The Role of Non-Coding RNAs in Cancer Progression: A Concise Comprehensive Review

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Abstract: Cancer is among one of the most widespread diseases globally and poses a great threat to human wellbeing. Non-coding RNAs (ncRNAs) compose most transcripts but cannot undergo translation. Thus, no proteins are made by them. However, studies have shown that ncRNAs can mimic both oncogenes and tumour suppressor genes involved in cancer. This review discusses recent research on the involvement of ncRNAs in the progression, diagnosis, and treatment of cancer. These ncRNAs consist of microRNAs, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). This concise paper aims to inform researchers, clinicians, and scientists in navigating the dynamic field of ncRNAs in cancer with the goal of fostering collaboration to translate discoveries into practical clinical advancements.

Keywords: Non-coding RNAs, cancer, ncRNAs; microRNAs; cancer progression.

Introduction

Cancer is a global disease considered a continuous threat to the safety and wellbeing of humankind due to the large-scale challenges associated with its diagnosis and treatment. A survey carried out in the United States identified cancer as the second-leading cause of human mortality after heart disease (Siegel et al., 2019). Decades of research on the biology of cancer has primarily concentrated on the role of genes that code for proteins. Only recently was it publicized that a family of molecules that do not undergo translation, called non-coding RNAs (ncRNA), also perform a consequential role in regulating cell-based activities. Since their discovery, the understanding of ncRNA has greatly advanced, with scientists identifying a diverse and widespread class of ncRNAs that comprise both carcinogenic and tumor-suppressive varieties. As a result, ncRNAs have been used as novel biomarkers for therapeutics in hundreds of clinical studies focused on cancer. This review aims to highlight the appreciable contribution of ncRNAs in cancer biology by exploring their complex molecular mechanisms and evaluating their potential contribution to the accurate diagnosis and effective treatment of cancer, while advancing current dialogue on medical advancements in the field of oncology.

Overview and classification of ncRNAs

The central dogma of molecular biology posits that genetic information in the form of DNA is transcribed into RNA and that RNA is subsequently translated into proteins. Non-coding RNAs, or ncRNAs, are functional RNA molecules transcribed from DNA that are not translated into proteins (Ding et al., 2021). High-throughput sequencing technology has revealed that about 98% of the human genome is transcribed into ncRNAs (Birney et al., 2007).

There are 15 different classes of ncRNAs that are further divided into subgroups based on criteria applied during the classification process, including endogenous function, size, and capping (Figure 1). The endogenous function of ncRNAs can be categorized as regulatory ncRNAs and structural (also called housekeeping) ncRNAs. Regulatory ncRNAs operate as regulators, taking part in chromatin

remodeling, transcription, post-transcriptional processes, and signal transmission (Anastasiadou, Jacob, et al., 2018). Housekeeping ncRNAs, like ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs), are engaged in cellular genetic processes including protein synthesis, RNA modification, and RNA splicing (Dozmorov et al., 2013).

On the basis of size, ncRNAs can be classified as long ncRNAs (lncRNAs) (>200 nucleotides (nt)) and small ncRNAs (<200 nt) (Uppaluri et al., 2023). lnccoding RNAs are characterized as untranslated RNAs comprised of two subgroups called circRNAs and pseudogenes (Zhang et al., 2019). There are three short ncRNAs known to be involved in cancer. These include piwi-interacting RNAs (piRNAs), small interfering RNAs (siRNAs), and microRNAs (miRNAs). Of these, microRNAs are the most prevalent and well-researched.

Moreover, ncRNAs exhibit diverse structural features, and they can be classified into two types based on capping. Capping is the first modification made to RNA polymerase II-transcribed RNA and takes place co-transcriptionally in the nucleus as soon as the first 25–30 nucleotides are incorporated into the nascent transcript (Moteki & Price, 2002; Shatkin & Manley, 2000). Capping ncRNAs include mRNA-like ncRNAs, characterized by a 7-methylguanosine cap at the 5′ end, enhancing stability for various cellular functions. Certain small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) also undergo capping, facilitating their roles in pre-mRNA splicing and rRNA modification, respectively.

On the other hand, uncapped ncRNAs, such as circRNAs, lack a 5′ cap and form covalently closed loop structures, often interacting with miRNAs. lncRNAs may or may not have a cap, contributing to their diverse functions in gene regulation and cellular processes. tRNAs are generally uncapped, relying on post-transcriptional modifications for their crucial role in translation (Uppaluri et al., 2023).

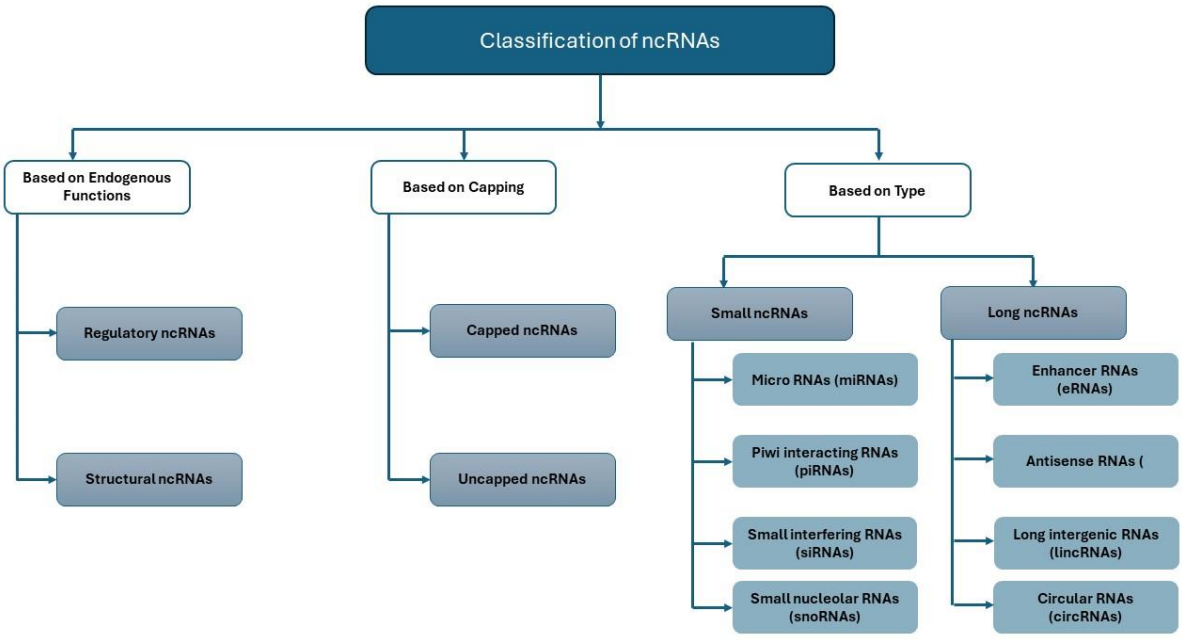

Figure 1: *Classification of ncRNAs based on their type, capping, and endogenous functions*

Role of ncRNAs in Cancer

Cancer is marked by cells that grow uncontrollably, invade other tissues (metastasize), and lack the capacity to undergo programmed cell death (apoptosis). Knowledge of the causes and potential treatments of cancer has increased owing to the discovery of ncRNAs and the advancement of RNA sequencing (RNA-seq) technology has made it

possible to investigate the transcriptome of cancerous cells and tissues (Luo, 2016). RNA-seq makes it possible to determine the frequency and sequences of dysregulated ncRNAs in cancer (Choudhari et al., 2020; Luo, 2016). There is substantial evidence that dysregulated ncRNA expression and downstream signaling pathways have a direct association with development and progression of cancer. Figure 2 illustrates the three distinct ways in which ncRNAs influence cancer progression.

miRNAs have received the greatest research attention when it comes to the roles played by ncRNAs in human malignancies (Hayes et al., 2014; Y. Wang & Lee, 2009). Recent studies have demonstrated that secreted miRNAs not only cause RNA interference (RNAi), but may additionally mimic ligands that trigger prometastatic inflammatory responses in the microenvironment of the tumor (Eichmüller et al., 2017).

There is minimal knowledge regarding the cancer-associated functions of piRNAs. Although more recent research has looked at the interaction between PIWI (P-element Induced WImpy testis in Drosophila) and piRNA in cancers, most of these investigations to date have focused on the PIWI clade of Argonaute proteins, including regulatory roles in stem cell and germ cell differentiation, which operate independently of piRNAs (Yu et al., 2019; Y. Zhao et al., 2012). Numerous well-established lncRNAs (e.g., HOTAIR, H19, MEG3, MALAT1) have been associated with cancer. They play varied roles in the development of cancer, particularly in the areas of drug response, the formation of blood vessels (angiogenesis), metastasis, cell proliferation, and post-transcriptional gene regulation. Generally, the impact of lncRNAs may be classified as either tumor suppressive or tumorigenic based on the understanding gained from functional investigations. However, many lncRNAs may exhibit both depending on the context (Esquela-Kerscher & Slack, 2006; Svoronos et al., 2016).

The number of examples from research on ncRNAs is far fewer than that of protein-coding genes, even though genetic changes in genes producing ncRNAs have been linked to cancer. One well-known example is the deletion of the miR-15/16 tumor suppressors in chronic lymphocytic leukemia (CLL) at chromosome position 13q14.3 (Calin et al., 2002). Cancer is also related to the amplification of chromosomal areas expressing carcinogenic ncRNAs, such as FAL1 (Hung et al., 2014) and PVT1 (Jin et al., 2019). The lncRNAs CCAT2 (B. Chen, Dragomir, et al., 2020), H19 (Hua et al., 2016), and ANRIL (Aguilo et al., 2016) are reportedly linked to the risk of cancer cell proliferation due to single nucleotide polymorphisms (SNPs).

Apart from the genetic changes inside of transcribed areas, mutated promoters of ncRNAs can also result in altered levels of gene expression. For instance, it has been documented that promoters of the lncRNAs NEAT1 and RMRP undergo frequent driver mutations in breast cancer (Rheinbay et al., 2017). In addition to mutations, cancer has also been linked to ncRNAs producing enzymes, such as Drosha and Dicer, which are associated with the processing of miRNA, in addition to abnormalities in the sequences encoding ncRNA itself (Rupaimoole & Slack, 2017). Apart from genetic mechanisms, epigenetic, transcriptional, or post-transcriptional processes may also result in the up- or down-regulation of ncRNAs linked to cancer (Anastasiadou, Faggioni, et al., 2018; Budakoti et al., 2021; Slack & Chinnaiyan, 2019).

Overall, a range of genetic and epigenetic factors, such as gene amplification or deletion , repression of gene transcription , aberrant biosynthesis , alternative splicing , and epitranscriptome modifications or “RNA editing” , including nucleotide substitutions , methylation , and acetylation , can account for the dysregulation of ncRNAs in cancers. Moreover, lncRNAs—particularly circRNAs—have the ability to compete with mRNAs for miRNA binding sites, such as endogenous RNAs (ceRNAs) . As a result, miRNAs are unable to carry out their regulatory functions. For instance, H19 can "sponge" or lower the availability of let-7 to target by mRNAs by binding to the sites for let-7 .

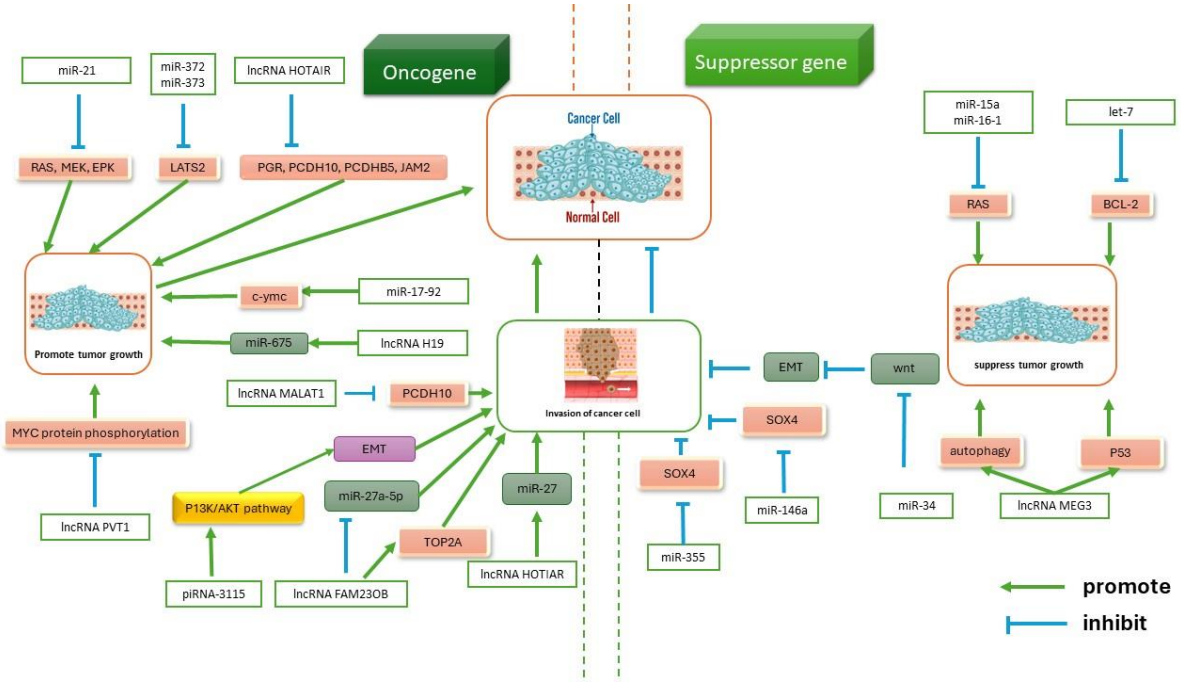

Figure 2: *Noncoding RNAs have three distinct ways for influencing caner progression: they might act as oncogenes, cancer suppressors, or mediators of cancer metastasis. LncRNA H19, miR-21, and miR-17-92 primarily increase the target when utilized as an oncogene; lncRNA PVT1, miR-372/373, and lncRNA HOTAIR, on the other hand, primarily reduce the target. Both miR-34 and lncRNA MEG3 inhibit tumors, but they also help target P53. Moreover, miR-15a and miR-16-1 impact BCL-2 and prevent cancer, whereas lncRNA MEG3 influences autophagy and prevents cancer. Long noncoding RNA (lncRNA) affects the target and hence affects the development of cancer when it prevents tumours from spreading.*

Diagnostic and Therapeutic Implications

Research has shown that ncRNAs have utility in serving as biomarkers for diagnosing cancer and determining a patient's prognosis. Biomolecules linked to ncRNAs can be examined via a liquid biopsy, which is a minimally invasive procedure that allows for the analysis of biomolecules in the blood, such as extracellular vesicles (EVs), circulating tumor cells (CTCs), and cell-free DNA (cfDNA). ncRNAs are stable in blood and their connection to biomolecules found in the blood can be used an indicator of cancer type and state. For example, cancer progression and efficacy of therapy are correlated with expression levels of miRNAs in EVs isolated from blood samples. Moreover, lncRNAs found in cfDNA have the ability of distinguishing varieties of cancer (Chen, Zhang, et al., 2020; Cheng et al., 2020; Huang et al., 2013; Zhang et al., 2017).

Tissue-based diagnostics performed on tissue taken from surgeries or biopsies is another way that ncRNAs are used to diagnose and characterize cancer because ncRNAs express themselves differently in cancerous versus normal tissue. For example, lncRNAs are dysregulated in several types of cancer, like HOTAIR in breast cancer and MALAT1 in lung cancer. Examples of dysregulated miRNAs include the levels at which miR-21 and miR-155 are expressed in breast cancer and lymphoma, respectively (Grolmusz et al., 2018; Wang et al., 2017; Xiong et al., 2019; Zhao et al., 2018).

Beyond their potential for diagnosis, ncRNAs also have prognostic significance in cancer. Prognostic biomarkers estimate a patient's disease outcome and the probability of disease progression. For instance, low expression levels of miR-155 and miR-21 are correlated with a poor prognosis for lymphoma and breast cancer, correspondingly. lncRNAs with a poor prognosis across a variety of cancer types, such as HULC and HOTAIR, are persistent (Chiu et al., 2018; Liu et al., 2018; Ni et al., 2018).

Despite the potential benefits of ncRNAs for diagnosis and treatment, ncRNAs in the context of

cancer presents challenges. Functional characterization is impeded by intricate and poorly understood roles and interactions within cellular pathways. Because of these intricate functions, it is still difficult to determine the significance of specific ncRNAs in the initiation and progression of cancer. The high heterogeneity and contextual dependency of cancer further complicate ncRNA studies, as their expression varies based on cancer type, stage, and patient characteristics. Moreover, identifying and validating ncRNAs as diagnostic or prognostic biomarkers is complex, facing challenges such as technical variability and inter-patient variability. Utilizing therapeutic potential encounters hurdles in delivery and targeting, requiring efficient systems to minimize off-target effects. Regulatory considerations are crucial for development, requiring adherence to guidelines and safety assessments. Despite these challenges, understanding and harnessing ncRNA potential in cancer holds promise for improved diagnostic and therapeutic interventions. However, obstacles like lack of specificity and limited mechanistic understanding remain significant barriers (Di Leva & Croce, 2013; Uppaluri et al., 2023).

Conclusion and perspectives

In conclusion, the study of non-coding RNAs in cancer progression has unveiled a range of regulatory mechanisms and potential therapeutic options. MicroRNAs, due to their precise gene expression regulation, play a crucial role in coordinating cellular activities essential for tumor development. Long non-coding RNAs add complexity to the regulatory network, influencing various aspects of cancer biology as functional modulators and architectural planners. Targeting ncRNAs for therapeutic purposes shows promise for innovative cancer treatments, with opportunities for personalized and targeted interventions through small molecules and RNA-based therapeutics. However, challenges such as delivery methods, off-target effects, and understanding ncRNA interactions must be addressed. Ongoing research in ncRNAs in cancer biology remains a dynamic field with vast potential. Interdisciplinary collaboration will be crucial to overcome challenges and translate discoveries from research to clinical applications.

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