healing and cardiovascular disease [25]. Inhibiting miR-920 has been shown to improve wound healing, circulation following hind limb ischemia, and vascularization following heart attacks. It also mitigates the negative effects of miR-920's antiangiogenic effects on wound healing, which are partly due to the downregulation of pro-angiogenic

integrin alpha 5 [25, 37]. Whole blood miR-92a-3p is reduced in a dose-dependent manner by MRG-110 therapy. In experimental models of acute and chronic excision wounds in pigs and db/db mice, it also enhances the development of granulation tissue and stimulates angiogenesis [37]. Significant clinical potential was indicated by the fact that these effects were higher in the MRG-110 group compared to the positive control groups treated with rhVEGF-165 and rhPDGF-BB. There were no noteworthy safety issues. In human trials, the treatment's considerable effectiveness was observed at half-maximum dosages of 0.27 to 0.31 mg/kg [25]. After 24-72 hours of therapy, there was over 95% inhibition in the high dose groups, and this inhibition persisted for two weeks.

8. Leukemias and Lymphomas

As a treatment for many hematologic malignancies, such as cutaneous T-cell lymphoma (CTCL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL), MRG-106 (cobomarsen), an LNA-modified ASO, targets miR-155. Mycosis fungoides (MF), the most prevalent subtype of CTCL, has a significant etiology, which is supported by functional investigations and clinical data [38]. Cobomarsen's formulation promoted CD4+ T-cell and MF cell uptake [38]. Treatment with cobomarsen increased the expression of BACH1, PICALM, and JARID2, which are direct targets of miR-1550, and disrupted the pro-survival function of miR-155. [38] JARID2 (jumonji and AT-rich interaction domain containing 2) is a negative regulator of leukemia cell proliferation, PICALM (phosphatidylinositol binding clathrin assembly protein) is an endocytosis adaptor, and BACH1 (BTB and CNC homology 1, basic leucine zipper transcription factor 1) is a mediator of the oxidative stress response.[38] In patients with hematological malignancies, a phase 1 clinical trial (NCT02580552) showed that cobomarsen was safe and had minimal toxicity. In order to compare the safety and effectiveness of cobomarsen medication to vorinostat, a histone deacetylase (HDAC) inhibitor, in patients with CTCL of the MF subtype, a phase 2 clinical trial (NCT03713320) was started in 2018. One of the attractive things about cobomarsen treatment is that it can be given once a week instead of vorinostat's daily dosage; nevertheless, cobomarsen is given intravenously, whereas vorinostat is taken orally. Despite recruiting 37 patients, this research trial was stopped for business reasons without any particular concerns about the efficacy of cobomarsen. [39] Because there were few eligible participants, an expected crossover phase 2 clinical trial (NCT03837457) had to be canceled. The further clinical evaluation of cobomarsen is supported by genetic investigations in Mir-155-knockout mice models, successful treatment with anti-miR-155 ASO or comparable inhibitors in in vivo animal models. [41], and an unusual response in a single patient diagnosed with an aggressive subtype of DLBCL [40].

Non-Coding RNAs: Cancer Biomarkers and Diagnosis

Because of their distinct expression profiles, high relative stability, and ease of PCR characterisation, non-coding RNAs (ncRNAs) are a great class of prospective biomarkers [43]. Thus, in the last ten years, a number of clinical trials have been carried out to find ncRNA biomarkers in cancer patients in order to create screening instruments. Since this may affect patient cohort composition and specimen selection, it is crucial that the intended application of the proposed biomarker(s) be clearly specified as predictive, prognostic, or diagnostic. [44,45]

Early studies of identifying tumor ncRNAs implemented the strategy of comparative profiling between both healthy and malignant tissues [46]. Tissue biopsies have a long history of clinical use and are a useful tool, but they are invasive and impractical for patients who are fragile or have inaccessible malignancies [47, 48]. Moreover, tissue biopsies yield information that is reliant on both space and time, which means that it may give an erroneous picture of tumor heterogeneity and ongoing tumor processes such drug resistance [47–50]. Specialized signals of non-coding ncRNAs produced from cancer have been detected in bodily fluids such as blood, saliva, and urine [51–53], prompting investigators to investigate the feasibility of liquid biopsies [48]. Liquid biopsies are less invasive than tissue biopsies, making them ideal for therapy monitoring [202] and screening [54]. Nevertheless, the frequency of circulating tumor cells (CTCs) is comparatively low, and while free-traveling ncRNAs are vulnerable to destruction by circulating RNAses, ncRNAs can travel through physiological fluids without the assistance of cells [45,49]. Examining ncRNAs contained in extracellular vesicles (EVs), which are secreted by tumor cells, is an other strategy.[55] Studies have revealed that tumor cells secrete more vesicles than normal cells do, which may contribute to the development of pre-metastatic niches and the advancement of cancer. [45] It is imperative to ascertain if the observed changes in ncRNA levels are

obscured by variations in vesicle concentrations between individuals with cancer and healthy individuals. The whole genome expression profiles of patient and control samples can be compared to identify dysregulated non-coding RNAs (ncRNAs) since high-throughput sequencing technologies, such as next-generation sequencing, have been available [58,44]. Notably, the heterogeneity of human malignancies and the widespread expression of most ncRNAs make it unlikely that a single biomarker will be adequate for disease characterisation [56,57]. Instead, in order to achieve high sensitivity and specificity, bio classifier systems made up of a panel of biomarkers might be required. [56] Large-scale ncRNA expression profiles have previously shown promise in the classification of poorly differentiated tumors, and they may also add to our knowledge of the dynamics underlying cancers [59, 45]. Making sure these bio classifiers are repeatable, however, is a significant hurdle. As a result, standardizing bioinformatic analyses, normalization techniques, and protocols for RNA extraction and sample processing is crucial [44,53,57]. PCA3 is the only ncRNA to date to be approved as a biomarker by the FDA, despite the identification of many potential ncRNA biomarker candidates [68]. Prostate cancer has a distinct upregulation of the lncRNA PCA3 [50]. The upregulation of PCA3 in prostate cancer patient urine has been reported by Hessels et al. [61], which has led to the development of non-invasive PCA3 urine tests for the clinical identification of early prostate cancer [62]. Currently, this test is utilized in combination with other recognized assays (e.g., TMPRSS2:ERG urine test, PSA blood test) [68,63,64].

ncRNAs as Lung Cancer Biomarkers

Lung cancer has one of the lowest five-year survival rates of any malignancy (19%) [69]. There are few curative treatments available for the more than half of patients who arrive with advanced-stage disease [65,66]. As a result, a significant percentage of these patients receive no treatment [67]. Crucially, screening for lung cancer can raise high-risk individuals' survival rates. Eighty percent of lung cancers detected in the early stages are detected by screening programs; in the absence of screening, a staggering seventy percent of patients receive a late-stage diagnosis [70]. A low-dose CT scan is currently the gold standard for screening for lung cancer [71].

ncRNAs: Cancer Biology

Calin and Croce's seminal study [22,72] from 2002 revealed a connection between dysregulated miR-15a and miR-16-1 and chronic lymphocytic leukemia (CLL). Since then, numerous ncRNAs have been connected to well-known cancer pathways [79, 80]. Even if there aren't many well-studied ncRNAs included, it's important to remember that focusing on a single biomolecule or route in isolation oversimplifies the biological reality of multiple cancer pathways interacting with one another [76]. Additionally, a single ncRNA can interact with a wide range of proteins, mRNAs, DNA, and other ncRNAs [76,82,83] and be involved in the regulation of several biological processes [81].

Overview of ncRNAs in Cancer

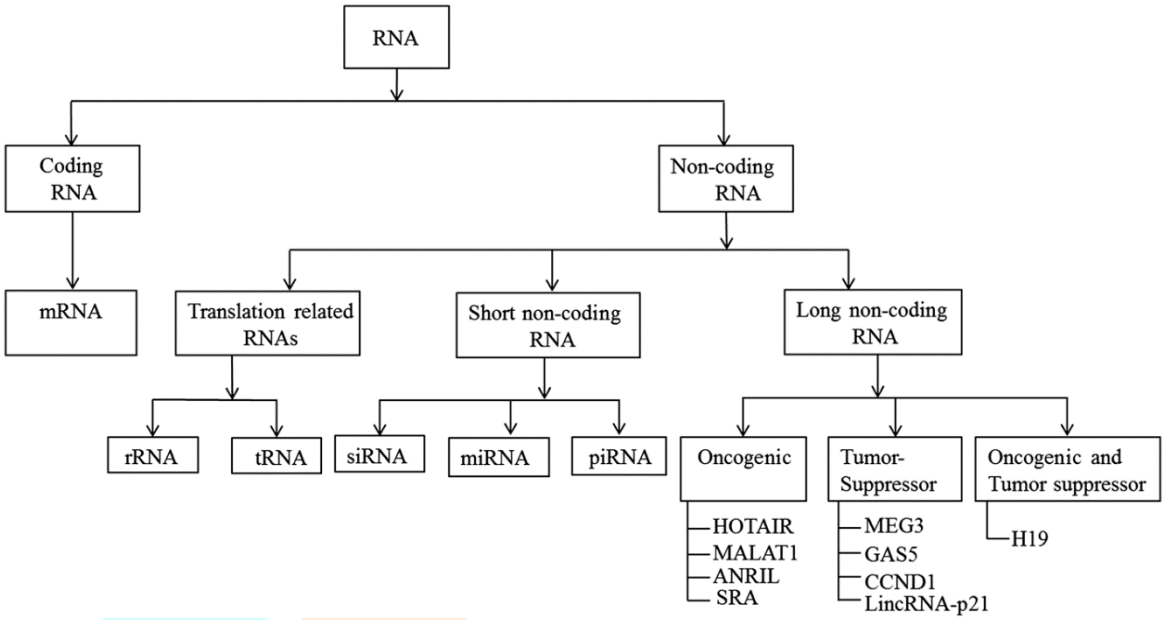
The transcriptome of cancer cells and tissues may be examined thanks to developments in RNA sequencing (RNA-seq) technologies [74]. This approach makes it possible to determine the frequency and sequences of dysregulated non-coding RNAs in malignancies [74, 75]. miRNAs have been explored the most in relation to the roles played by ncRNAs in human cancers [84, 85]. Numerous in vitro and in vivo research employ tactics of over- and under-expressing the miRNA(s) of interest in order to unveil the roles of miRNAs related to cancer. Examining the generated biological activity using a variety of functional tests comes next [73,78]. The function of miRNAs can also be ascertained by elucidating their mRNA targets using high-throughput sequencing or in silico methods (e.g., Targets can, miRanda) [73,86]. Remarkably, recent research has demonstrated that secreted miRNAs can function as ligands to initiate premetastatic inflammatory responses in the tumor microenvironment in addition to causing RNAi [87,88]. Less is known about piRNAs' roles in cancer. Although more recent research has looked at the PIWI/piRNA relationship in malignancies, the majority of studies to date have focused on the PIWI clade of Argonaut proteins independently of piRNAs [89, 90]. These complexes are generally overexpressed in malignancies, and this overexpression has been connected to aggressive cancer characteristics.[77] Numerous well-established lncRNAs (e.g., HOTAIR, H19, MEG3, MALAT1) have been associated with malignancies. They play a variety of roles in the development of malignancies, particularly in the areas of drug response, angiogenesis, metastasis, cell proliferation, and post-transcriptional gene regulation. The effect of non-coding RNAs (ncRNAs) can be broadly classified as either tumorigenic or tumor suppressive

based on the understanding gained from functional investigations. However, certain ncRNAs may exhibit both activities depending on the context [91,92].

Diverse Functions of ncRNAs

Non-translated or non-coding RNA (ncRNA) molecules are transcripts of genomic sequences that are not intended for translation. [93] The human genome encodes a large number of non-coding RNAs. The majority of these non-coding RNAs have been extensively linked to the regulation of cellular homeostasis. [94] Certain ncRNAs have a direct bearing on modifications and/or alterations in cells' epigenetic makeup. As shown in Figure 1, total cellular RNAs are categorized according to their functions. Long non-coding RNAs (lncRNAs) and small nuclear RNAs (snoRNAs), microRNAs, small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), transfer RNA (tRNA), ribosomal RNA (rRNA), and other functionally significant RNAs are produced from a subset of ncRNAs. X inactivation specific transcript (exist) and HOX antisense intergenic RNA (HOTAIR) are two extensively researched long noncoding RNAs. [103] Although the entire number of non-coding RNAs (ncRNAs) encoded in the human genome is unknown, thousands of ncRNAs with potential functions may exist, according to recent transcriptomic and bioinformatic research. It's probable that a large number of the recently discovered ncRNAs are non-functional because their functions haven't been confirmed. Examples of ncRNAs' roles and functions are still being discovered, though. ncRNAs are classified as either long non-coding RNA (lncRNAs > 200 nt) or short non-coding RNA (sncRNAs < 30 nt), depending on the length of RNA generated post-transcriptionally. Longer than 200 nt, non-protein coding transcripts are referred to as lncRNAs. Practical factors, such as the separation of RNAs in standard experimental methods, are the reason for this limit. Furthermore, Table 1 shows that this cutoff separates lncRNAs from small regulatory RNAs including siRNAs, piRNAs, miRNAs, and snoRNAs. Short noncoding RNAs, or miRNAs, range in length from 18 to 24 nt and play a role in skin fibrosis.[95] LncRNAs have a wide range of functions, including roles in telomere biology, higher order chromosomal dynamics, and subcellular structural organization.[96,97] T-UCR, a novel subclass of ncRNAs, is produced from an ultra-conserved region.[98] T-UCRs are a subset of DNA segments larger than 200 bp that are fully conserved across species (genomes of rats, mice, and humans).[100, 99] Furthermore, the type of the genes involved in oncogenesis and/or tumour suppression determines subsequent divisions of ncRNAs. Steroid receptor RNA activator (SRA), for instance, is an oncogenic non-coding RNA that, in response to insulin, increases adipogenesis and suppresses the expression of inflammatory genes linked to adipocytes.[100] Maternally expressed gene 3 (MEG3) is a ncRNA encoding gene that is found on human chromosome 14q32.3 on the DLK1-MEG3 locus. When this gene is inactivated, the brain develops micro vessels and genes that promote angiogenesis are expressed.[101] By competing with the DNA-glucocorticoid response element (DNA-GRE) at the glucocorticoid receptor's DNA binding domain, GAS5 ncRNA functions as a ruse and modifies growth arrest under hunger. [102]

NON-CODING RNAS: POWER AND PROMISES



Feature Prospective

It provides an in-depth exploration of the multifaceted roles of non-coding RNAs (ncRNAs) in gene regulation, with a focus on their involvement in cancer biology and potential applications as diagnostic and therapeutic targets. It discusses how ncRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), exert regulatory effects on gene expression through various mechanisms. In cancer, dysregulated expression of ncRNAs contributes to tumorigenesis, metastasis, and drug resistance, making them potential biomarkers for diagnosis and prognosis. Liquid biopsies, which utilize circulating tumor-derived ncRNAs, offer less invasive alternatives for cancer detection and monitoring. Additionally, advancements in RNA sequencing technologies enable comprehensive profiling of ncRNAs, aiding in the identification of cancer-specific signatures. Therapeutically, ncRNAs hold promise as targets for innovative treatments, such as RNA-based gene silencing therapies, with clinical trials showing encouraging results across diverse cancer types. However, challenges remain in ensuring efficacy and safety in ncRNA-targeted therapies. Overall, the burgeoning field of ncRNA research offers insights into the complex regulatory networks governing cancer biology and presents opportunities for the development of novel diagnostic tools and therapeutic interventions.

Conclusion

Non-coding RNAs (ncRNAs) represent a burgeoning field of research with profound implications for cancer biology and clinical practice. These molecules, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), exert intricate regulatory effects on gene expression, influencing key processes involved in tumorigenesis and cancer progression. Their dysregulation in cancer underscores their potential as diagnostic biomarkers and therapeutic targets. Advancements in RNA sequencing technologies have facilitated the identification of cancer-specific ncRNA signatures, offering promise for improved cancer diagnosis and prognosis. Liquid biopsies, harnessing circulating tumor-derived ncRNAs, provide less invasive alternatives to traditional tissue biopsies for monitoring disease progression and treatment response. Moreover, therapeutic targeting of dysregulated ncRNAs holds great potential for innovative cancer treatments. RNA-based gene silencing therapies, including those targeting miRNAs and lncRNAs, have shown encouraging results in preclinical and clinical studies, highlighting their promise for personalized medicine approaches. Overall, the study of ncRNAs in cancer represents a frontier in cancer research, offering insights into the complex molecular mechanisms driving malignancy and paving the way for the development of novel diagnostic tools and therapeutic interventions aimed at improving patient outcomes in the fight against cancer.

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