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The Role of Non-Coding RNAs in Gene Regulation and Cellular Signaling Pathways

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Abstract

Evidence has been mounting over the last decade demonstrating the crucial functions of ncRNAs, including miRNAs and long non-coding RNAs (lncRNAs), in cellular signalling networks and gene regulation. These ncRNAs are highly expressed and play a crucial role in regulating processes including metastasis and endothelial cell invasiveness. They facilitate crosstalk between interconnected signaling pathways, including PTEN/PI3K/AKT/mTOR, by acting as linking molecules within signal circuits. In addition to gene expression and conventional apical measures, studying miRNAs provides a better understanding of both beneficial and detrimental cellular reactions to external exposures. Additionally, miRNAs—which may be found in extracellular and intracellular environments, such as biofluids—have become potential early and precise molecular indicators of tissue and cellular conditions. This review highlights the regulatory functions of ncRNAs, their involvement in cellular homeostasis, and their potential as biomarkers, shedding light on their significance in gene regulation, toxicological studies, and precision medicine.

Keyword: Non-Coding RNAs (ncRNAs), Gene Regulation or Gene Expression, Intracellular and Extracellular, Cellular Signaling Pathways.

INTRODUCTION

Non-coding RNA

Non-coding RNAs (ncRNAs) are functional RNA molecules that do not change into proteins. The DNA sequence required to transcribe a functioning non-coding RNA is known as an RNA gene [1]. "Transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs)" are two examples of common and functionally significant non-coding RNAs. Other short RNAs include "microRNAs, siRNAs, piRNAs, snoRNAs, snRNAs, exRNAs, scaRNAs, and lengthy ncRNAs" like Xist and HOTAIR [2]. The human genome may include thousands of non-coding transcripts, according to recent transcriptomic and bioinformatic studies, while the exact number of non-coding RNAs remains unknown. Many of the recently discovered ncRNAs have no known function [3]. The amount of non-coding transcription that is functional is up for debate. While some people think that the majority of ncRNAs are spurious transcriptions or non-functional "junk RNA," others anticipate that many non-coding transcripts have roles that need to be identified [4].

Types of Noncoding RNAs

Non-coding RNAs may be divided into three main categories: housekeeping, short, and long ncRNAs. Different cell compartments have been shown to contain long noncoding RNAs, and the biological actions of these molecules rely on where they are located within the cell [5]. Long ncRNAs include more than 200 nucleotides. Transfer RNAs and ribosomal RNAs which are engaged in translation are examples of "housekeeping ncRNAs and regulatory RNAs". Splicing, translation, and neurodegenerative disorders are all significantly impacted by small ncRNAs [6]. "Small nucleolar RNAs (snoRNAs) and microRNAs (miRNAs)" both have a role in cancer. Their function in the regulatory apparatus is reinforced by the fact that ncRNAs function independently of proteins.

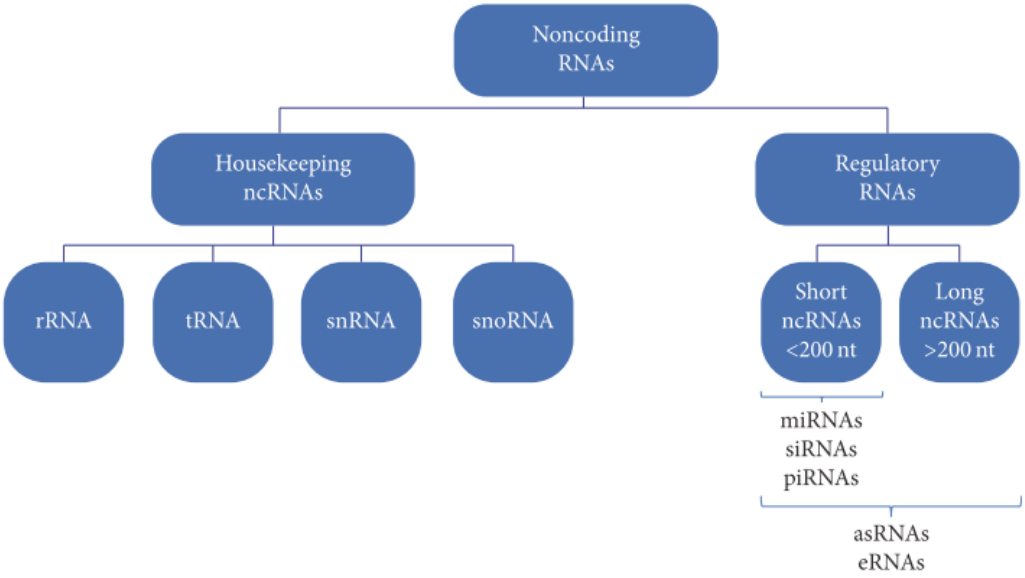

Figure 1 Types of ncRNAs [2]

Table 1 Examples of ncRNAs, average nucleotide (nt) lengths and known function(s)

	Type	Length (nt)	Function
Small ncRNAs (<200 nt)	Small interfering RNA (siRNA)	20–25	RNAi; Antiviral defense
	MicroRNA (miRNA)	18–22	RNAi; Protein translation regulation
	Trans-activating CRISPR (tracr) RNA	~65	CRISPR/Cas adaptive immunity in bacteria
	Piwi RNA (piRNA)	26–31	Regulation of transposable elements
	U-rich snRNA (snRNA)	100–300	snRNA subclass; intron splicing
	Small nuclear RNA (snRNA)	100–300	Intron splicing; RNA processing
	Signal recognition particle RNA (7SL)	300	RNA component of the signal recognition particle (SRP); protein synthesis
	Small nucleolar RNA (snoRNA)	60–200	rRNA processing
	Small Cajal body-specific RNA (scaRNA)	200–300	Biogenesis of small nuclear ribonucleoproteins
	Y RNAs	80–120	Components of ribonucleoproteins; DNA replication and RNA processing
Long ncRNAs (>200 nt)	Circular RNA (circRNA)	100–999	miRNA decoy, protein regulation
	Long intergenic ncRNA (lincRNA)	1 kb	Protein scaffolding
	Natural antisense transcript (NAT)	>200	RNAi, alternate splicing, genome imprinting
Housekeeping ncRNAs	Transfer RNA (tRNA)	76–90	Protein synthesis
	Ribosomal RNA (rRNA)	>1,500	Protein synthesis

RNA structure

In most situations, RNA is a single-stranded biopolymer. However, intrachain base pairing is brought about by the self-complementary sequences of the RNA strand, and the ribonucleotide chain folds into complex structural geometries with bulges and helices [7]. The three-dimensional structure of RNA is crucial to its stability and usefulness because it allows cellular enzymes to affix chemical groups (such as methyl groups) to the chain and alter "the ribose sugar and nitrogenous bases" in a number of ways [8]. These changes make it possible for distant parts of the RNA strand to create chemical interactions with one another, causing intricate RNA chain contortions that further stabilise the RNA structure. It is possible for molecules with poor stabilisation and structural changes to be easily destroyed [9]. A modification at position 58 of the tRNA

chain, for instance, renders "an initiator transfer RNA (tRNA) molecule" lacking a methyl group (tRNAiMet) unstable and, thus, nonfunctional; the nonfunctional chain is terminated by cellular tRNA quality control mechanisms [10].

Gene regulation

Cells use a variety of strategies to either raise or reduce the creation of certain gene products, such as proteins or RNAs, which is known as gene regulation or control of gene expression. It is common in biology to see intricate gene expression programs, such as those that start developmental processes, respond to environmental stimuli, or assist organisms in adapting to new food sources. Nearly every step of gene expression may be regulated, including protein post-translational modification, RNA processing, and transcriptional initiation. One gene regulator often controls another in "a gene regulatory network", and so on [11].

Since gene regulation enables the cell to generate protein when necessary, it enhances an organism's flexibility and versatility, making it crucial for viruses, prokaryotes, and eukaryotes. The lac operon, discovered by François Jacob and Jacques Monod in 1961, demonstrates that E. coli only expresses certain enzymes involved in lactose metabolism when lactose is present and glucose is not [12]. Although Barbara McClintock showed in 1951 that two distinct "genetic loci, Activator (Ac) and Dissociator (Ds)", interact to generate the colour of maize seeds, this is generally considered the first discovery of a gene control system.

In multicellular organisms, the control of genes in the embryo drives cellular differentiation and morphogenesis, resulting in the development of diverse cell types with varying patterns of gene expression from the same genomic sequence. Gene regulation is a key component of evolutionary developmental biology ("evo-devo"), which evolutionary scientists use to partially explain how evolution works at the molecular level, even if it does not explain how gene regulation came to be [13].

Cell Signaling

The dynamic capacity to continuously coordinate one's actions with changes in the environment is a trait shared by all species. Several pathways allow cells to receive and process information from the external environment, other cells inside the body, and internal components of the cell, allowing them to interact with their surroundings [14]. Both the signal-directed adaptability of an organism's function to environmental changes and the coordinated control of cellular activities are essential for other basic traits of multicellular creatures [15]. Coordinated control of cell quantity, shape, location, and expression of diverse activities is necessary for the development and upkeep of multicellular organisms' specialised tissues. This kind of coordination is the outcome of a sophisticated cell-to-cell communication network where signals are generated, impact target cells, and are then translated into intracellular biochemical processes that determine the target cell's physiological activity (Figure 2) [16]. The basis of a multicellular organism's physiological process coordination is intercellular signalling, commonly referred to as intercellular communication. It allows one cell to precisely influence how other cells behave. Multicellular creatures have specialised cells that create unique tissues and organs with particular roles, in contrast to single-cell organisms, where all cells operate identically within a wide frame.

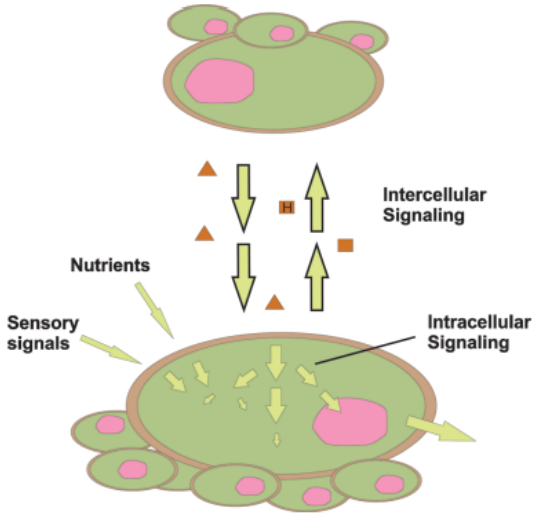

Figure 2 Intercellular and intracellular signaling. [16]

Intercellular Signaling

Transduction of signals between cells affects almost all physiological responses. A signal is received and transformed by all cells of a certain kind. In this way, cells of the same kind respond to a stimulus in unison. Intercellular communication also helps cells of different tissues coordinate their metabolite fluxes. Cell division coordination and regulation are crucial functions of intercellular signalling pathways in higher organisms. The routes guarantee that cells divide in unison and, if required, stop cell division and go into a state of rest.

Intracellular Signaling

In particular, receptors recognise external signals like hormones, electrical impulses, or sensory signals and

convert them into an intracellular signalling chain. The transcription program, morphology, cell division activity, intermediate metabolism, and all other aspects of the cell are governed by the intracellular signalling pathways.

LITERATURE REVIEW

(Ghahramani Almanghadim et al., 2025) [17] A complicated, and ever-changing gene expression pattern controlled by transcriptional and post-transcriptional mechanisms governs all immune system cells. In the nucleus of cells, LncRNAs alter gene expression by controlling transcription or post-transcriptional processes that affect "mRNA splicing, stability, or translation". Immunology research have shown that lncRNA expression changes during innate immune system activation, T cell maturation, differentiation, and activation. Inflammatory chemical production, cell differentiation, and cell migration are regulated by these lncRNAs. By changing base pairing with DNA and RNA or protein-protein interactions, they do this. We review the current understanding to determine how lncRNAs, as novel immune-related regulators, impact both pathological and physiological immune system processes, including autoimmune illnesses. We emphasise the developing gene expression control pattern in critical immunology and lncRNA biology research fields.

(Hashemi et al., 2025) [18] With some functioning as oncogenes and others as tumour suppressors, non-coding RNAs (ncRNAs) play a role in the formation of tumours. "The phosphoinositide 3-kinase (PI3Ks)/AKT serine/threonine kinase pathway" is one of the key and most frequently targeted ncRNAs in cancer. These ncRNAs are used to modify the cell cycle and a number of biological processes, such as protein synthesis, cell growth, mobility, and survival. Understanding ncRNA-PI3K/AKT signalling biology might improve cancer detection and therapy. In order to better understand the clinical features of lung cancer and the possible biomarkers for "lung cancer diagnosis, prognosis, and therapy", we looked at the expression and activity of PI3K/AKT-related ncRNAs.

(Mitić & Caporali, 2023) [19] Over ninety-eight percent of the genome of humans is transcriptionally active but fails to produce proteins; there are several noncoding genomes that play critical regulatory and structural roles. Understanding the role of endothelial cells (ECs) in vascular biology has been essential to comprehending how ischaemic tissue and cardiovascular disorders are repaired. Only a small percentage of the noncoding region of the human genome has been examined to learn more about its function in novel EC biology pathways. We provide a summary of endothelium's non-coding RNAs (ncRNAs) here. We also go over the most recent studies on ncRNA biology, including canonical and noncanonical features, ncRNA, cell-to-cell communication, and ncRNA's control of transcription and epigenetics in the endothelium.

(Dey et al., 2023) [14] EC is the most prevalent gynaecological cancer and is killing more women. Studies on targeting ncRNAs to identify and treat endometrial cancer have showed potential and limits. "Tumour grade, lymph node metastasis, myometrial invasion depth, FIGO stage, and patient survival" have all been related to the dysregulation of LncRNAs, which are expressed differently in ECs than in normal tissues. "CCAT2, BANCR, NEAT1, MALAT1, LINP1, SRA, and LSINCT5" are among the oncogenic and tumour suppressor lncRNAs that alter important signalling pathways implicated in EC metastasis, including p53, RAS/RAF/MEK/ERK, WNT/β-catenin, and PTEN/PI3K/AKT/mTOR. MiRNAs have an impact on post-transcriptional gene expression. Multiple studies suggest that miRNAs regulate EC crucially. Reviews are given of the biological role, prognostic significance, patterns of EC cell ncRNA expression, and roles in the cancer microenvironment in EC-associated pathways. Depending on their profile, we also discuss how ncRNAs might be used as therapeutic targets for different EC subtypes and as biomarkers for EC diagnosis.

(Statello et al., 2021) [20] Over the last decade, "long non-coding RNAs (lncRNAs)" have been shown to regulate genes and be broadly expressed. Research has begun to elucidate the differences between mRNA biogenesis and lncRNA biosynthesis, as well as how their subcellular locations and functions relate to one other. Depending on their location and interactions with proteins, RNA, and DNA, LncRNAs alter "cytoplasmic mRNA stability and translation", membraneless nuclear body assembly and function, chromatin function, and signalling pathways. Physiopathological settings including neurological diseases, immunological reactions, and cancer impact gene expression in many of these processes. LyncRNA expression patterns are tissue- and condition-specific, suggesting they may be biomarkers and warrant therapeutic targeting. This Review discusses lncRNA synthesis, localisation, functions, and possible therapeutic uses in transcriptional, post-transcriptional, and other gene regulatory pathways.

(Woolard & Chorley, 2019) [11] Noncoding RNA (ncRNA) regions found in the genome have important

regulatory functions in the transcription of genes and the translation of proteins. This article provides a short overview of the various ncRNA forms, with an emphasis on microRNAs (miRNAs), which are tiny ncRNAs that play significant roles in controlling cellular phenotype and gene expression. They may also be useful biomarkers in toxicology. Furthermore, we discuss recent biogenesis hypotheses and new research directions that describe the many and distinct biological activities of miRNA, such as improved function via molecular feedback loops and cell-to-cell communication via biofluids.

(Crespi, 2022) [21] With the rise of transcriptome sequencing, eukaryotes contain many non-coding RNAs. In addition to the well-known genes that code for proteins, such as "ribosomal RNA and transfer RNA", there are hundreds of transcripts that have no relation to a gene that codes for proteins. Non-coding RNAs may code for vital gene expression regulators, tiny si/miRNAs, short peptides (translated under certain circumstances), or large RNA molecules. In gene regulation, lncRNAs interact with various machinery. This review discusses how plant lncRNAs revealed novel epigenetic regulation, chromatin 3D structure, and alternative splicing regulatory mechanisms. Novel regulatory changes in target protein-coding gene expression and protein variations are crucial to plants' response to environmental challenges and adaptability to changing environments.

(Cajal et al., 2019) [22] Specialised cells, tissues, and organs form via intercellular communication, which is crucial in many disorders, including cancer. Current theory holds that various cytokines, growth factors, and hormones are secreted into the extracellular environment and bind to receptors that are particular to different types of cells. It is starting to become clear that ncRNAs (non-coding RNAs) communicate in both normal and abnormal states. MiRNAs, lncRNAs, and other ncRNAs are members of this class. RNAs regulate transcription, induce epigenetic modifications, and directly regulate protein activity. Their length, order, and form (circular or linear) might differ. Sponge miRNAs bind to miRNA and change how much of it is available to endogenous mRNAs. It is possible that lncRNAs are exclusive to certain cell types. Akin to the consequences of receptor-ligand interactions, this work suggests that lncRNA-miRNA interactions can vary depending on the cell type. The binding of microRNAs to long non-coding RNAs (lncRNAs) has the potential to define "cell identity and stress response" by activating biochemical feedback loops and signalling cascades that are particular to cell types.

(Ghasemian et al., 2023) [23] Colorectal cancer (CRC) is a leading killer. Cell signalling like JAK/STAT dramatically affects "gene expression and cell growth". Cell signalling, proliferation, and cancer destiny are regulated by lncRNAs. Therefore, lncRNAs are cancer biomarkers. Different lncRNAs block or activate the JAK/STAT pathway to control cancer cell growth or repression. LncRNAs also impact immunotherapy. Through JAK/STAT, lncRNAs control adhesion, inflammation, apoptosis, invasion, metastases, and cell proliferation in colorectal cancer. More research is needed to determine if lncRNA activation or repression inhibits CRC cell growth. We gathered in vitro and in vivo data to investigate CRC lncRNA cross-talk via the JAK/STAT signalling pathway. Future discoveries may lead to new CRC diagnostics, treatments, and personalised care.

(Sun et al., 2018) [24] "Long non-coding RNAs (lncRNAs)" are transcripts >200 nucleotides. LincRNAs outnumber coding RNA in the entire genomic transcript. Though first thought of as gene transcriptional noise, lncRNAs now regulate biological functions via their interactions with “DNA, RNA, and protein”. Several studies have linked lncRNAs to complex signalling circuits. This section covers several research on lncRNAs and key signalling pathways. Comprehensively shown, lncRNAs modulate metabolic components and signalling pathway regulatory variables to alter tumour cell biology. A basis and potential target for cancer diagnosis and treatment may be provided by aberrant lncRNA expression or mutation in human tumour cells and their interaction with signalling pathways.

(Fernandes et al., 2019) [25] A major discovery was the discovery of non-protein-translated RNAs, which revealed the variety of eukaryotic gene expression regulator molecules. "Short (miRNAs) and long (lncRNAs)" are the two length groups into which these non-coding RNAs may be divided. Cancer and viral disorders may be caused by lncRNA malfunction, which coordinates various physiological processes with other molecules. They impact post-translational modifications, transcription, splicing, chromosomal structural modulation, and the stability and availability of mRNA. Depending on sequence and secondary structure, long non-coding RNAs interact with "DNA, mRNAs, miRNAs, and proteins". Putative lncRNAs have been detected by new-generation sequencing, although it is challenging to characterise transcriptomes functionally.

With consequences for host and pathogen physiology as well as immune response modulation, we investigate the role of lncRNAs as regulatory factors in the control of gene expression across physiological and pathological processes.

CONCLUSION

In summary, RNA derived from non-coding regions of the genome is essential for cellular processes and gene control. Although many "non-coding RNAs (ncRNAs), such as lncRNAs and miRNAs", still have undefined functions, emerging evidence highlights their critical involvement in cellular responses to pharmaceutical and chemical exposures, as well as in early disease progression. ncRNAs act as key regulators of endothelial cell invasiveness and metastasis, linking and facilitating crosstalk between signaling pathways such as PTEN/PI3K/AKT/mTOR. The regulatory roles of miRNAs extend across multiple layers of cellular control, both during biogenesis and after maturation, underscoring their centrality in maintaining cellular homeostasis and responding to toxicological perturbations. By integrating miRNA analysis with traditional gene expression studies, researchers can gain deeper insights into adaptive and adverse responses to external exposures. Furthermore, miRNAs—which are present in both extracellular and intracellular environments—have gained attention as possible early and precise indicators of tissue and cellular conditions. These biomarkers are intimately associated with biological pathways of adversity and may be tested non-invasively in both people and animals. They provide potential tools for study in toxicology and precision medicine. As our understanding of ncRNAs evolves, their roles in complex cellular processes and signaling networks will continue to shape future advancements in biomedical science.

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